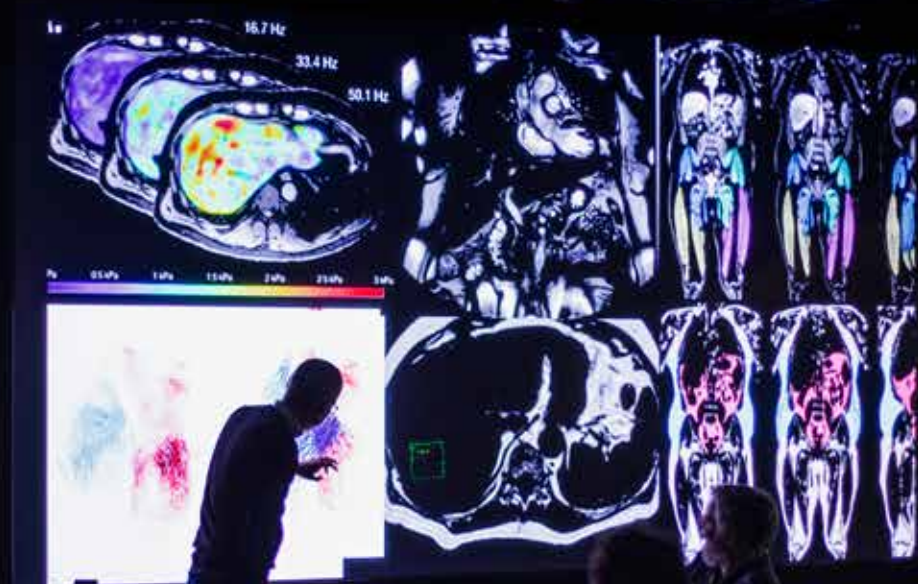


# Welcome to the exciting world of CMIV

**ANNUAL SCIENTIFIC REPORT 2020**



The image shows the auditory ossicles of the middle ear by our photon counting detector computed tomography scanner.

Project Leader, CMIV: Maria Kvist

Production: Futurniture

Photography: CMIV, Johan Sandlund, Mikael Sjöberg,  
Peter Holgersson, Wallenbergstiftelserna

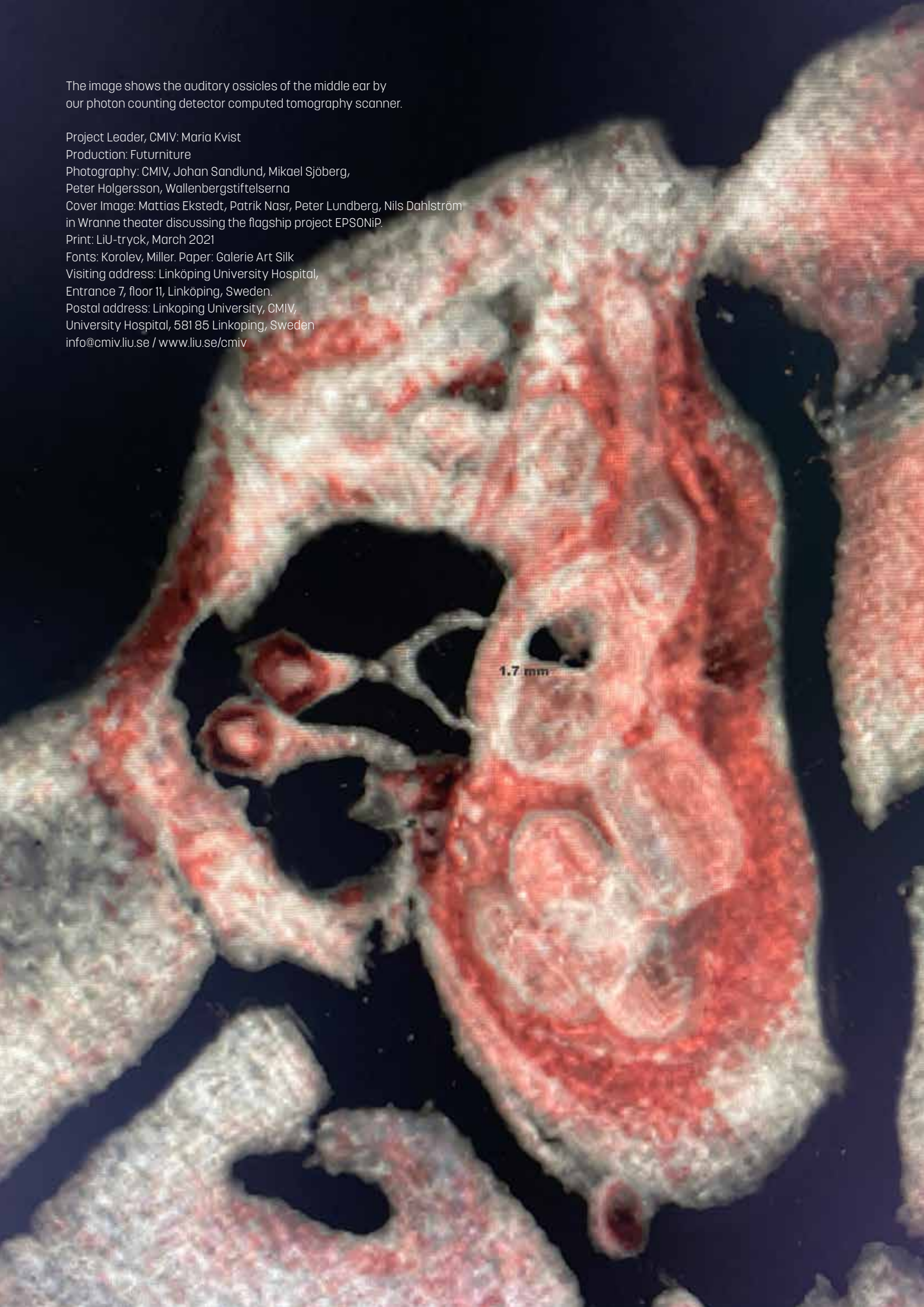
Cover Image: Mattias Ekstedt, Patrik Nasr, Peter Lundberg, Nils Dahlström  
in Wranne theater discussing the flagship project EPSONiP.

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# Preface

2020 was not an ordinary year. The pandemic has affected operations at CMIV, from individual research groups and supporting staff to our clinical duties. CMIV's most important meeting room, the coffee room to a large extent has been replaced by the virtual digital meeting rooms "Teams", "Zoom" and "Skype". Despite this, it has been possible to conduct clinical production and also planned research activities. Through fast remote connection that enables unlimited distance work, researchers at CMIV have been able to fulfill their work in an impressive way.

One of the biggest highlights in 2020 was when the CMIV landscape was expanded with a new modality. In July a research photon counting computed tomography scanner (PCD-CT) was installed. This technology is currently limited to very few centers in the world. It conveys excellent possibilities and unimagined opportunities for future translational research.

During the year, several of the increasing number of CMIV researchers have received large research grants from Swedish Research Council and Knut and Alice Wallenberg Foundation. Professor Markus Heilig has been elected member of the Royal Swedish Society of Science and awarded by the European College of Neuropsychopharmacology. Another event to highlight is the AIDA project, where its "Data Sharing Policy" gains attention and the data hub share data for AI projects all over the world. The arena has evolved during the year and the future is looking very promising in this field. In addition to that, Professor McCollough was appointed Honorary Doctor at Linköping University. For many years now CMIV has collaborated with the Mayo Clinic and Professor McCollough.

There is a vast number of ongoing research projects at CMIV and from these the flagship projects of 2020 were elected. They are three outstanding projects that visualize the broad competence among the CMIV researcher. They represent CMIV well in showing different areas and how we work close to the clinic combining technical and medical knowledge.

The first is "EPSONIP - Evaluating the Prevalence and Severity Of NAFLD in Primary Care". The second is "Experiencing the Self through Touch". And finally, the third flagship project is "Advanced CT Exams for Heart and Vessels".

Even if 2020 has been a tough and challenging year, excellent future-oriented interdisciplinary research has been produced that resulted in high impact publications, patient benefit, and several awards during the year. All thanks to the outstanding individuals at CMIV as well the unique twinning between medical and technical research in a clinical setting.



Anders Persson, DIRECTOR OF CMIV

# Highlights

As always, a lot of things have happened during the past year. The CMIV infrastructure expanded with the installation of the new photon counting detector computed tomography scanner last summer. AIDA installed an extremely powerful server for AI.

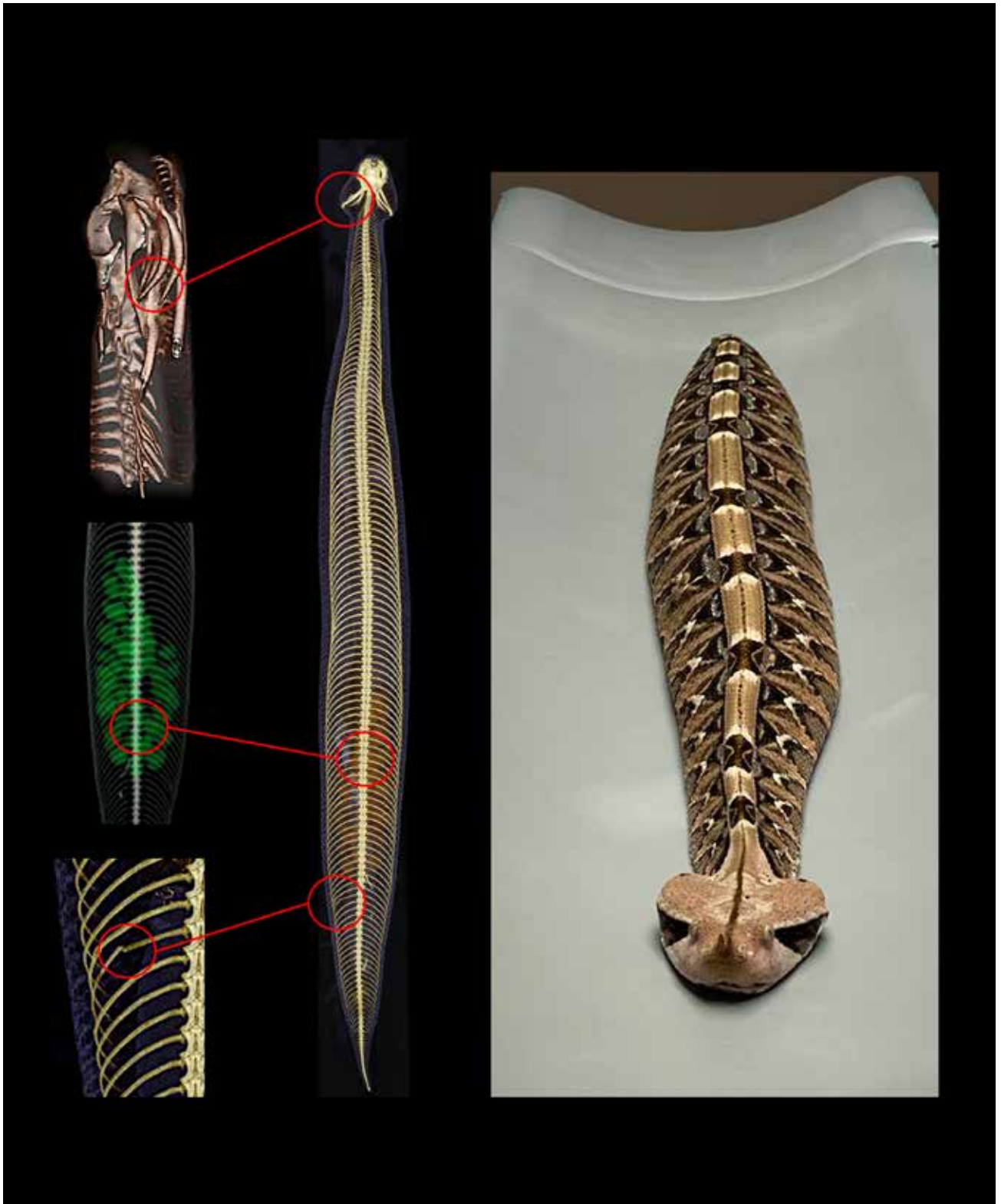


## Unique Photon Counting Detector CT Installed

**C** MIV was appointed one of three research centers in the world to install a completely new type of computed tomography (CT) which has the potential to offer significant improvements over current CT scanners.

The machine arrived at the end of June and during the autumn several new unique research projects started. With





this research scanner we will have the possibilities to obtain images of considerably higher resolution, and the use of several energy bins will give the possibility to distinguish multiple contrast agents, as well as obtaining images at lower radiation doses. This will be of great importance for the patient once we have the ethical approval on site.

Right now, we have ongoing research on phantoms and forensic cases in the musculoskeletal and cardiovascular area, among others. Thanks to the fruitful collaboration with the veterinarians at Kolmården Wildlife Park we also have the great opportunity to test the new technique on living animals that need diagnoses. ◀

Gaboon Viper with a broken rib, from Kolmården Wildlife Park, examined in the PCD-CT.



Professor Cynthia McCollough.

## Professor McCollough **Appointed Honorary Doctor**

**C**ynthia H. McCollough has been appointed Honorary Doctor of Technology for her efforts in the intersection between medicine and technology. She is an internationally renowned

researcher in the development and evaluation of computed tomography (CT) technology and dose reduction methods. She is a Professor of both medical physics and biomedical engineering at the Mayo Clinic in Rochester, Minnesota, USA.

CMIV has for many years collaborated with the Mayo Clinic and Professor McCollough. During the past years, the collaboration has deepened further around photon counting detector computed tomography (PCD-CT). The Mayo Clinic is one of the other research centers to install the same PCD-CT as CMIV. One of CMIV's PhD students, Mårten Sandstedt, spent the fall 2019 at the Mayo Clinic to learn more about the new technology and work on common research projects. ◀



Swedish  
Research  
Council

## **SEK 9.7 million to three CMIV Researchers**

**T**he Swedish Research Council is the largest governmental research funding body in Sweden and distributes almost SEK 7 billion every year to support Swedish research.

The three CMIV researchers Kajsa Uvdal, Karin Wårdell and Peter Lundberg received project grants within Natural and Engineering Sciences.

Professor Kajsa Uvdal at the Department of Physics, Chemistry and Biology, received research funding for her project Nanoparticle-activated neutrophils and the formation of extracellular traps.

Professor Karin Wårdell at the Department of Biomedical Engineering received research grants for her project within multiparametric analysis of cerebral blood flow in the detection of ischaemia.

Professor Peter Lundberg at the Department of Health, Medicine and Caring Sciences received grants to develop new techniques for modelling liver function. ◀

## *Unique Resource for AI Research in Medical Imaging*

**O**ne of the world's most powerful servers for artificial intelligence (AI) computation has been installed at CMIV. The system will serve as a national resource for projects within the Analytic Imaging Diagnostics Arena (AIDA).

The NVIDIA system, DGX-2, is the second of its kind in Sweden and has 16 GPU's, which means that it can process extensive volumes of data in a short period of time. Since medical imaging often generates a considerably large amount of data the powerful system is fundamental for large-scale computation in AI projects.

Such an investment is not possible for individual research groups, but through AIDA they will now have the opportunity to realize highly challenging projects.

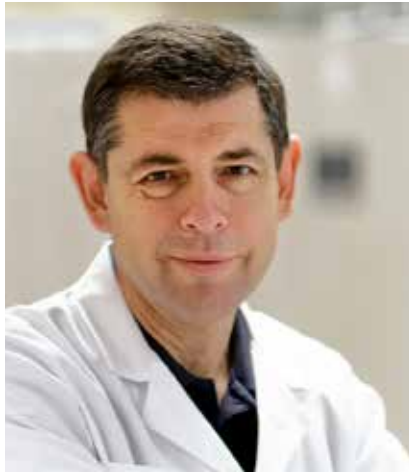
The projects within AIDA all develop AI solutions intended to become helpful tools in healthcare. Transferring technological innovations to clinically useful solutions is a challenge and the close collaboration with healthcare is a necessity for success. AIDA's task is to facilitate this process. ◀



Inauguration of the DGX-2.



# Great Accomplishments of Markus Heilig



Professor Markus Heilig.

In the beginning of the year, Markus Heilig, professor of psychiatry and founding director of the Center for Social and Affective Neuroscience (CSAN), was elected member of the Royal Swedish Society of Science and is part of the groups Class for Medical Sciences, and Health Committee.

In addition to that, in May, he also received the 2020 ECNP Neuropsychopharmacology Award by the European College of Neuropsychopharmacology. He was awarded the prize in recognition of his achievements as notable researcher in addictive disorders and other stress-related conditions. ◀



Facsimile of Scientific Data.

## AIDA Data Sharing Policy Gains Attention

In Sweden, the national community in AIDA, Analytic Imaging Diagnostic Arena, has developed a policy to help remove uncertainties of ethical and legal sharing of clinical imaging data. These key insights were discussed in an article in Scientific Data, a Nature Research Journal.

The presented policy was designed to be accessible to anyone in the medical imaging domain, while providing law-reference precision sufficient for talking to legal experts. It also provides practical guidance for research projects.

The Scientific Data article goes on to discuss our conclusions on key sharing issues, such as the legal basis for sharing, drilled-down definition of anonymization, and use of cloud services. The project group hope that the AIDA policy will provide a useful footing for similar policy development efforts in other countries and disciplines.

Joel Hedlund and Anders Eklund have presented the policy on several conferences, among others the NVIDIA's GPU Technology Conference. ◀

## Håkan Olausson Appointed Wallenberg Clinical Scholar

Professor Håkan Olausson receives a research grant of SEK 15 million over five years for his research on the clinical significance of an ultrarapid pain signaling system, which recently was discovered by him and his research group. Håkan is one of four medical researchers in Sweden to receive this grant from the Knut and Alice Wallenberg Foundation.

The grant will make it possible to further investigate the rapid pain system and its significance for the diagnosis and treatment of various pain conditions. ◀



Professor Håkan Olausson.



# 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, engineers, technicians and medical doctors could 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 2002, CMIV has grown into the vision and it is now our everyday routine.

**T**oday, 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 health care 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 where the university strives for scientific publications in high quality

journals and development of new products, and Region Östergötland 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 then can result in scientific publications, and improved patient care.

The CMIV research projects can be described 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. Nowadays, the imaging chain perspective is complemented with additional research areas like artificial intelligence and precision medicine.

We are in the middle of a paradigm shift in 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





Mischa Woisetschläger, Lilian Henriksson and Tino Ebbers at the reconstruction computer of the PCD-CT.

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 molecular 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 patients' 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. Since 2020, CMIV is one of the few clinical research centers in the world that has access to new photon-counting CT technology that offers unimaginable possibilities. CMIV has several exciting new studies in all of these fields. Another interesting field with an increasing contribution is microscopy, where the ongoing digitiza-

tion of the clinical routine has opened up for new applications in image analysis and deep learning.

#### **Biomedical Research Area**

CMIV has 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. ◀

# A SELECTION OF CMIV PROJECTS DEVIDED BY RESEARCH AREA

	Imaging Data Source					Biomedical Research Area							Technical Research Area							
	Computed Tomography	Magnetic Resonance Imaging	Digital Microscopy	Ultrasound	Other	Cardiovascular	Neurology	Oncology	Musculoskeletal	Gastrointestinal	Gynecological	Pulmonary	Metabolism	Acquisition	Modeling	AI/Data Analytics	Visualization	Simulation	Imaging Biomarkers	No Method Development
EPSONIP	●	●				●			●	●			●	●	●		●		●	
Experiencing the Self through Touch	●						●													●
Advanced CT Examinations of Heart and Vessels	●					●								●	●	●	●	●		
Analytic Imaging Diagnostic Arena	●	●	●	●	●	●	●	●	●	●	●					●	●			
MeDigiT	●	●				●			●						●	●	●			●
Tissue Classification Using DECT and MBIR	●							●							●	●				
Evaluation of Reconstruction Methods in CT	●							●				●		●			●			
Statistical Analysis of Neuroimaging Data	●						●								●	●				
SouthEast Sweden Neuroinflammation Cohort	●						●							●						●
Quantitative MRI on Brain Tumors	●						●	●					●	●						●
Pathophysiology Behind Prolonged Whiplash Associated Disorders	●						●													●
New Diagnostic Tools for the Diagnosis of Parkinson's Disease	●						●													
Odor Memory in Parkinson's Disease	●						●													
Localization of Seizure Onset Zone in Focal Epilepsy	●						●							●	●		●			
Clinical Application of Synthetic MRI on Malignant Gliomas	●						●													●
Imaging for Stereotactic Neurosurgery	●						●								●				●	
Clinical Implementation of Synthetic MRI	●						●	●						●	●		●	●	●	
Image-Based Biomarkers of Brain Disorders	●						●							●	●			●	●	
MRI-Based Body Composition Analysis	●						●													●
Effects of the Hormone Ghrelin on Decision Making	●						●		●											●
Modulating Inflammation in the CNS in Major Depression	●						●													●
Working Memory in Visual Noise	●						●													●
Detection and Neurological Effects of Manganese	●						●							●						●
Implementation of Syntetic MRI in the Abdomen	●							●		●				●						●
Optimizing the Use of Hepatobiliary MRI in Metastatic Liver Disease	●									●							●			
Semiautomatic Liver Volume Determination and Segmentation	●									●						●	●			
Liver Function Evaluation	●									●				●	●					●
Assessment of Hepatic Function in Health and Disease	●									●				●	●		●			●
Neuroplasticity in Irritable Bowel Syndrome	●									●										
MR-Mammography	●							●						●	●					●
Pain Mechanisms in Widespread Pain	●						●		●					●						●
Bone Structure Analyses for Reducing Future Osteoporotic Fractures	●								●					●			●			
CT-MOCAP: Visualization of skeletal joint movement	●								●								●			
The NACOX-study	●	●							●					●			●			●
Muscle Adaptation after Achilles Tendon Rupture	●								●											●
SCAPIS	●		●			●							●							●
SCAPIS-Health	●					●			●	●			●	●			●			●
Diffuse Myocardial Fibrosis	●					●														●
Myocardial Perfusion by MRI without Contrast Media	●					●														●
Ascending Aortic Dilation (AscA)	●		●			●								●		●				●
Assessment of Cardiovascular Blood Flow	●					●								●	●	●		●		
4D Flow CT	●	●				●								●	●			●		

a

SIEMENS





A woman with long dark hair, wearing a dark lab coat, is shown in profile, smiling and looking towards the left. She is in a laboratory setting with blue ambient lighting. In the background, a microscope is visible, and there are curved architectural elements. The overall scene is dimly lit, emphasizing the woman and the scientific environment.

# Flagship Projects

The 2020 flagship projects were selected by the CMIV scientific council in the autumn. 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.



# EPSONiP

## *–Evaluating the Prevalence and Severity of NAFLD in Primary Care*

The liver has many important functions in the body, including storing fat and sugar. Fatty liver is when the liver has stored too much fat. Type 2 diabetes and fatty liver are both part of the metabolic syndrome and share several risk factors for developing cardiovascular disease. In this research project a multidisciplinary team of researchers have the common interest to explore the link between fatty liver, epicardial fat and cardiovascular disease in type 2 diabetes.



It has long been known that visceral adipose tissue is associated with the development of cardiovascular disease (CVD). Ectopic fat accumulation in the liver can lead to inflammation and progressive fibrosis and is defined as Non-Alcoholic Fatty Liver Disease (NAFLD). This is the most common liver disease today. The most common cause of mortality in NAFLD is CVD. This project is called EPSONIP – Evaluating the Prevalence and Severity of NAFLD in Primary Care and Mattias Ekstedt, Associate professor and Senior Consultant at the Gastrointestinal Clinic, is the Principal Investigator.

One of the main objectives of the EPSONIP-trial is to investigate how common fatty liver and more advanced liver disease is in patients with type 2 diabetes in the primary care in Östergötland.

The goal is to include 400 patients from four different health care units within the region. This is done with the help of diabetes nurses, who ask patients when they come for their regular diabetes checkup if they want to participate in the study. The project group expects that this cohort will reflect the general diabetes patient in Sweden.

The data collection consists of several blood tests, blood and urine sample that will be saved in a biobank, surveys and fitness tests, among others how far you can walk in 6 minutes.

At a later visit, they will perform a magnetic resonance imaging (MRI) exam at Vrinnevi, Norrköping or at the university hospital in Linköping. Half of the cohort i.e., 200 patients will also perform a heart exam in the MR scanner. That examination is much more advanced and is therefore only done at CMIV.

However, all patients do an MR liver exam and an MR full body exam to look at body composition and distribution of fat and muscles. Main issue is to investigate if they have fatty liver and also the degree of damage to the liver.

Scarring can be divided into five stages, the most serious of which is cirrhosis.

– We are also interested in seeing what it looks like with fat storage in other organs, such as muscles, pancreas and around the heart, Mattias Ekstedt explains. They also look at how the fat is distributed in different fat depots, in the abdomen and hips. Both men and women are included, 35–70 years regardless of how long they have been ill with type 2 diabetes.

– One of the primary goals was to connect all those locally, who are interested in fat storage, and the network is important, Mattias explains.

– This is really a collaboration between primary care and specialist care; the gastrointestinal clinic, the radiology clinic, CMIV, the cardiology clinic and diabetes in primary care, he continues.

A follow-up study in three years is planned to see the progress of liver change.

The aim is to learn how the primary care will identify the patients who are at risk of advanced liver disease. Next is then to understand which patients may develop severe liver disease and this will become important in the three-year follow-up.

The third purpose is to understand how fatty liver affects the development of other disease states such as cardiovascular disease and kidney disease.

*“This is really an important collaboration between primary care and specialist care; the gastrointestinal clinic, the radiology clinic, CMIV, the cardiology clinic and diabetes specialists in primary care.”*

MATTIAS EKSTEDT

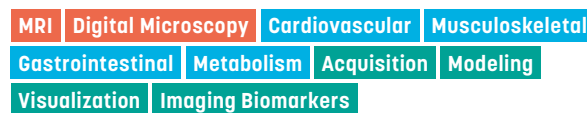
There are conflicting results, which makes the study even more exciting.

There are data that indicate that patients with type 2 diabetes together with fatty liver tend to have more changes in their coronary arteries and hence a higher risk profile of developing cardiovascular disease.

At the same time, there are other data that show that fatty liver does not increase the risk of having a heart attack.

The research group is collaborating with the health economy researchers to look at different models for when it is cost-effective to use MRI and when it is better to use, for example, ultrasound.

The EPSONIP-trial is truly a translational multi-disciplinary research project bringing researchers together. This project has the potential to be the starting point for a dynamic research network that will produce interesting scientific results for many years to come. ◀



## Project information

### PROJECT NAME

Evaluating Prevalence and Severity Of NAFLD In Primary care

### PROJECT LEADER

Mattias Ekstedt, Department of Medical and Health Sciences, Division of Diagnostics and Specialist Medicine (DISP)

### MAIN PROJECT PARTICIPANTS

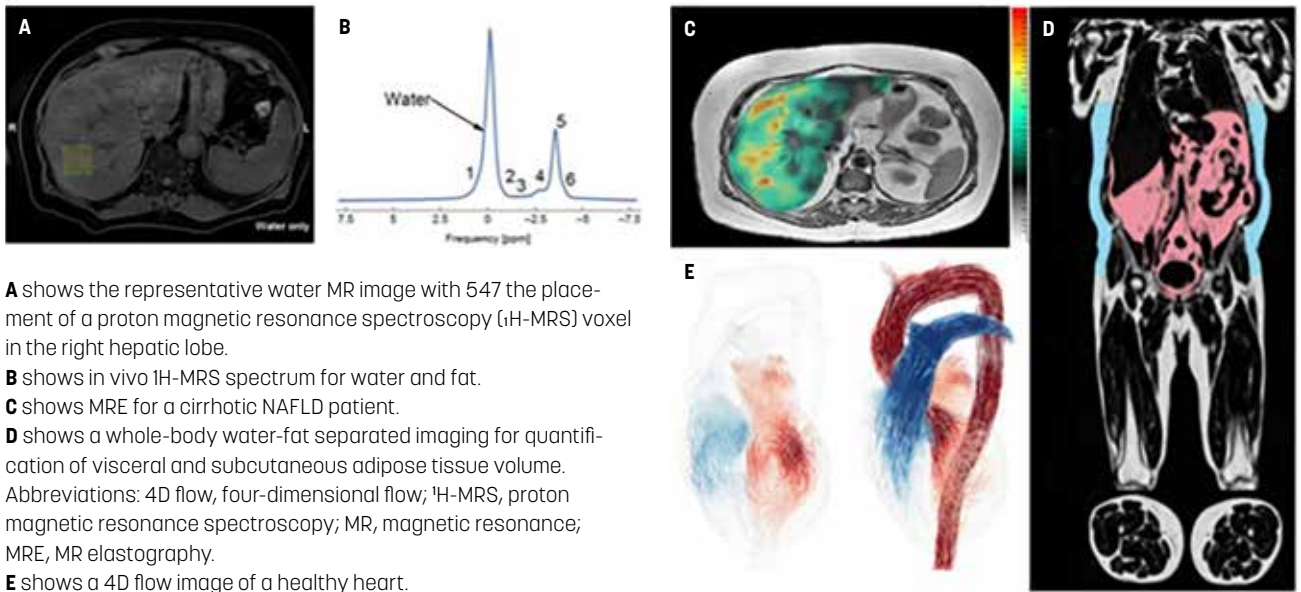
Joakim Alfredsson, Martin Bergram, Carl-Johan Carlhäll, Gunnar Cedersund, Tino Ebbens, Nils Dahlström, Martin Henriksson, Fredrik Iredahl, Stergios Kechagias, Peter Lundberg, Patrik Nasr, Karin Rådholm, Christian Simonsson

### GRANTS

ALF-Grant

### KEY PUBLICATIONS

Nasr P, Fredrikson M, Ekstedt M, Kechagias S. The amount of liver fat predicts mortality and development of type 2 diabetes in non-alcoholic fatty liver disease. Liver Int. 2020 May;40(5):1,069–1,078. doi: 10.1111/liv.14414. Epub 2020 Mar 10. PMID: 32087038.



Patrik Nasr, Nils Dahlström, Peter Lundberg, Mattias Ekstedt and Tino Ebbers.





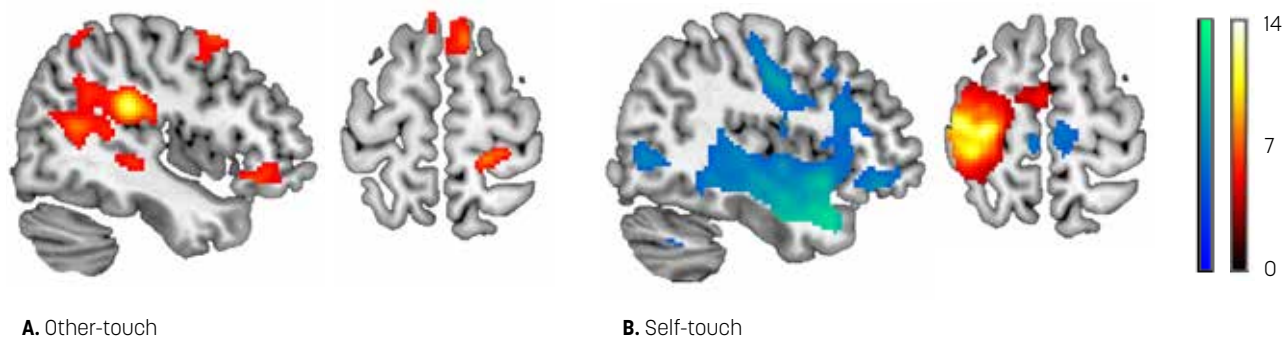




# *Experiencing the Self through Touch*

Social touch is a powerful force in human development from infancy and throughout life. Now perhaps more relevant than ever, as the pandemic entails that we must keep our distance and not touch each other at all in the same way as before, no handshakes or hugs. Already in the womb the fetus starts touching itself on the face and on the walls of the womb of the mother. It is a way of early determining where the self ends and the other begins.

Through functional magnetic resonance imaging (fMRI) this project gathers information about the boundaries between the self and others and compares the outcome of the reactions of neurotypical volunteers with participants with a psychiatric disorder.



*“It is important to have the actual skin- to skin touch to make it social.”*

REBECCA BÖHME

**S**omatosensation, the sense of touch, and interoception, the perception of sensations from inside the body are necessary for the establishment of the bodily self.

Rebecca Böhme, research fellow at Center for Social and Affective Neuroscience, and Håkan Olausson, professor in Clinical Neuroscience, are investigating how neurotypical volunteers, i.e., people without a psychiatric diagnosis, and participants with a psychiatric disorder are experiencing the self through touch. This flagship project is a composition of several projects within the same area. They have examined participants with attention deficit hyperactive disorder (ADHD), Anorexia nervosa, autism and schizophrenia.

When people who are close to us touch us, certain messenger substances are released in our body, which tells us that we are safe and not alone. This makes us feel less stressed, anxious, or worried.

– The self – other differentiation is very important, not just in relation to touch, but very broadly. We have to be able to know that this is me and that is another person, Rebecca Böhme explains. How does the brain understand that certain signals are coming from me touching myself and not from another person? This relates to the idea that there is a minimal self, which means basically the perception of the own body as “self”.

– We all need this minimal self, and it develops very early in life, already in the womb. The other senses as for example visual and auditory are lagging behind in development. Therefore, we think that the tactile sense is a very interesting sense to look at,

when we want to understand the self – other distinction. We are specifically interested in the context of psychiatric disorders with dysfunctions in the self-domain, Rebecca continues.

For autism e.g., there seems to be a stronger self – other distinction. People with autism have clearer borders of themselves. Everything other is further away and that could explain lower level of empathy abilities.

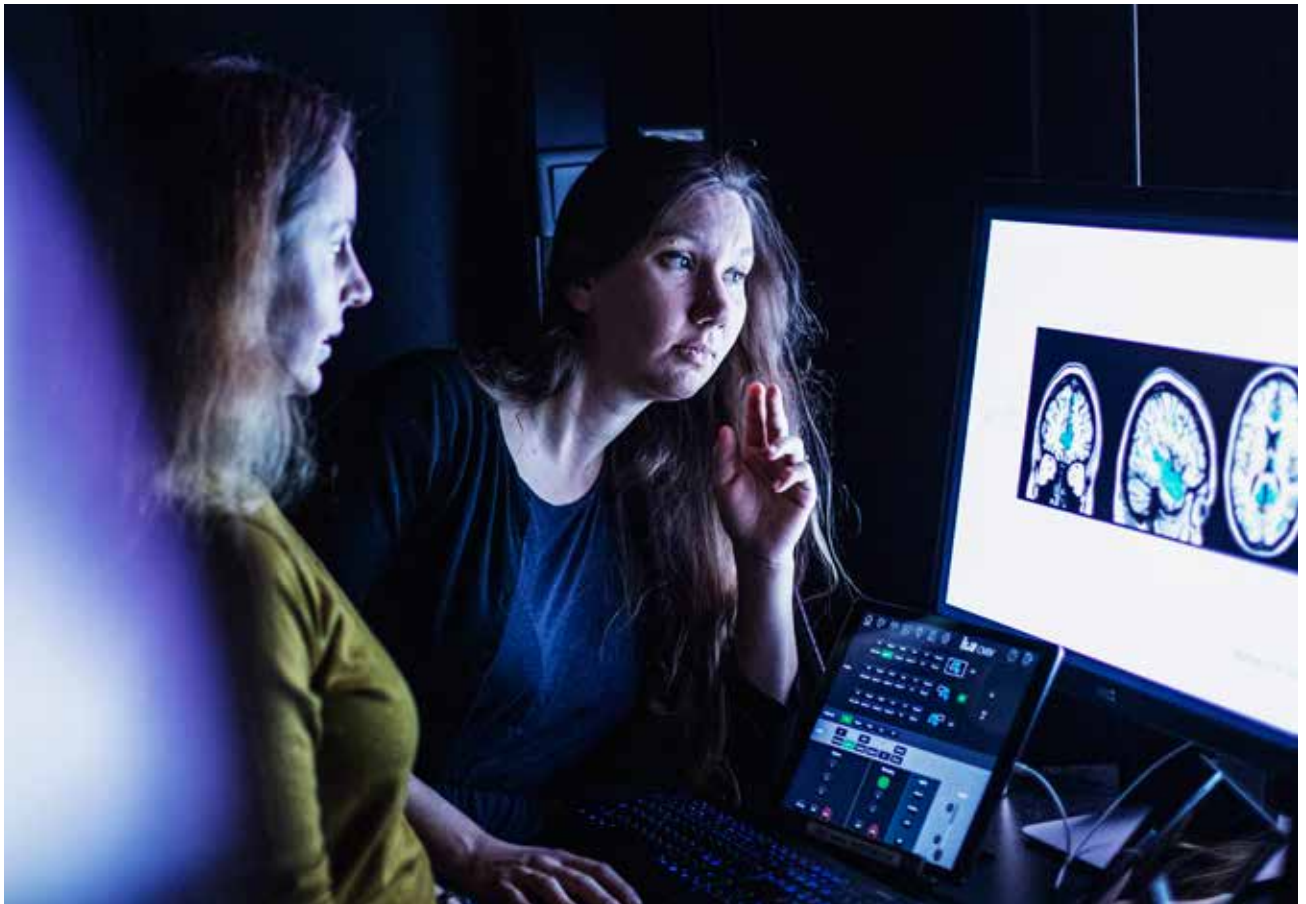
In case of anorexia on the other hand, there seems to be a reduced perception of the self – other distinction. Patients often think of themselves as bigger than they are. This group of participants generally has a skewed perception of their own body and where the body ends.

– They often have the sensation for example, when sitting on a chair that their own body overflows the chair, Rebecca says.

When looking at schizophrenia, this group has issues identifying the signals that come from their own body as self-produced. Sensations in the stomach deriving from the digestions might be misidentified as “non-self”, so they might come up with an explanation that this is somebody else, e.g., that an alien has implanted something in their body.

In all projects they use the skin-to-skin touching, since it should be social touch. This is a less controlled, stimulus but it is important to have the actual skin- to skin touch to make it a social situation.

Since these tasks are used to compare participants with a psychiatric disorder to neurotypical controls, it is important



PI Rebecca Böhme and research assistant Morgan Frost Karlsson.

that the task is simple enough, to avoid the risk of the confounding effect of one participant group not understanding the instructions. Hence, it is very important to have an easy task design. So, the studies are all performed in the same way. The participant places one arm on the belly and the other arm stroking the arm on the belly. It should be a nice soft stroking, no rubbing.

The other touch condition is when another person is stroking the arm trying to imitate the self-stroking.

There is one more control condition where the participant also strokes a pillow to calculate out the movement from the touching, since when you stroke your own arm, you move.

In all the previously explained studies they have compared participants with a psychiatric disorder with neurotypical controls.

The project Spinal and Cortical fMRI during Social Touch, however, does not include the psychiatric condition, but only healthy volunteers. In this project they image the brain with fMRI and simultaneously the spinal cord grey matter to see if a distinction between self-touch and other-touch can be found and if so, if there are interactions between the brain and the spinal cord.

All these projects lay the groundwork for the development of new interventions for treating the symptom domain of the bodily self in many psychiatric disorders. Such an intervention will use touch to establish or re-establish a functioning bodily self-perception – or as a patient puts it: “to awaken the silenced self”, Rebecca concludes. ◀

**MRI** **Neurology** **Imaging Biomarkers**

## *Project information*

### **PROJECT NAME**

Experiencing the Self through Touch

### **PROJECT LEADER**

Rebecca Böhme and Håkan Olausson, Department of Biomedical and Clinical Sciences, Center for Social and Affective Neuroscience

### **MAIN PROJECT PARTICIPANTS**

Rebecca Böhme, Håkan Olausson, Andrea Johansson Capusan, Morgan Frost Karlsson

### **GRANTS**

RB: Vetenskapsrådet startbidrag 2019-01873, Lions Forskningsfond LiU-2019-01191, Åke Wiberg stiftelse M19-0369, Svenska Läkarsällskap SLS-878101

H0: Vetenskapsrådets projektbidrag 2019-01119

### **KEY PUBLICATIONS**

Boehme R, Karlsson M F, Heilig M, Olausson H, Capusan A J. (2020). Sharpened self-other distinction in attention deficit hyperactivity disorder. *NeuroImage: Clinical*, 102317.

Boehme R, Hauser S, Gerling G, Heilig M, Olausson H. Distinction of self-produced touch and social touch at cortical and spinal cord levels. *Proceedings of the National Academy of Sciences (PNAS)*, Jan 22, 2019.



# *Advanced CT Exams for Heart and Vessels*

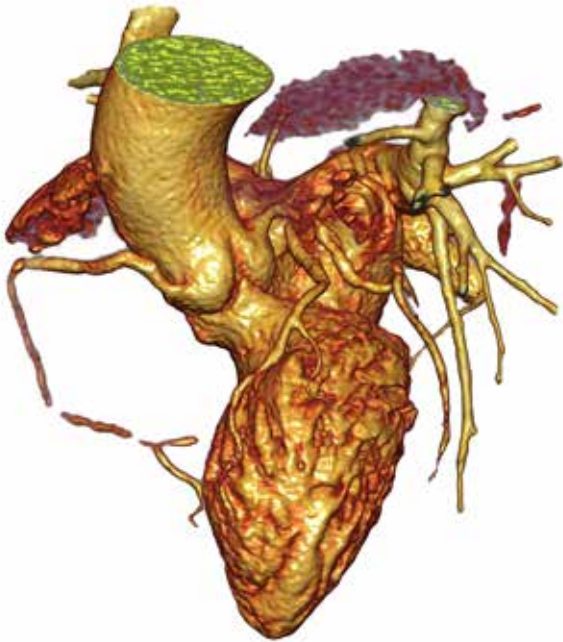




Cardiovascular disease (CVD) in general and coronary artery disease (CAD) in particular are the most common causes of death in the world. CVD is also the most expensive disease group, accounting for approximately 9% of the total health care expenditure in the European Union. Computed tomography (CT) is an increasingly used modality for investigations of patients with suspected CAD. A number of modalities for imaging of the coronary arteries are currently used among them coronary computed tomography angiography (CCTA), first described in 1995. Since then, CT technology has taken quantum leaps.

A man in a dark suit and glasses is seen from the side, looking into the gantry of a Siemens Healthineers CT scanner. The scanner is white with orange accents. The Siemens Healthineers logo is visible on the side of the gantry. The background shows the interior of a hospital room with some medical equipment.

**SIEMENS**  
**Healthineers**



Cardiac CT image.

**T**his flagship project combines mainly coronary artery morphology and cardiac function research with CT at CMIV. The research is carried out in close collaboration between the coronary artery group, led by CMIV director and professor Anders Persson, together with Mårten Sandstedt PhD and senior physician, Magnus Janson head at the department of cardiology, Associate Professor and the cardiac imaging and modelling group with Tino Ebbers, professor in Physiological Measurements and Matts Karlsson, professor and director of National Supercomputer Center. With translational research approach, we expect to improve the in-depth understanding and diagnostics of cardiovascular disease and treatment strategies.

The European Society of Cardiology published new guidelines in 2019 suggesting that “Coronary Computed Tomography Angiography (CTA) is the preferred test in patients with a lower range of clinical likelihood of CAD, no previous diagnosis of CAD, and characteristics associated with a high likelihood of good image quality.”



Magnus Janson, Mårten Sandstedt, Anders Persson and Tino Ebbers.



As the first university hospital in Sweden CCTA were introduced at CMIV in 2004 into clinical routine for patients with suspected CAD.

As part of Mårten's thesis, an AI software for automatic calcium scoring was evaluated. A calcium scoring is performed by scanning the heart without intravenous contrast, and is used for a coronary artery calcification quantification, which is employed for a clinical cardiovascular risk analysis. The quantification process is traditionally performed using semi-automatic post-processing softwares and is not very difficult, yet it takes significant expert time and is considered tedious. This CMIV project found a very good agreement between the semi-automatic and AI-based automatic methods, but AI was shown to have time-saving potential, which is valuable both for the work environment and for health economy.

Another work in Mårten's thesis has been performed together with the Mayo Clinic, Mn, USA. In this project, coronary specimens from human cadavers were examined with a conventional CT and a photon counting detector CT (PCD-CT). Subsequently, a coronary calcification quantification was performed, demonstrating the PCD-CT technology to be more accurate than the conventional CT.

With constantly decreasing radiation doses, it has become possible to acquire 3D images of a complete heartbeat. This so called 4D information can be used for functional assessment of the heart by using advanced post-processing, machine learning and simulations. Functional information, as for example blood flow in the whole heart, can be obtained which can give valuable information in the prediction of the risk for formation of blood clots, which can cause a heart attack or stroke. It can also be used to compare the effect of different surgical treatment options, like the choice prosthetic heart valve, as shown by Jonas Lantz.

#### Future aspects

The new research PCD-CT that CMIV installed in July offers new opportunities in imaging of the coronary arteries and assessment of cardiac function. This technology is currently limited to very few centers in the world and conveys excellent possibilities for further cardiac CT developments. The scanner has several benefits compared to clinically available CT scanners, such as higher resolution and lower radiation dose. In cardiac imaging, the improved spatial resolution facilitates the assessment of coronary artery calcifications more accurately and new types of functional imaging possible. The PCD-CT scanner's high-resolution abilities may evaluate coronary artery calcifications more accurately, and unnecessary invasive examinations can thereby be minimized. It gives us unimagined opportunities for the future and great advantages in cardiac diagnostics. ◀



Computed Tomography   Cardiovascular   Acquisition   Modeling  
AI/Data analytics   Visualization   Simulation

### Project information

#### PROJECT NAME

Advanced CT Exams for Heart and Vessels

#### PROJECT LEADER

Anders Persson, Department of Health, Medicine and Caring Sciences, Division of Diagnostics and Specialist Medicine

#### MAIN PROJECT PARTICIPANTS

Tino Ebberts, Matts Karlsson, Mårten Sandstedt, Magnus Janzon, Joakim Alfredsson, Jan Engvall, Carl-Johan Carlhäll, André Da Luz Moreira, Sophia Beeck, Faisal Zaman, Lilian Henriksson, Petter Quick

#### KEY PUBLICATIONS

Lantz J, Beeck S, Carhäll C-J, Bolger A, Persson A, Karlsson M, Ebberts T. Impact of prosthetic mitral valve orientation on the ventricular flow field: Comparison using patient-specific computational fluid dynamics. *Journal of Biomechanics*, Vol 116, 2021.

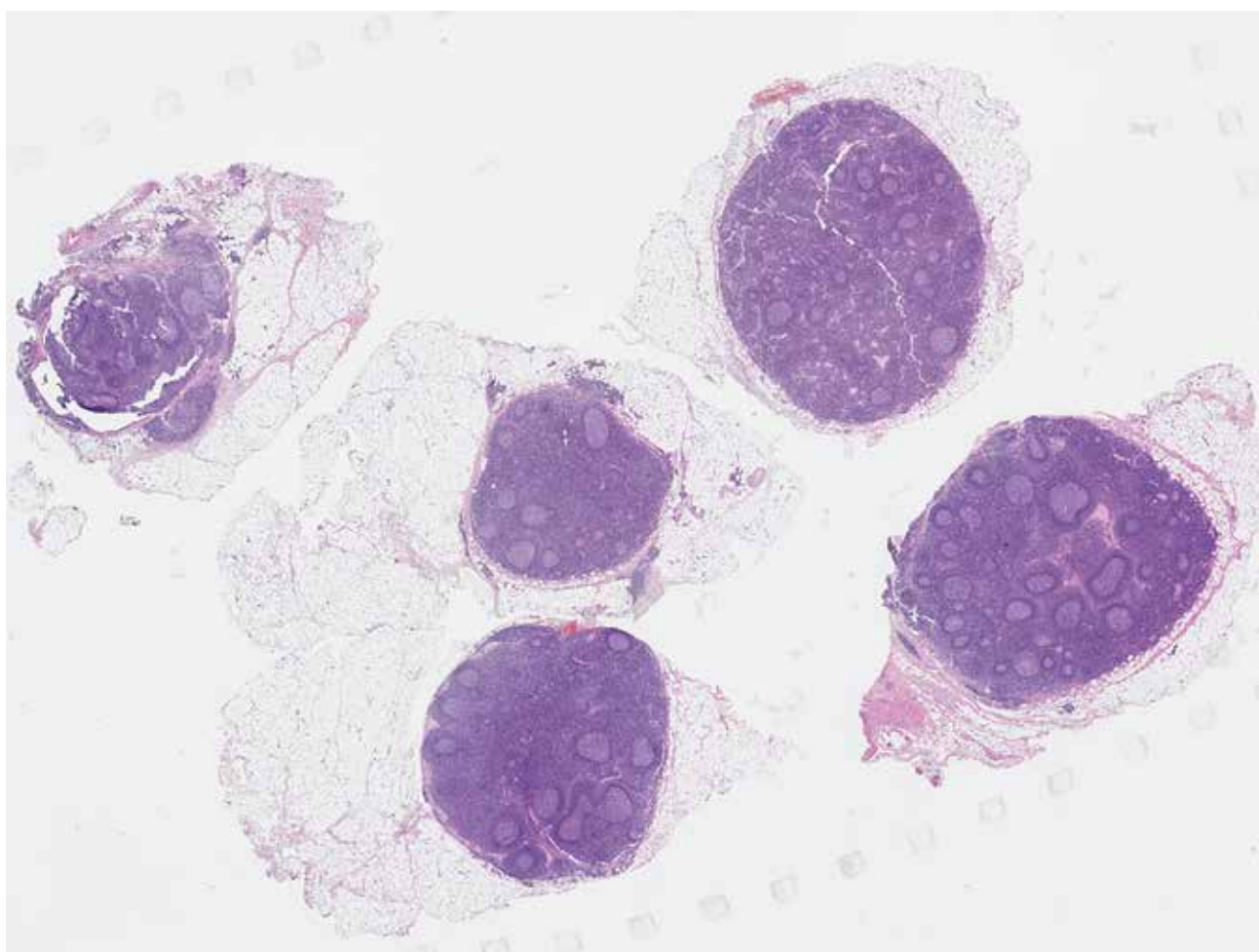
Sandstedt M, Henriksson L, Janzon M, Nyberg G, Engvall J, De Geer J, Alfredsson J, Persson A. Evaluation of an AI-based, automatic coronary artery calcium scoring software. *European Radiology*, Vol 30, no 3, p. 1,671–1,678, 2020.



# 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 of the research projects at CMIV.





An example from the LNC02 data set, showing a whole slide pathology image with colon lymph nodes. The LNC0 and LNC02 data sets are one of the biggest shared histology data sets in the world.

# AIDA

**A**nalytic 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 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.

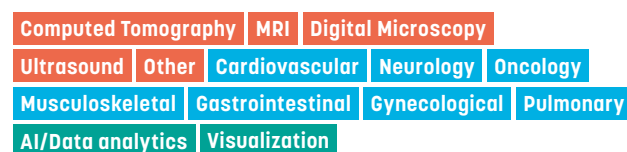
AIDA’s objective is to develop AI-based decision support solutions for imaging diagnostics that reach all the way to clinical use. An underpinning fundamental insight is that this complex challenge requires both interdisciplinary and cross-sectoral collaboration.

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 for efficient AI development, with the flagship resource being the heavy-load computational system DGX-2 shared between the groups across the country. AIDA also hosts a data hub with clinically relevant data available for AI research, currently over 5 TB and growing. Perhaps even more important is the meeting place aspect of the core environment, where workshops and meetings 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, ITN

### MAIN PROJECT PARTICIPANTS

Caroline Bivik Stadler, Joel Hedlund, Daniel Forsberg, Jonas Unger, Marie Waltersson, Catrin Nejdeby, Gabriel Eilertsen, Darren Treanor, Neda Haj-Hosseini, Anders Eklund, Tino Ebbers, Martin Lindvall, Karin Stacke, Sven-Patrik Hallsjö

### GRANTS

VINNOVA, Medtech4Health

### KEY PUBLICATIONS

Hedlund J, Eklund A, Lundström C.

Key insights in the AIDA community policy on sharing of clinical imaging data for research in Sweden. *Nature Scientific Data* (2020).

Bivik Stadler C, Lindvall M, Lundström C, Bodén A, Lindman K, Rose J, Treanor D, Blomma J, Stacke K, Pinchaud N, Hedlund M, Landgren F, Woisetschläger M, Forsberg D.

Proactive Construction of an Annotated Imaging Database for Artificial Intelligence Training. *Journal of Digital Imaging* (2020).

Maras G, Lindvall M, Lundström C.

Regional lymph node metastasis in colon adenocarcinoma, second collection series. doi:10.23698/aida/Inco2. (2020).

# Medical Digital Twin -MeDigiT

**A** medical digital twin is a computer model that contains so much information about a patient that it can work as a digital copy. The digital twin can be used to simulate disease progression and treatment response before the patient has begun a medication or a surgical procedure.

Medical Digital Twin, MeDigiT, is a platform project financed by Visual Sweden aiming to facilitate the use of individualized digital models in healthcare for better diagnostics, more individualized treatment of illness, and simplified and improved education for healthcare professionals. The platform also aims to create and promote a network for research and exchange of knowledge and experience between Linköping University, Region Östergötland and companies in medical visualization.

The platform was formed in early 2019 and has since then connected several partners and created demonstrator projects in various areas.

One of the demonstrator projects, a collaboration between CMIV, Clincum, Sectra and Region Östergötland, investigates the use of time-resolved digital twins of the body's joints in teaching. An interactive software for visualization of moving joints where the images are collected using advanced computed tomography (CT) is developed. The software will be evaluated in the training of physiotherapists and physicians.

Another MeDigiT demonstrator project is focusing on CMIV's cutting edge research on imaging of the cardiovascular system. Using simulations of heart flow based on CT images, individualized digital twins are tested for diagnosis and treatment evaluation in heart disease. The research aims amongst others for improving valve surgery and risk assessment of blood clot formation in atrial fibrillation. Other parts partici-

pating in the project are Siemens and Region Östergötland.

In collaboration with Scandinavian Real Heart and Region Östergötland, a unique digital twin of an artificial heart has been created. The artificial heart has a design not previously used and the possibility to use time-resolved CT and MRI data provides valuable knowledge of the heart's function in the development of the product.

Access to digital, functional models of the organs in the body offers invaluable opportunities for research and for the development of products related to visualization of medical data. ◀

Computed Tomography MRI Cardiovascular  
Musculoskeletal Modeling AI/Data analytics Visualization  
Imaging Biomarkers

## Project information

### PROJECT NAME

Medical Digital Twin

### PROJECT LEADER

Tino Ebbers, Department of Health, Medicine and Caring Sciences, Division of Diagnostic and Specialist Medicine

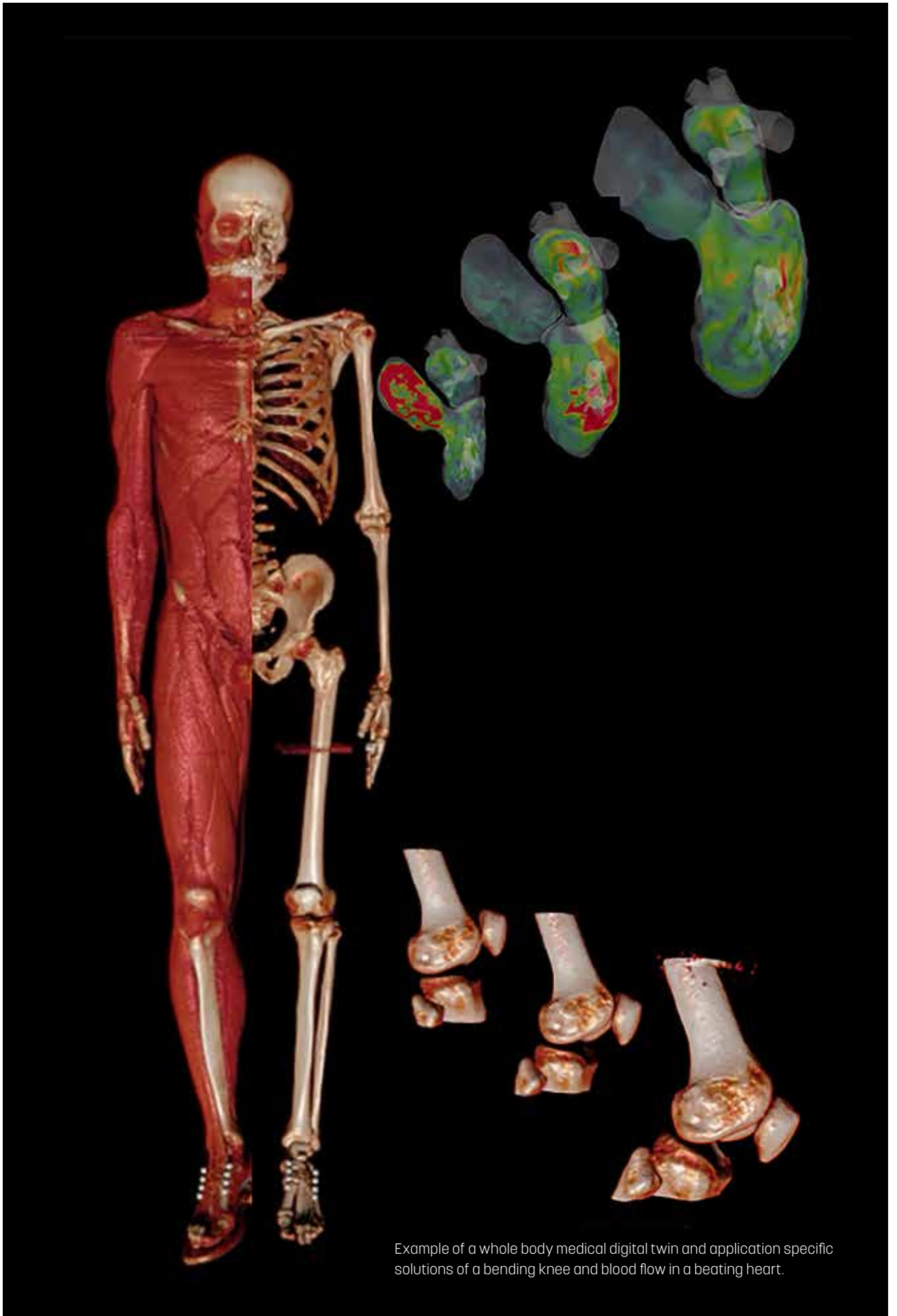
### MAIN PROJECT PARTICIPANTS

Marie Waltersson, Anders Persson, Nils Dahlström, Faisal Zaman, André Da Luz Moreira, Federica Viola, Mariana Bustamante  
Several participants from companies

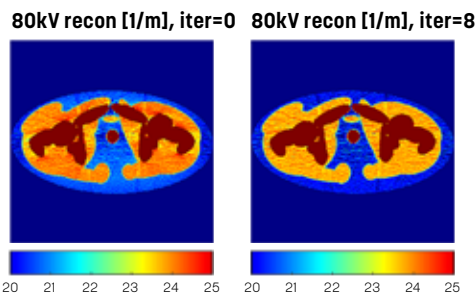
### GRANTS

Visual Sweden 2019–2020, 2020–2021

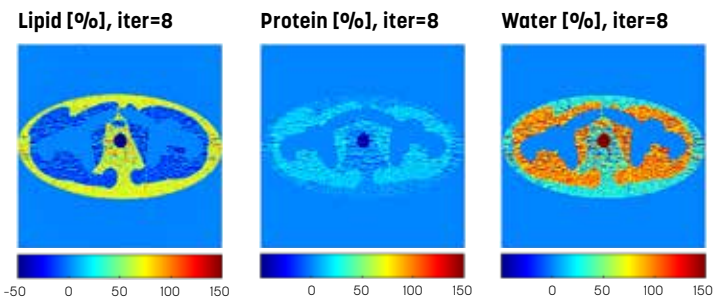




Example of a whole body medical digital twin and application specific solutions of a bending knee and blood flow in a beating heart.



**Figure 1.** Suppression of the beam hardening artifact for the mathematical pelvic phantom. The image reconstructed via conventional filtered back-projection with water beam hardening correction (left) and the corresponding image obtained via DIRA in iteration 8 (right).



**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.

# Tissue Classification Using DECT and MBIR

**T**oday'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 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.

The ability of DIRA to suppress the beam hardening artifact is shown in Figure 1. A material decomposition of soft tissues to the lipid, protein and water is shown in Figure 2. Knowledge of these mass fractions allows the estimation of the elemental composition of the phantom, which is of interest in dose calculations for radiotherapy planning.

Recently, we have implemented helical scanning geometries (Magnusson et al 2019) and segmentation of bones using a deep learning algorithm (González Sánchez et al, 2020). Results of our deep learning algorithm for segmentation of pelvic bones is shown in Figure 3. We try to use deep learning for the segmentation of other tissues, suppression of noise, and generation of data for radiation therapy. In parallel, we extend DIRA to multi-energy CT so that it can process data generated by photon counting CT that uses energy resolving detectors. This approach is expected to further improve the accuracy in dose calculations for radiotherapy planning. ◀

Computed Tomography | Oncology | Modeling | AI/Data analytics

## Project information

### PROJECT NAME

Tissue Classification Using Dual Energy CT and Iterative Reconstruction

### PROJECT LEADER

Åsa Carlsson Tedgren, Department of Health, Medicine and Caring Sciences, Division of Diagnostics and Specialist Medicine

### MAIN PROJECT PARTICIPANTS

Alexandr Malusek, Maria Magnusson, Michael Sandborg, Gudrun Alm Carlsson

### GRANTS

Cancerfonden 2019–2021  
Swedish Research Council 2017–2020

### KEY PUBLICATIONS

Malusek A, 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. *Medical Physics* 44, p. 2,345–2,357, 2017.

Magnusson M, Björnftot M, Carlsson Tedgren Å, Alm Carlsson G, Sandborg M, Malusek A.

DIRA-3D – a Model-based Dual-Energy Iterative Algorithm for Quantitative 3D Helical CT *Biomed. Phys. Eng. Express* 5 065005, 2019.

González Sánchez J, Magnusson M, Sandborg M, Carlsson Tedgren Å, Malusek A.

Segmentation of bones for radiation therapy from medical dualenergy computed tomography volumes using the 3D U-Net. *Physica Medica: European Journal of Medical Physics* 69, p. 241–247, 2020.



# Evaluation of Reconstruction Methods in CT



**Figure 1.** Axial image examples from a study patient showing image quality produced by the different reconstruction algorithms compared in Kataria et al, 2018. FBP = Filtered Back Projection, ADMIRE = Advanced Modeled Iterative Reconstruction at strengths 3 and 5 (out of 5).



**Figure 2.** Coronal image examples from a study patient showing image quality produced by the different reconstruction algorithms and slice thicknesses compared in Kataria et al, 2020.

In all diagnostic x-ray examinations there are ionizing radiation. It is imminent to produce images of good diagnostic quality while simultaneously keeping the radiation dose to human organs as low as reasonably achievable (ALARA principle) to minimise detrimental radiation effects. Abdominal and thoracic Computed Tomography (CT) are common examinations and irradiate radiosensitive tissues in humans.

Image quality in CT is related to the radiation exposure. A reduced exposure can increase the image noise and hence may reduce the image quality and visibility of anatomical structures as well as pathology. Therefore, reductions in patient exposure need to be evaluated carefully without impairment in diagnostic accuracy. New technology presents a wide range of noise and dose reduction strategies, the latest being iterative image reconstruction (IR). The aim of this project is to evaluate the performance and dose reduction potential of advanced modeled iterative reconstruction (ADMIRE); a model-based reconstruction algorithm used by radiology departments in Region Östergötland.

In prospective visual grading experiments radiologists evaluated the clinical image quality by comparing images of the same patient, simultaneously exposed to different doses using a novel technique with two x-ray tubes, to determine the potential dose reductions without compromising image quality. Established European guidelines on image quality criteria were used and the responses from the evaluation by experienced radiologists were analysed statistically with ordinal logistic regression models. This allows computation of potential patient dose reduction from the regression's coefficients of the statistical model.

The performance of ADMIRE strengths 3 and 5 (out of five) in abdominal CT, showed a positive correlation between ADMIRE strength and increasing potential dose reduction for all image criteria assessed but one (Kataria et al. 2018) (figure 1). For the highest strength 5, the image quality in the liver parenchyma was negatively affected, and a decline in diagnostic confidence was observed. However, the visibility of other image criteria was improved also with ADMIRE 5 allowing further potential dose reductions (27–50%) in task-specific exams. Figure 2 show the effect on image slice thickness where a 25–35% dose reduction were indicated by the statistical model (Kataria et al. 2020) using the thicker slices.

Objective quantitative measurements in anthropomorphic phantoms do, to some extent, support our results from the qualitative subjective assessment by radiologist, but subtle changes in noise texture due to the reconstruction algorithm indicate that phantom measurement alone are not sufficient, but need to be complemented with human evaluations.

Our experimental design has been successful, and the novel statistical analysis is presently used to optimise ADMIRE in thoracic CT and to explore any change in radiologists' evaluation of image quality over time, when using the ADMIRE reconstruction algorithm.

The important conclusion is that the model-based reconstruction algorithm, ADMIRE improves image quality in abdominal CT allowing for significant dose reductions. However, the clinical utility of the highest strength of the algorithm is limited to certain criteria. ◀

Computed Tomography Oncology Pulmonary Acquisition  
Visualization

## Project information

### PROJECT NAME

Visual Grading Evaluation of Reconstruction Methods in Computed Tomography for Improved Patient Safety

### PROJECT LEADER

Bharti Kataria, Department of Health, Medicine and Caring Sciences, Division of Diagnostics and Specialist Medicine

### MAIN PROJECT PARTICIPANTS

Michael Sandborg, Anders Persson, Örjan Smedby, Jonas Nilsson Althén, Hannibal Sökjer

### GRANTS

ALF  
FoU 2020–2022

### KEY PUBLICATIONS

Kataria B, Nilsson Althén J, Smedby Ö, Persson A, Sökjer H, Sandborg M.

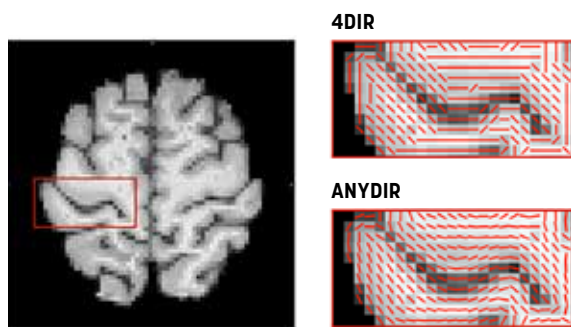
Assessment of image quality in abdominal CT: potential dose reduction with model-based iterative reconstruction. *European Radiology* 2018; 28: 2,464–2,473.

Kataria B.

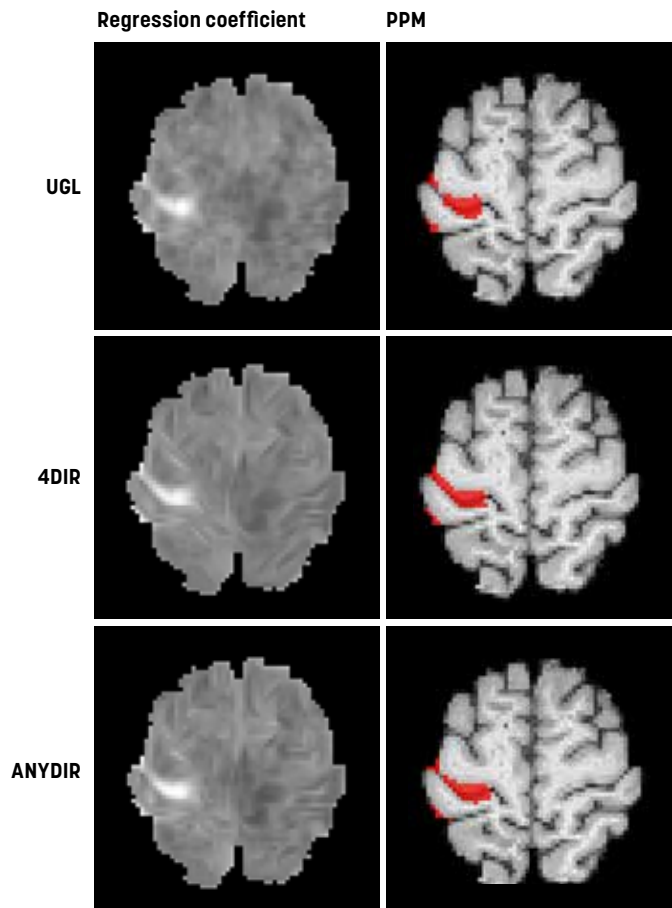
Visual grading evaluation of reconstruction methods and dose optimisation in abdominal Computed Tomography. Thesis Linköping University No 1683, 2019.

Kataria B, Nilsson Althén J, Smedby Ö, Persson A, Sökjer H, Sandborg M.

Assessment of image quality in abdominal CT: Effect of model-based iterative reconstruction, multi-planar reconstruction and slice thickness on potential dose reduction. *European Journal of Radiology* 122 (2020) 108703.



Anatomical information from a T1-weighted volume is used to inform Bayesian spatial priors on how to smooth the fMRI data in each part of the brain. Two approaches are proposed, an approach that can only select four different smoothing directions, and an approach that works for any direction.



Resulting brain activity maps (posterior probability maps), where UGL represents the standard smoothing used in fMRI which is isotropic and for example mixes signal from white matter and gray matter. The adaptive smoothing respects the tissue boundaries.



# Statistical Analysis of NeuroImaging Data

**F**unctional magnetic resonance imaging (fMRI) is a popular tool for studying brain activity, as it can non-invasively image the human brain without any ionizing radiation. Similarly, diffusion MRI (dMRI) is a popular tool for studying structural brain connectivity, by for example measuring how easily water can travel along different directions. From a statistical perspective, analyzing fMRI and dMRI data is a challenging task for several reasons. One reason is that the noise has a complex spatio-temporal structure, which is virtually impossible to simulate in a computer. Another reason is that there are several noise sources which distort the signal of interest, for example head motion, breathing and pulse. In this project we validate and improve existing statistical models for neuroimaging data, often using open data available through data sharing.

In our most recent work, we propose a new adaptive model of the BOLD (blood oxygenation level dependent) signal that can detect more brain activity compared to existing methods (Wilzén et al., 2020). We also propose how to use anatomically informed Bayesian spatial priors for fMRI analysis, to for example not mix signal from gray matter and white matter (Abramian et al., 2020). Finally, we propose a graph filtering approach to analyze brain activity in white matter, which requires anisotropic smoothing as nerve fibers normally have a clear orientation (Abramian et al., 2020). ◀

MRI Neurology Modeling AI/Data analytics

## *Project information*

### **PROJECT NAME**

Statistical Analysis of NeuroImaging Data

### **PROJECT LEADER**

Anders Eklund, Department of Biomedical Engineering

### **MAIN PROJECT PARTICIPANTS**

David Abramian, Josef Wilzén, Mattias Villani, Hans Knutsson, Per Sidén, Bertil Wegmann

### **GRANTS**

Swedish Research Council 2018–2021  
VINNOVA / ITEA3 IMPACT 2019–2021  
CENIT 2018–2023

### **KEY PUBLICATIONS**

Wilzén J, Eklund A, Villani M.  
Physiological Gaussian process priors for the hemodynamics in fMRI analysis, *Journal of Neuroscience Methods*, 2020.

Abramian D, Sidén P, Knutsson H, Villani M, Eklund A.  
Anatomically informed Bayesian spatial priors for fMRI analysis, *IEEE International Symposium on Biomedical Imaging (ISBI)*, 2020.

Abramian D, Larsson M, Eklund A, Behjat H.  
Improved functional MRI activation mapping in white matter through diffusion-adapted spatial filtering, *IEEE International Symposium on Biomedical Imaging (ISBI)*, 2020.

# SouthEast Sweden Neuro Inflammation Cohort

**M**ultiple 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 advocates a shift from conventional MRI to the use of more advanced MR-methods including quantitative MRI methods (qMRI). 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.

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. ◀

**MRI** **Neurology** **Acquisition** **Imaging Biomarkers**

## *Project information*

### **PROJECT NAME**

SouthEast Sweden Neuroinflammation Cohort (SESNIC)

### **PROJECT LEADER**

Anders Tisell, Department of Health, Medicine and Caring Sciences, Division of Diagnostics and Specialist Medicine

### **MAIN PROJECT PARTICIPANTS**

Johan Møllergård, Peter Lundberg, Jan Ernerudh, Ida Blystad, Magnus Vrethem, Angie Liu, Jonas Lind, Maria Kristoffersen Wiberg, Marcel Warntjes, Kristina Söderberg

### **GRANTS**

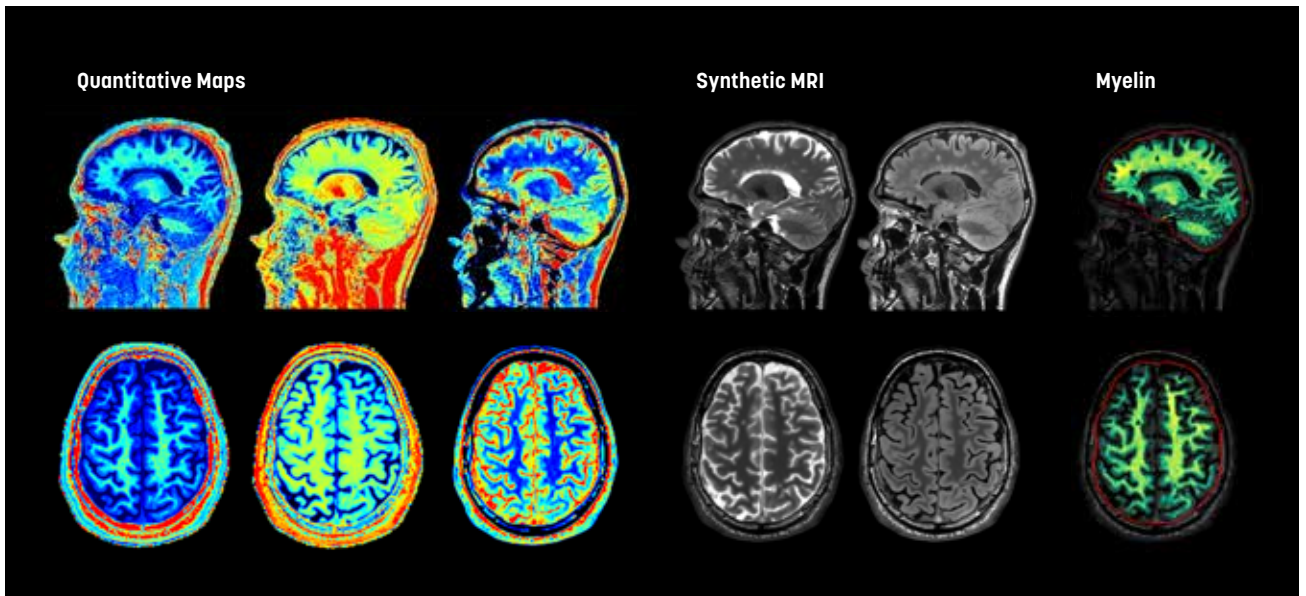
Swedish Research Council  
FORSS  
ALF

### **KEY PUBLICATIONS**

Møllergård J, Tisell A, Blystad I, Grönqvist 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.

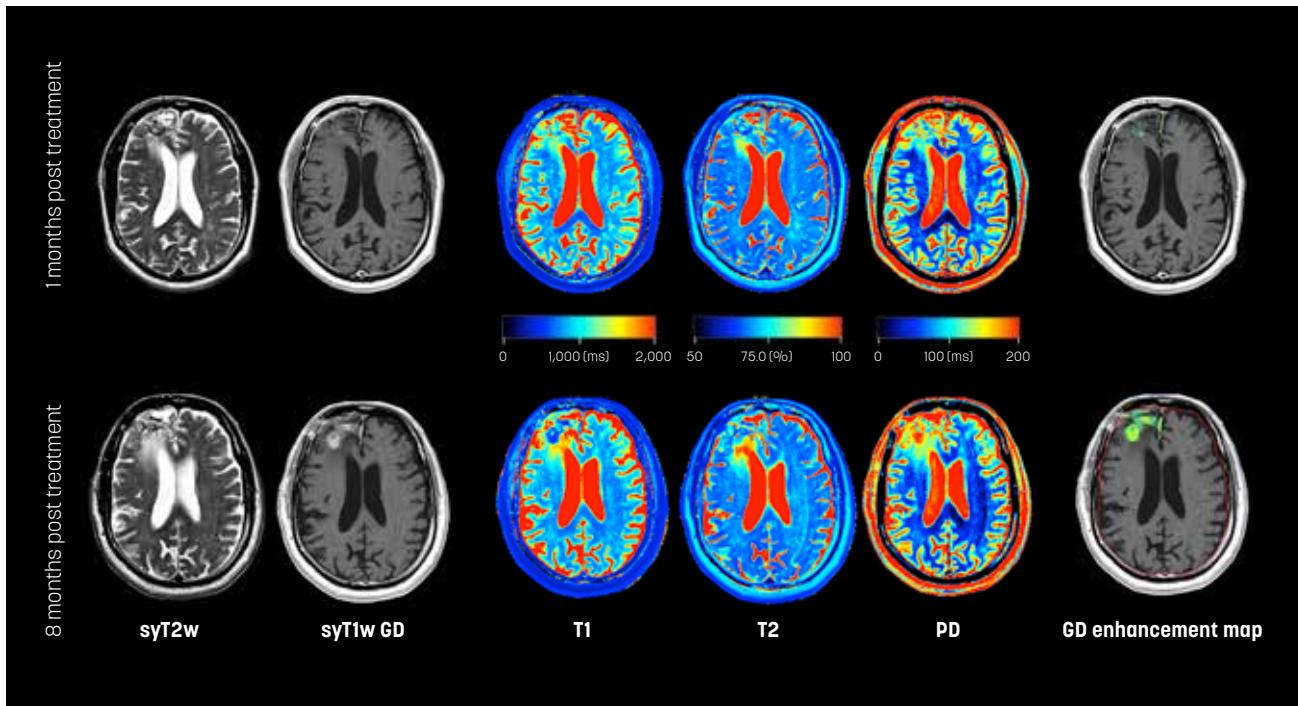


QALAS images of a 22-year-old MS patient. All images are calculated from a single acquisition of 6 min.



POPULAR SCIENTIFIC SUMMARY

*Anders Tisell*



QMRI data from a glioma patient one month and eight months after completed adjuvant radiation- and chemotherapy. In the examination one-month post treatment a small residual tumor is visible and detected as enhancing lesion. And, in the examination eight months post treatment the volume of the residual tumor has increased.

# Quantitative MRI on Brain Tumors

**S**tandard treatment for a high-grade brain tumor glioblastoma consists of radical surgical resection, followed by adjuvant radiation- and 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 pseudoprogression 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 pseudoprogression. ◀

MRI Neurology Oncology Metabolism 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 Health, Medicine and Caring Sciences, Division of Diagnostics and Specialist Medicine

### MAIN PROJECT PARTICIPANTS

Peter Lundberg, Ida Blystad, Maria Kristoffersen Wiberg, Annika Malmström, Munila Mudaisi, Angie Liu, Anna Ljusberg, Faris Durmo, Pia Sundgren, Linda Knutsson

### GRANTS

LiU Cancer  
ALF  
RFOU  
FORSS

### KEY PUBLICATIONS

Blystad I, Warntjes M, Smedby O, Lundberg P, Larsson EM, Tisell A. Quantitative MRI using relaxometry in malignant gliomas detects contrast enhancement in peritumoral oedema. *Sci Rep* 10, 17986 (2020).

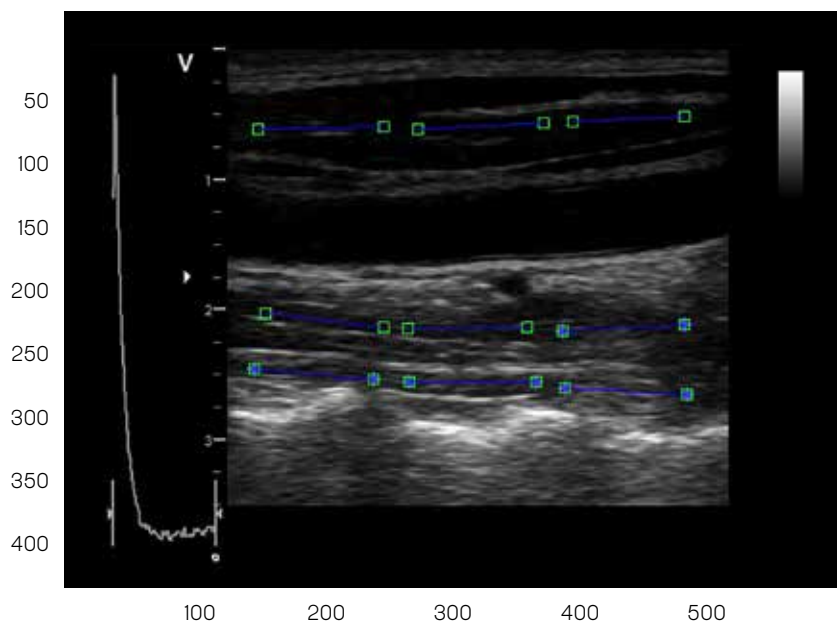
Blystad I, Warntjes JBM, Smedby Ö, Lundberg P, Larsson E-M, Tisell A (2017).

Quantitative MRI for Analysis of Peritumoral Edema in Malignant Gliomas, *PLoS ONE*, 2017 May 23;12(5):e0177135. doi: 10.1371/journal.pone.0177135. eCollection 2017. PMID: 28542553.

Warntjes JBM, Blystad I, Tisell A, Larsson EM. Synthesizing a Contrast-Enhancement Map in Patients with High-Grade Gliomas Based on a Postcontrast MR Imaging Quantification Only. 2018 *AJNR*.



Ultrasound registration in real time of ventral neck muscles during an arm lift.



Longitudinal Ultrasound imaging of ventral neck muscles at C4 level.  
From above: M Sternocleidomastoideus, M Longus capitis and M Longus colli.



# Pathophysiology Behind Prolonged Whiplash Associated Disorders

**T**here is insufficient knowledge of pathophysiological parameters to understand the mechanism behind prolonged Whiplash Associated Disorders (WAD) and yet unknown whether changes can be restored by rehabilitation or not.

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. Another purpose is to compare individuals with WAD with healthy controls. The participants are 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 improved rehabilitation methods for WAD. ◀

**MRI** **Neurology** **Imaging Biomarkers**

## *Project information*

### **PROJECT NAME**

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

### **PROJECT LEADER**

Anneli Peolsson, Department of Health, Medicine and Caring Sciences, Division of Prevention, Rehabilitation and Community Medicine

### **MAIN PROJECT PARTICIPANTS**

Anette Karlsson, Bijar Ghafouri, Tino Ebberts, Maria Engström, Margaretha Jönsson, Karin Wåhlén, Thobias Romu, Magnus Borga, Eythor Kristjansson, Hilla Sarig Bahat, Dmitry German, Peter Zsigmond, Gunnel Peterson, Nils Lund

### **GRANTS**

Swedish Research Council  
Vinnova  
Region Östergötland

### **KEY PUBLICATIONS**

Björkkvist J, Peterson G, Peolsson A.

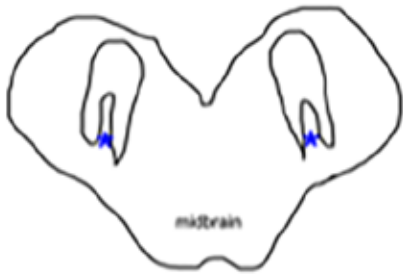
Ultrasound investigation of dorsal neck muscles during neck rotation exercise. Which muscles are in use? *J Manipulative Physiol Ther*, 2020 Sep 3;S0161-4754(20)30070.

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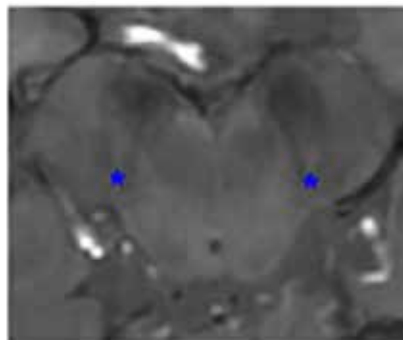
The effects of deep neck muscle-specific training versus general exercises on deep neck muscles thickness, pain and disability in patients with chronic non-specific neck pain: protocol for a randomized clinical trial (RCT). *BMC Musculoskeletal Disorders* 2019;20:540.

Moodie K, O’Leary S, Tucker K, Phil S, Peolsson A.

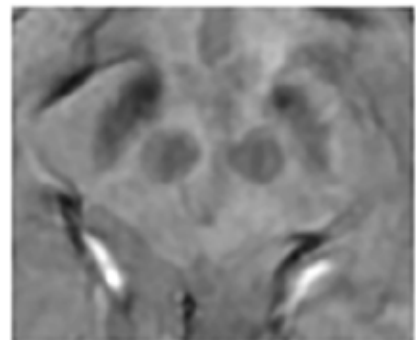
Are ultrasound measurements of muscle deformation well correlated with force and electromyography? *J Manipulative Physiol Ther* 2020;43:284–293.



Normal appearance of the posterior part of substantia nigra, known as nigrosome-1 (marked with \*)



Nigrosome-1 in a healthy participant.



Absence of nigrosome-1 in a PD patient.

# New Diagnostic Tools for the Diagnosis of Parkinson's Disease

**P**arkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease, with approximately 1% prevalence in people over 60 years of age. The hallmark of the disease is the abnormal aggregation of a protein, namely Lewy bodies, in a centrally located part of the brain that plays an important role in movement coordination (substantia nigra). This leads to a progressive loss of dopaminergic neurons in the brain, which results in the classical motor symptoms of PD: rigidity, bradykinesia, resting tremor and postural imbalance. There is, however, a group of clinically heterogeneous disorders, known as atypical parkinsonian syndromes, sharing similar signs and symptoms with PD. As a result, diagnosing PD is often challenging and time-consuming for both clinicians and patients alike.

The diagnostic work-up of patients with suspected PD includes thorough neurological examination, positive response to dopaminergic treatment, genetic testing and neuroimaging with nuclear medicine examinations such as Single Photon Emission Computed Tomography (SPECT) and Positron Emission Tomography (PET). There is, to date, no diagnostic Magnetic Resonance Imaging (MRI) examination for PD; most patients with suspected parkinsonism undergo an MRI scan in order to exclude other pathology that may explain their symptoms. However, certain MRI techniques can potentially detect disease related abnormalities in the brain. Recently, it has been demonstrated that susceptibility weighted imaging (SWI) can detect degeneration in substantia nigra. Additionally, a novel MRI technique, Synthetic MRI, can quantify brain tissue properties, allowing volumetric measurements of white matter, grey matter and cerebrospinal fluid in the brain.

The aim of this study is to survey whether degeneration in

substantia nigra can be visualized with SWI and Synthetic MRI, and to compare the diagnostic accuracy of these two methods with that of common nuclear medicine examinations, which are widely used in these patients. For that purpose, patients that have undergone PET or SPECT examination due to suspected parkinsonism are also examined with MRI, including SWI and Synthetic MRI. Preliminary results verify that SWI can detect degeneration in substantia nigra, a part of which (nigrosome-1) disappears in PD patients (figure). The study is ongoing, and analysis is expected to be concluded during the first half of 2021. Our goal is to help accelerate the diagnostic process in PD, by establishing a new and reliable MRI examination. ◀

**MRI** **Neurology**

## *Project information*

### **PROJECT NAME**

New Diagnostic Tools for the Diagnosis of Parkinson's Disease

### **PROJECT LEADER**

Charalampos Georgiopoulos, Department of Health, Medicine and Caring Sciences, Division of Diagnostics and Specialist Medicine

### **MAIN PROJECT PARTICIPANTS**

Anders Tisell, Miguel Ochoa Figueroa, Anette Davidsson, Sven Haller

### **GRANTS**

Lions forskningsfond 2020–2022  
LFOU, Region Östergötland 2020–2021



# Odor Memory in Parkinson's Disease

**P**arkinson's disease (PD) is a debilitating neurodegenerative disorder, characterized by both motor and non-motor symptoms. Olfactory impairment and cognitive impairment are two of the most common non-motor symptoms in PD. Olfactory impairment affects more than 90% of patients, often heralding motor symptoms, and it has been identified as a predictive feature of cognitive decline. Moreover, olfactory dysfunction is generally associated with lower quality of life, whereas cognitive decline is associated with higher mortality and disease burden. Nonetheless, non-motor symptoms are often overshadowed by the dominance of motor symptoms, being therefore poorly recognized and inadequately treated.

Functional MRI (fMRI) has been widely used to identify entire networks of brain regions that are activated when we perform certain tasks or when we rest. In a recent fMRI study, our group has identified two olfactory brain networks, both of which are less recruited by PD patients due to their olfactory dysfunction. The longitudinal comorbidity reliably observed between olfactory dysfunction and cognitive decline raises the question whether fMRI of odor memory can successfully predict which patients will later develop dementia and which neural substrates are associated with it. For this purpose, we have established an fMRI protocol with three different olfactory paradigms: a) firstly, patients passively smell 2 odors, b) then, they smell 8 different, well-known odors and try to memorize them (odor encoding), and lastly c) they smell 16 odors, 8 of which were present during encoding (odor retrieval). This examination allows us to identify three hierarchically different olfactory networks, associated with passive smelling, encoding and retrieval.

The study is currently ongoing and data collection will continue throughout 2021. Preliminary results from healthy controls show that passive smelling activates parts of the brain that are intrinsically related to olfaction, namely the olfactory cortex (figure). During odor retrieval, a more extensive pattern of

brain activation is observed, including centrally located brain areas such as thalamus and the basal ganglia (figure). Future analysis including data from PD patients, will allow us to better understand how odor memory is affected in this disease. By elevating the importance of non-motor symptoms, we expect to establish new prognostic tools foreseeing the development of dementia in PD. ◀

**MRI** **Neurology**

## *Project information*

### **PROJECT NAME**

Odor Memory in Parkinson's Disease

### **PROJECT LEADER**

Charalampos Georgiopoulos, Department of Health, Medicine and Caring Sciences, Division of Diagnostics and Specialist Medicine

### **MAIN PROJECT PARTICIPANTS**

Tom Eek, Paul Hamilton, Fredrik Lundin, Nil Dizdar

### **GRANTS**

Lions forskningsfond 2020–2022

LFoU, Region Östergötland 2020–2021

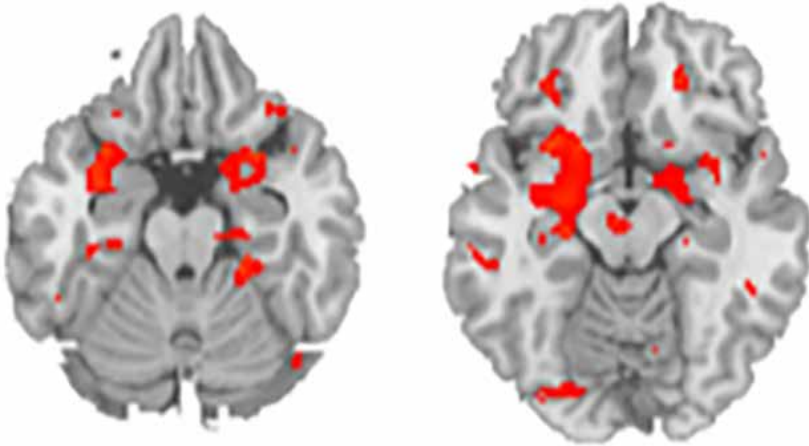
### **KEY PUBLICATIONS**

Georgiopoulos C, Witt ST, Haller S, Dizdar N, Zachrisson H, Engstrom M, Larsson EM (2019).

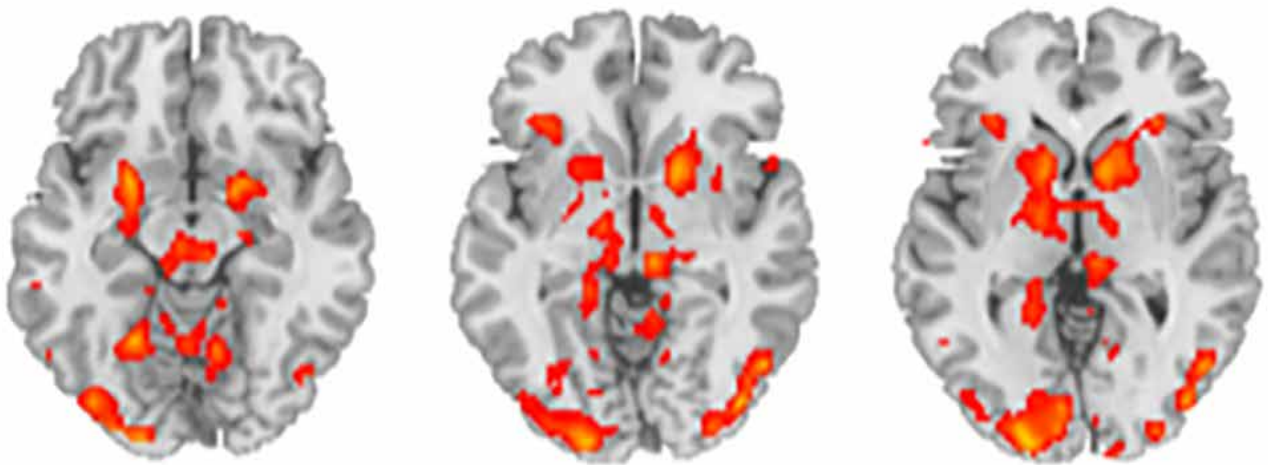
A study of neural activity and functional connectivity within the olfactory brain network in Parkinson's disease. *Neuroimage Clin.* 2019;23:101946. doi: 10.1016/j.nicl.2019.101946.

Georgiopoulos C, Witt ST, Haller S, Dizdar N, Zachrisson H, Engstrom M, Larsson EM (2018).

Olfactory fMRI: Implications of Stimulation Length and Repetition Time. *Chem Senses* 43, 389–398.



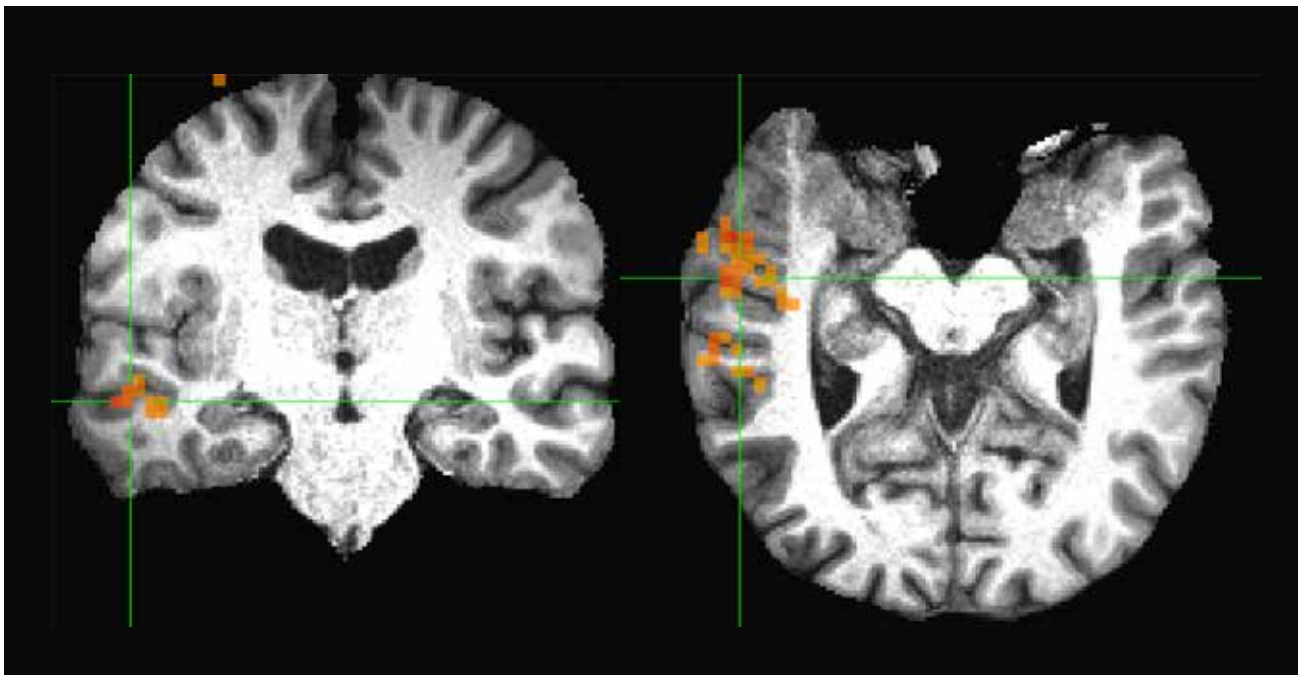
**Passive smelling.** Activation of intrinsically olfactory related brain areas.



**Odor retrieval.** Broader activation including thalamus and basal ganglia.

POPULAR SCIENTIFIC SUMMARY

*Hans Lindehammar*



BOLD signal changes correlated to interictal epileptiform activity recorded in the scanner in a patient with focal epilepsy. This is not the seizure but the area in the brain that is electrically overactive and have an increased metabolic demand between seizures.



# Localization of Seizure Onset Zone in Focal Epilepsy

**E**EG-fMRI is a method that combines EEG (electroencephalogram) and fMRI (functional magnetic resonance imaging) to localize the epileptogenic zone in patients with medically refractory focal epilepsy who are candidates for epilepsy surgery. The method is in use in some epilepsy centers around the world but not in clinical practice in Sweden. The aim of this study is to implement the method in epilepsy surgery evaluation and to compare the results with other investigations.

Epilepsy is a disorder with uncontrolled electric activity in the cortex of the brain. In most people with epilepsy, the seizures are controlled by medication. About 30% of patients continues to have seizures despite medication with one or more antiepileptic drugs. The disease is then defined as medically refractory and some of these patients are evaluated for epilepsy surgery. Epilepsy surgery is a treatment option that can cure patients with epilepsy. In most cases, a small part of the brain is resected. Before this operation, it is very important to define the area where the seizures starts, called the seizure onset zone. There are many different methods such as MRI (structural lesion), EEG (electrical activity), PET (metabolism) and SPECT (blood flow) used to localize this zone. Sometimes invasive methods like intracranial EEG must be used. Combined EEG-fMRI allow mapping of BOLD (blood oxygen level dependent) signal changes correlated to epileptiform discharges in the EEG. The electrical discharges in the cortex that is typical for epilepsy correlates to localized changes in oxygen consumption and blood flow, which alters the BOLD-signal (the hemodynamic response function). The EEG defines the time for epileptiform discharges and fMRI is recorded continuously. Studies in other centers have concluded that this method can accurately localize the seizure onset zone. It is difficult to record EEG of good quality in the MR scanner because of artifacts induced by the magnetic and electromagnetic fields. Special equipment is necessary to be successful in recording a good quality EEG in the MR scanner. CMIV and The Department of Clinical Neurophysiology at the University Hospital in Linköping has the equipment for recording of EEG in the MR scanner.

**Method:** With an MR safe EEG cap, EEG is recorded with 64 electrodes during fMRI scanning (3T) for 30 minutes. Offline analysis of EEG to identify epileptiform discharges and timing of these events. Analysis of fMRI data with different hemodynamic

response functions in relation to the events in EEG. This gives maps with the strongest BOLD changes.

**Material:** 20 adult patients with medically refractory focal epilepsy who are evaluated for epilepsy surgery are included in the study. The collection of data started in September 2019 and so far, 16 patients with epilepsy have been examined. The EEG has been analyzed and the correlation between epileptiform activity and BOLD-changes is now processed. Preliminary result exists for one patient (picture). ◀

MRI Neurology Acquisition Modeling Visualization

## Project information

### PROJECT NAME

A Study Using the Combination of EEG and fMRI to Localize the Seizure Onset Zone in Focal Epilepsy

### PROJECT LEADER

Hans Lindehammar, Department of Clinical Neurophysiology, Region Östergötland

### MAIN PROJECT PARTICIPANTS

Helena Gauffin, Mats Svantesson, Paul Hamilton, Katarina Henell Eklund

### GRANTS

Region Östergötland  
Föreningen Margarethahemmet

### KEY PUBLICATIONS

Pittau F, Dubeau F, Gotman J.  
Contribution of EEG/fMRI to the definition of the epileptic focus. *Neurology* 2012;78:1,479–1,487.

Khoo HM, Hao Y, von Ellenrieder N et al.  
The hemodynamic response to interictal epileptic discharges localizes the seizure-onset zone. *Epilepsia* 2017;58(5):811–823.

Kowalczyk MA, Omidvarnia A, Abbott DF et al.  
Clinical benefit of presurgical EEG-fMRI in difficult-to-localize focal epilepsy: A single-institution retrospective review. *Epilepsia* 2020;61:49–60.

# Clinical Application of Synthetic MRI on Malignant Gliomas

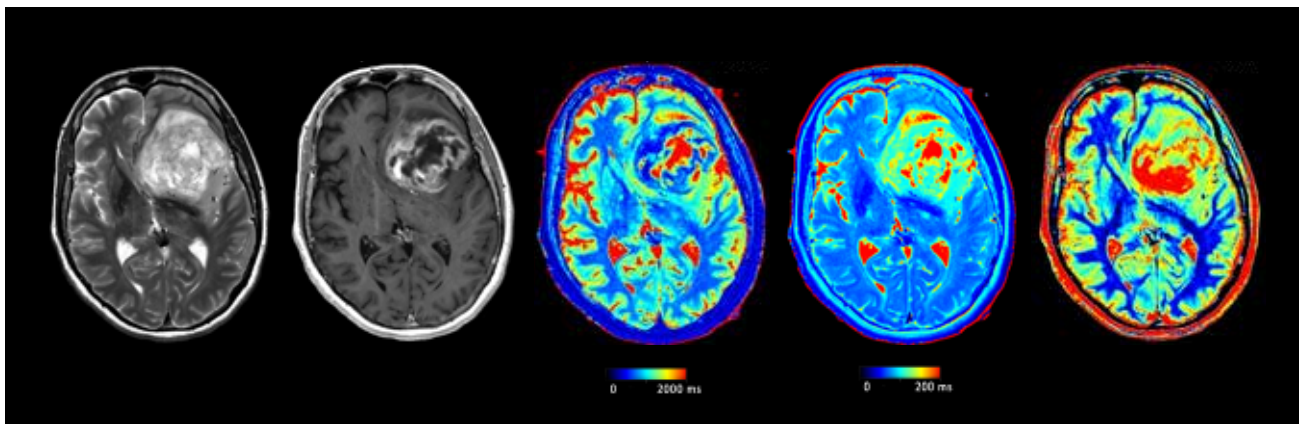
**C**onventional MR images are assessed visually by the radiologist to obtain a diagnosis or to evaluate treatment effects. New MR sequences can offer the possibility of quantitative assessment of physical properties of the tissue, which gives a more objective tool for evaluation. Synthetic MR is a quantitative MR sequence with a scan time of approximately 6 minutes, developed at CMIV. In this project the aim is to apply this sequence in different clinical settings, mainly in patients with primary brain tumors; malignant gliomas.

Patients with high-grade malignant gliomas (primary brain tumors) are treated with surgery, chemo- and radiotherapy and then followed with MRI-examinations to evaluate treatment response and to detect early signs of tumor recurrence. Due to their infiltrative nature, gliomas are difficult to treat and to assess. Surgery aims for maximum safe resection of the tumor, and complete removal of the contrast-enhancing portion

is regarded as radical resection. However, glioma infiltration extends beyond the visibly contrast enhancing border of the tumor, and these changes are not easily differentiated from the peritumoral oedema on conventional MR images.

Using quantitative MR techniques, tumor infiltration can be analysed for diagnosis and prognosis, and during recent years, such new quantitative MRI sequences using relaxometry have been applied for brain tumor analysis in research. In this project, we follow patients with malignant gliomas from diagnosis during the follow-up after surgery and oncological treatment. If it is possible to find tumor specific quantitative values, it might be possible to distinguish tumor from healthy brain, and from treatment effects and thereby improving the diagnostic arsenal in these difficult cases.

This would be of great significance for the radiologists as well as the neurosurgeon and oncologist in treatment planning, and of benefit for the patient. ◀



Images and quantitative maps derived from the quantitative scan of one of the brain tumor patients. From left: synthetic T2W image, synthetic T1W image post-contrast agent injection, T1-, T2- and PD-maps.

**MRI** **Neurology** **Imaging Biomarkers**

## *Project information*

### **PROJECT NAME**

Clinical Application of Synthetic MRI on Malignant Gliomas

### **PROJECT LEADER**

Ida Blystad, Department of Health, Medicine and Caring Sciences, Division of Diagnostics and Specialist Medicine

### **MAIN PROJECT PARTICIPANTS**

Anders Tisell, Peter Lundberg, Marcel Warntjes, Anders Eklund, Evren Özarlan

### **GRANTS**

Medical Research Council of Southeast Sweden

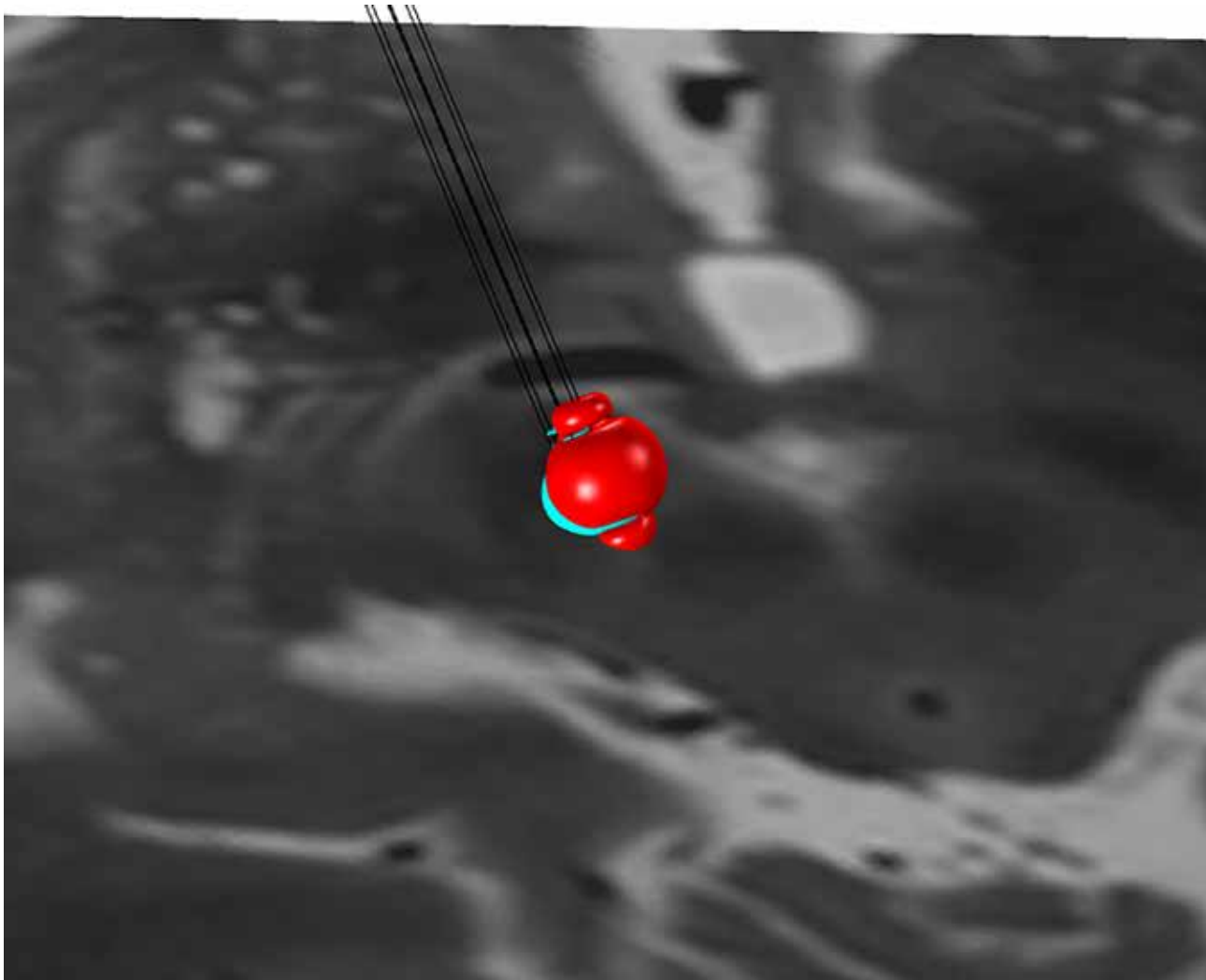
### **KEY PUBLICATIONS**

Blystad I, Warntjes JBM, Smedby Ö, Lundberg P, Larsson EM, Tisell A. Quantitative MRI using relaxometry in malignant gliomas detects contrast enhancement in peritumoral oedema. *Sci Rep* 10, 17986 (2020).

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;12(5):e0177135.

Blystad I, Warntjes JB, Smedby O, Landtblom AM, Lundberg P, Larsson EM.

Synthetic MRI of the brain in a clinical setting. *Acta Radiol.* 2012 Dec 1;53(10):1158-63. doi: 10.1258/ar.2012.120195. Epub 2012 Sep 27. PMID:23024181.



Typical changes in stimulation volume from deep brain stimulation in the first month after implantation (red: day after surgery, cyan: 1 month after surgery). The electrode lead tends to move slightly anterior and inferior and the stimulation volume is estimated to shrink as electrically conducting postoperative edema disappears and is replaced with gliosis around the lead.



# Imaging for Stereotactic Neurosurgery

**D**eep brain stimulation (DBS) is an established technique to disrupt pathological activity in the central parts of the brain by the use of a permanently implanted electrode that continuously sends nerve-stimulating electric pulses. It can give symptom relief in motor disorders such as Parkinson's disease, essential tremor and cervical dystonia and is investigated for severe, treatment-resistant cases of Tourette disorder and obsessive-compulsive disorder. In this project, we use patient-specific 3D computer simulations of the electric field in the brain to estimate how the tissue surrounding the DBS electrode is affected by the stimulation. The preoperative MRI of each patient is used to classify the brain tissue into grey matter, white matter, blood, and cerebrospinal fluid. These tissues have different electric conductivities, which affects how the electric fields spread in the brain around the DBS electrode. The simulations can for example be used to estimate optimal targeting area affected by the DBS or identify areas responsible for detrimental side effects. White brain matter is anisotropic, i.e., the electric conductivity is greater along the neuron axons than perpendicular to them. We have recently investigated when this effect is important to consider. It was found that the anisotropy will greatly change the shape of the electric field for the most anisotropic tissue but have little impact for lesser anisotropy (Nordin et al., 2020).

The DBS electrode is implanted in the central brain through a small hole made in the skull. The electrode lead is secured with a plate covering the hole but can still move slightly in the month after surgery due to strains on the lead and brain movements from receding air that can enter the skull during surgery. The implantation of the lead also causes a small reaction of the surrounding tissue, increasing the cellular water content (edema) in the neurons closest to the lead and thereby increasing the electric conductivity of that tissue. The edema will also recede in the first month. We have recently performed a study (Göransson et al., 2020) on how these effects affect the stimulated area in the brain which can explain why DBS settings usually needs to be changed if set directly after surgery. This supports the view among the neurosurgeons that it is more time-efficient to wait a month with the DBS programming after the surgery as the settings otherwise often needs to be changed anyway.

We have also released free software for use in science and ed-

ucation where it is possible for the user to set up patient-specific simulations without needing experience in computer modelling. The software is available at [liu.se/en/article/ne-downloads](https://liu.se/en/article/ne-downloads).

Our future aims are to further develop this software package and disseminate it to researchers and neurosurgeons around the world. ◀

MRI Neurology Modeling Simulation

## Project information

### PROJECT NAME

Imaging for Stereotactic Neurosurgery

### PROJECT LEADER

Karin Wårdell, Department of Biomedical Engineering, Neuroengineering Lab

### MAIN PROJECT PARTICIPANTS

Johannes Johansson, Nathanael Göransson, Peter Zsigmond, Teresa Nordin

### GRANTS

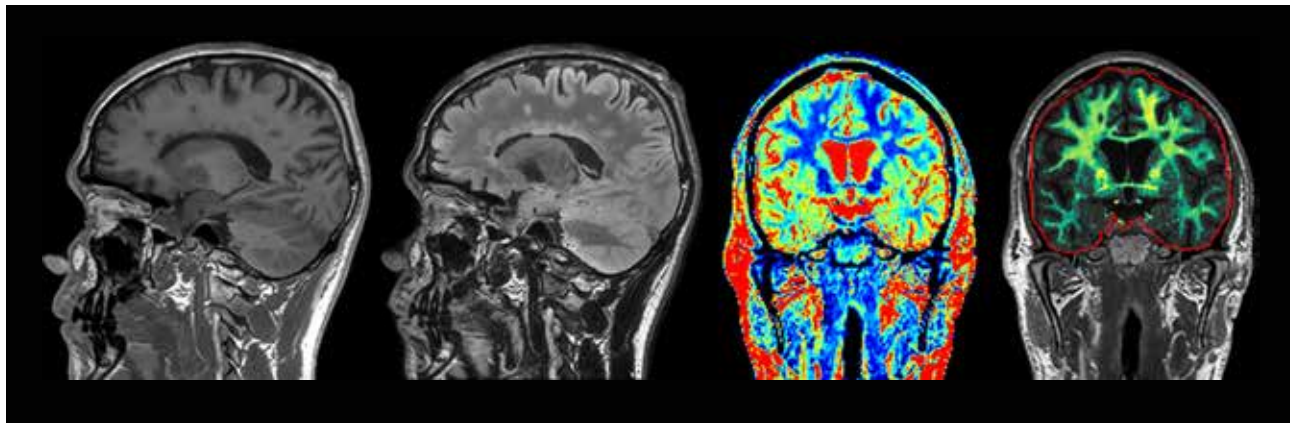
Swedish research council 2017–2020  
Swedish Foundation for Strategic Research 2017–2022

### KEY PUBLICATIONS

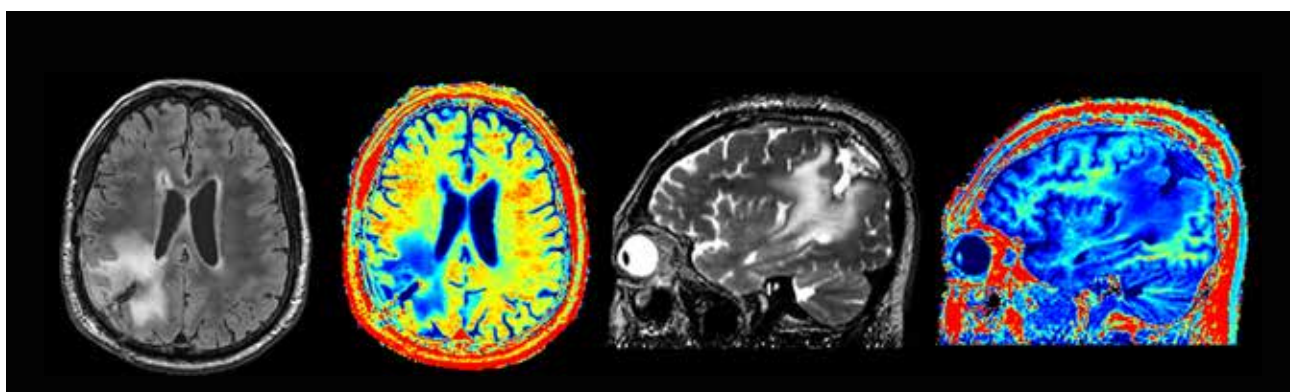
Göransson N, Johansson JD, Wårdell K, Zsigmond P. Postoperative lead movement after deep brain stimulation surgery and the change of stimulation volume. *Stereot Funct Neuros In Press*, 2020.

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Nordin T, Wårdell K, Johansson JD. The Effect of Anisotropy on the Impedance and Electric Field Distribution in Deep Brain Stimulation, Springer Nature Switzerland AG 2021, T. Jarm et al. (Eds.): EMBC 2020, IFMBE Proceedings 80, pp.1,069–1,077, 2021.



**Figure 1.** Example of 3D-QALAS on a hydrocephalus patient acquired on a Siemens 3T. The axial T2W and CSF segmentation as well as the coronal T1W and grey matter segmentation are based on a single acquisition.



**Figure 2.** Example of 3D-QALAS on a Multiple Sclerosis patient acquired on a Philips 3T. The sagittal T1W and FLAIR image as well as the coronal proton density map and myelin segmentation are based on a single acquisition.



**Figure 3.** Example of 3D-QALAS on a tumor patient acquired on a GE 3T. The axial FLAIR image and R2 relaxation map as well as the sagittal T2W and R1 relaxation map are based on a single acquisition.

# Clinical Implementation of Synthetic MRI

**C**onventional MRI is mainly qualitative: the MRI scanner acquires an image with a certain contrast setting, such that there is a signal difference with the various tissues of the human body. Only the difference in intensity is important, the signal values themselves are randomly scaled. At CMIV a sequence has been developed to actually measure MRI characteristics, providing objective values to MRI. This sequence, called 3D-QALAS, is in full 3D, which means that the body is imaged with the same resolution in all directions, allowing visualization in any plane. The scan time for the 3D sequence is 6–8 minutes, measuring the most important characteristics for MRI: the R1 relaxation rate ( $1/T1$ ), the R2 relaxation rate ( $1/T2$ ) and proton density PD.

For more familiar visualization, a range of conventional MR images can be recreated based on the R1, R2 and PD maps, an approach called synthetic MRI. The single quantification sequence can generate conventional contrasts such as T1W, T2W, FLAIR, but even Double IR and Phase-Sensitive IR. Moreover, being objective data, tissue can be recognized and assessed automatically. This means that a relatively short scan time is sufficient to reproduce a large part of a normal MR examination and, additionally, to provide more objective means of patient follow-up. Examples of tissue recognition are brain volume measurement, myelin detection and GD-enhancement detection. These clinical parameters can be used for monitoring development and degeneration of the brain, for example in pediatrics, Multiple Sclerosis, hydrocephalus, cancer and dementia. Quantification also provides robust input to recognize pathologies automatically.

A spin-off company, SyntheticMR AB, was created to ensure an installable, safe product including the necessary regulatory requirements for several markets around the globe. The 3D sequence is now available on all major vendors and clinical evaluation has started. There is a high demand to move to 3D and that has now become possible.

In the history of MRI, images were generally acquired which were then subjectively interpreted by radiologists. With the advent of quantitative 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. Quantitative MRI is a clear example of excellent cooperation between university, hospital and commercial companies, made possible by CMIV. ◀

MRI | Neurology | Oncology | Acquisition | Modeling  
Visualization | Simulation | Imaging Biomarkers

## Project information

### PROJECT NAME

Clinical Implementation of Synthetic MRI

### PROJECT LEADER

Marcel Warntjes, Department of Health, Medicine and Caring Sciences, Division of Diagnostics and Specialist Medicine

### MAIN PROJECT PARTICIPANTS

Ida Blystad, Peter Lundberg, Anders Tisell, Peter Johansson, Catharina Petersen, Johanna Alfredsson, Ken Hwang

### GRANTS

Swedish Research Council 2017–2020  
Swedish Foundation for Strategic Research 2017–2022

### KEY PUBLICATIONS

Kvernby S, Warntjes M, 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;16:102.

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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Myelin Detection Using Rapid Quantitative MR Imaging Correlated to Macroscopically Registered Luxol Fast Blue-Stained Brain Specimens. *AJNR Am J Neuroradiol.* 2017 Jun;38(6):96–102.

# Image-Based Biomarkers of Brain Disorders

**W**ith functional magnetic resonance imaging (fMRI) we can visualise brain areas that are activated by certain tasks or sensory stimuli. Despite the fact that fMRI is widely used in both research and clinic, the biological mechanisms behind the visualised brain activation are largely unknown. This means that we have only little knowledge about the relation between activated neuronal cells and the subsequent changes in blood oxygenation – the neurovascular coupling – which underlies the blood oxygen level dependent (BOLD) response in fMRI.

This lack of knowledge can be overcome by mathematical modelling and systems biology, where different hypotheses describing e.g., excitatory and inhibitory neurons are translated to mathematical equations (= models). These models are tested against multimodal data describing e.g., cerebral blood flow, oxygenation and metabolism. If a model cannot explain data the hypothesis is rejected, if a model can explain the data the model is further investigated and tested against new experimental data. In this way, we can deepen our knowledge about the mechanisms behind the BOLD response, and we can also obtain model-based biomarkers (Figure 2).

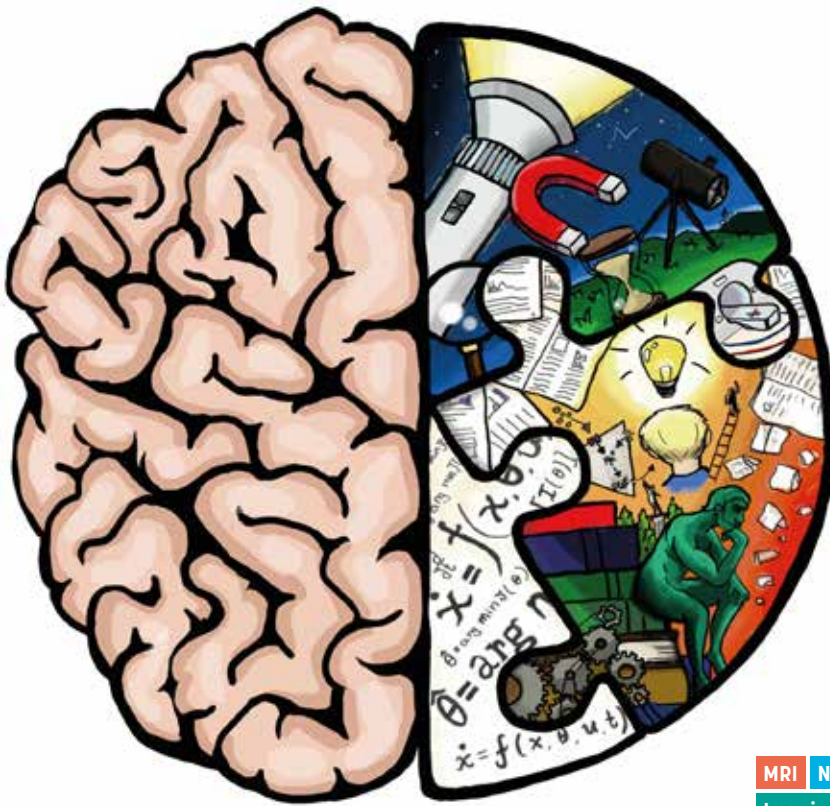
By a mechanistic model based on the influence of neurotransmitters on the brain's blood flow, we have rejected the hypothesis of brain metabolism being the driving force behind the BOLD

response in fMRI. We have also shown that neural inhibition can explain so-called negative BOLD responses, thus providing a more complete explanation of fMRI data (Sten et al., 2017).

Recent research has been focused on explaining the interactions between excitatory and inhibitory neurons and their influence on the neurovascular coupling, including explanations of changes in vascular dynamics in response to an anesthetic agent (Sten et al., 2020). Most recently, we have suggested a quantitative model for the neurovascular coupling, including mechanisms of different neural cell types, cerebral oxygenation and metabolism, cerebral blood flow and volume in different blood vessels, and a comprehensive model for the fMRI signal (Sten, dissertation, 2020). With this multi-dimensional model, we were able to explain several datasets from different experimental conditions.

In summary, with our modelling approach we can firmly reject hypotheses that cannot explain data and we can obtain new knowledge about brain mechanisms e.g., neurotransmitter action in excitatory and inhibitory neurons. We can also explain pharmacologically induced brain responses. We are aiming to define model-based biomarkers of brain function, that is to say biomarkers that can express *brain activation in terms of biological properties*. ◀





**Figure 1.** Cover Sebastian Sten thesis. Courtesy Christian Simonsson.

**MRI** **Neurology** **Modeling** **AI/Data analytics** **Simulation**  
**Imaging Biomarkers**

### Project information

**PROJECT NAME**

Image-Based Biomarkers of Brain Disorders

**PROJECT LEADER**

Maria Engström, Department of Health, Medicine and Caring Sciences, Division of Diagnostics and Specialist Medicine

**MAIN PROJECT PARTICIPANTS**

Sebastian Sten, Gunnar Cedersund, Fredrik Elinder, Henrik Podéus, Nicolas Sundqvist, Charalampos Georgiopoulos

**GRANTS**

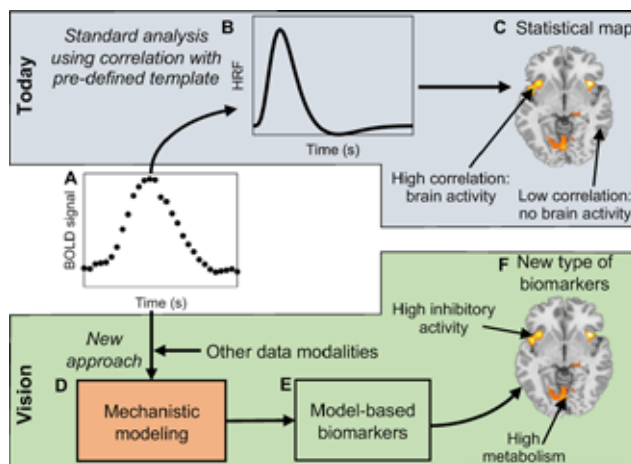
Swedish Research Council  
 Swedish Brain Foundation

**KEY PUBLICATIONS**

Sten S, Cedersund G, Elinder F, Engström M. A quantitative analysis of cell-specific contributions and the role of anesthetics to the neurovascular coupling. *NeuroImage*, 2020; 215:116827.

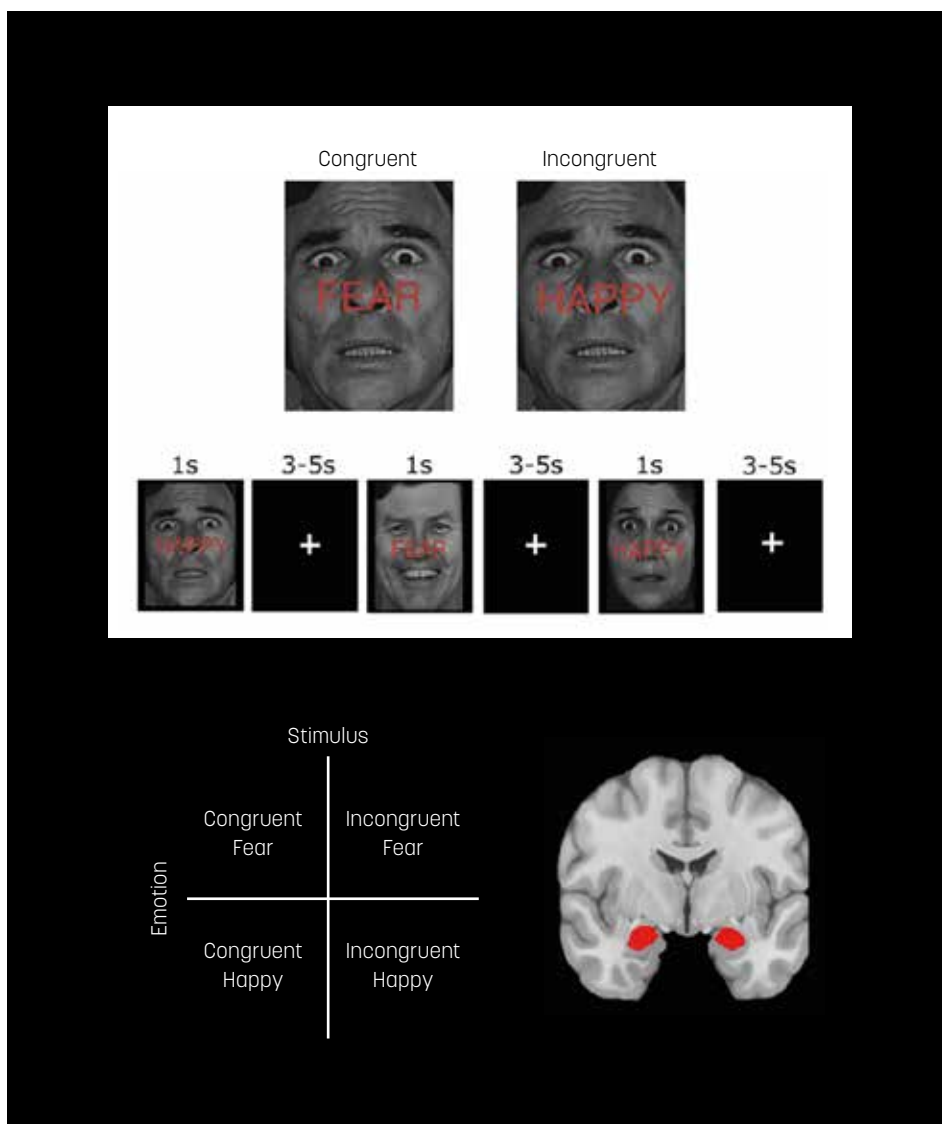
Sten S, Lundengård K, Witt S T, Cedersund G, Elinder F, Engström M. Neural inhibition can explain negative BOLD responses: a mechanistic modelling and fMRI study. *NeuroImage*, 2017;158:219–231.

Sten S. Mathematical modeling of neurovascular coupling. Linköping University Medical Dissertation No. 1742, 2020 (Fig. 1).



**Figure 2.** fMRI analysis: today and visions for the future. BOLD-fMRI data (A) are analysed with a standard template, the hemodynamic response function (HRF) (B) resulting in statistical maps interpreted as brain function (C). The new approach uses mechanistic modelling (D) which provides model-based biomarkers (E) resulting in visualization of biologically relevant biomarkers (F). Image from Sebastian Sten’s thesis, 2020.

POPULAR SCIENTIFIC SUMMARY  
*Markus Heilig*



Top: emotional conflict task stimuli and timeline. Bottom: factorial analysis plan and amygdala location.

# Affective Processing in Early Life Trauma

**T**he 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 addiction or other psychiatric disorders. Importantly, this group of individuals is selected using prospective registry and not subjective retrospective report.

The specific aim regarding the MRI data collection of this project is to investigate experimentally whether the regulation of affect and stress responses differs across two dimensions: childhood trauma (present, absent) and addiction. (present, absent). The study includes therefore four populations:

- adults who were exposed to childhood trauma and that have addiction
- adults who were exposed to childhood trauma and that do not have addiction
- adults who were not exposed to childhood trauma and that have addiction
- adults who were not exposed to childhood trauma and that do not have addiction

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

## Matching of images

Negative-affect images taken from a set of normative stimuli, are shown to the subjects to investigate cerebral responses following emotional processing. This task has previously been shown to result in activation of insular cortex in response to negative-affect images.

## Matching alcohol and non-alcohol images

Alcohol related, and non-alcohol related pictures are shown to the subjects to measure brain responses to alcohol related stimuli. Brain responses to pictures depicting alcoholic and non-alcoholic beverages are assessed.

## Emotion conflict task

This task has been used to characterize brain regions involved in emotional regulation as it triggers the experience of emotional

conflict. Brain mechanisms following emotional regulation have been previously described using this task in healthy subjects and in patients with generalized anxiety disorder. Participants are instructed to identify the facial emotion (fearful or happy) presented in a picture 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. Compared to the congruent condition, the incongruent condition triggers emotional conflict and activates the amygdala. The use of facial expressions depicting opposite valence allows to discern brain substrates implicated in coding emotions in general from emotional conflict processing in particular.

Thus, we plan a factorial analysis across the dimensions of “stimulus” and “emotion”. The analysis will particularly focus on the amygdala, a subcortical region depicted in Figure. Finally, behavioral and brain results will be investigated between groups, across the dimensions of childhood trauma and addiction.

The data collection started in January 2017 and was completed in June 2020. A total of 103 participants were collected. The analysis is ongoing. ◀

MRI Neurology No Method Development

## 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

Paul Hamilton, Robin Kämpe, Elisabeth Paul, Irene Perini, Adam Yngve, Andrea Capusan, Per Gustavsson, Åsa Kastblom

### GRANTS

The Swedish Medical Research Council

# Effects of the Hormone Ghrelin on Decision Making

**Background:** Ghrelin, a 28-amino acid peptide, acts as the endogenous ligand for the growth hormone secretagogue receptor (GHS-R), and stimulates appetite through hypothalamic mechanisms. GHS-R is also expressed in other brain areas involved in motivation and decision making, such as the mesolimbic dopamine (DA) pathway. We hypothesize that an adaptive response to the induction of hunger by signals such as ghrelin will involve a shift in decision making processes that are involved in solving the trade-off between exploring and exploiting the environment.

**Objective:** The primary objective of this study is to investigate whether IV ghrelin will alter decision making processes including those that involve a) evaluation of reward; b) propensity to take on risk; and c) trading off of small immediate rewards vs larger, temporally more distant ditto (delay discounting); as well as the neural substrates associated with these decision making processes, measured using fMRI.

**Design.** Within-subject, double-blind, placebo-controlled study. Visit 1 will be an initial screening visit. Visit 2 and 3 will be challenge sessions with IV ghrelin or placebo, on separate days, and counterbalanced for order.

**Outcome measures.** We will measure a range of behavioral outcomes in a paradigm that assesses reward processing (monetary incentive delay, MID task), a risky decision-making paradigm, and a delay discounting paradigm. These measures will be obtained in conjunction with functional magnetic resonance imaging (fMRI), to determine the neural substrates of these decision-making processes, and of the effects of ghrelin.

- *Reward processing:* To probe reward circuitry, subjects will

carry out the widely used monetary incentive delay (MID) task. The MID task has been used extensively to investigate changes in neural activity in response to the processing of reward in healthy subjects, and also in clinical populations. The task requires an individual to react to a target stimulus presented after an incentive cue to win or to avoid losing the indicated reward. In doing so, this paradigm allows a detailed examination of different stages of reward processing like reward prediction, anticipation, outcome processing, and consumption as well as the processing of tasks under different reward conditions.

- *Risky decision making:* Subjects will carry out a forced-choice risk-taking task. Risk taking is evaluated by measuring the proportion of times the uncertain (50% win) choice is taken. This task is known to result in an activation of the insula. In prior experiments, alcohol administration (compared to placebo) led to a significant decrease of this activation, associated with increased risk-taking.

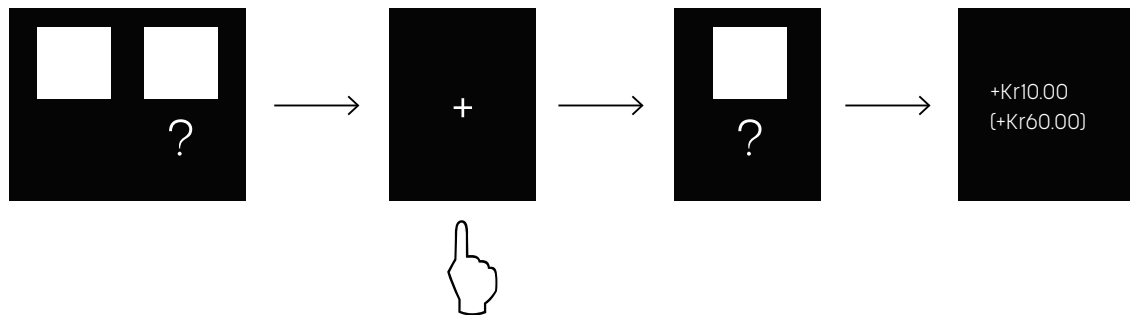
- *Delay discounting:* Preferences in intertemporal choices will be assessed. Participants will in each trial chose between hypothetical amounts of money available that day (1-105 SEK) and 1,000 SEK available after a delay of 0, 7, 30, 90, 180, 365, or 1,825 days (5 years).

- *Probabilistic reversed learning task:* To assess whether ghrelin affects goal-directed learning, compared with habit-like learning two symbols will be displayed randomly assigned to left and right side of the screen. One of the stimuli will be associated with 80% monetary reward and 20% loss and vice versa. These probability assignments will be dependent (i.e. if option 'a' provided a reward, option 'b' provided a punishment) and will be reversed after the participant reaches the learning criterion (five correct choices out of a sliding window of the last six trials). ◀



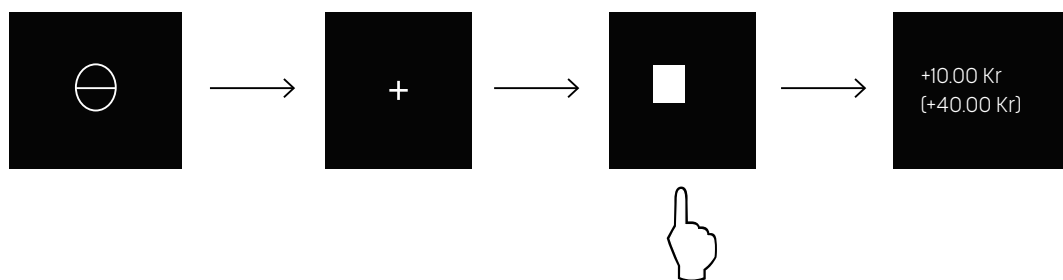
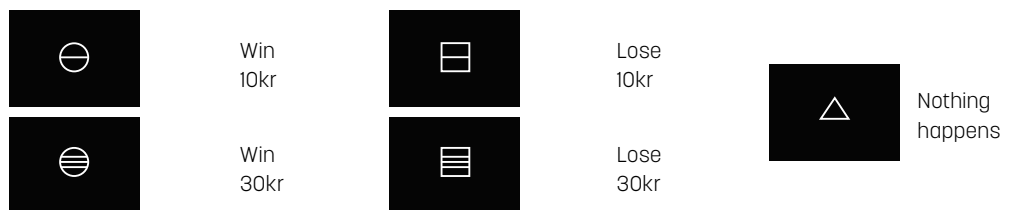
## Forced-choice risk-taking task:

- a safe choice of 2:50 Kr or a chance to win/lose 10 Kr or 50 Kr
- 4 s to make a choice
- 50 Kr to begin with
- risk taking – the number of times the uncertain choice is taken



## Reward function: monetary incentive delay (MID) task

- react to win or to avoid losing the indicated reward
- reward stages: reward prediction, anticipation, outcome processing, consumption
- 30 Kr to begin with



**MRI** **Neurology** **Gastrointestinal** **No Method Development**

### *Project information*

#### **PROJECT NAME**

Effects of the Appetite-Inducing Hormone Ghrelin on Decision Making in Healthy Volunteers

#### **PROJECT LEADER**

Markus Heilig, Department of Biomedical and Clinical Sciences, Center for Social and Affective Neuroscience

#### **MAIN PROJECT PARTICIPANTS**

Michal Pietrzak, Andrea Johansson Capusan, Lisbet Severin, Adam Yngve, Gustav Tinghög, Paul Hamilton, Irene Perini, Robin Kämpfe

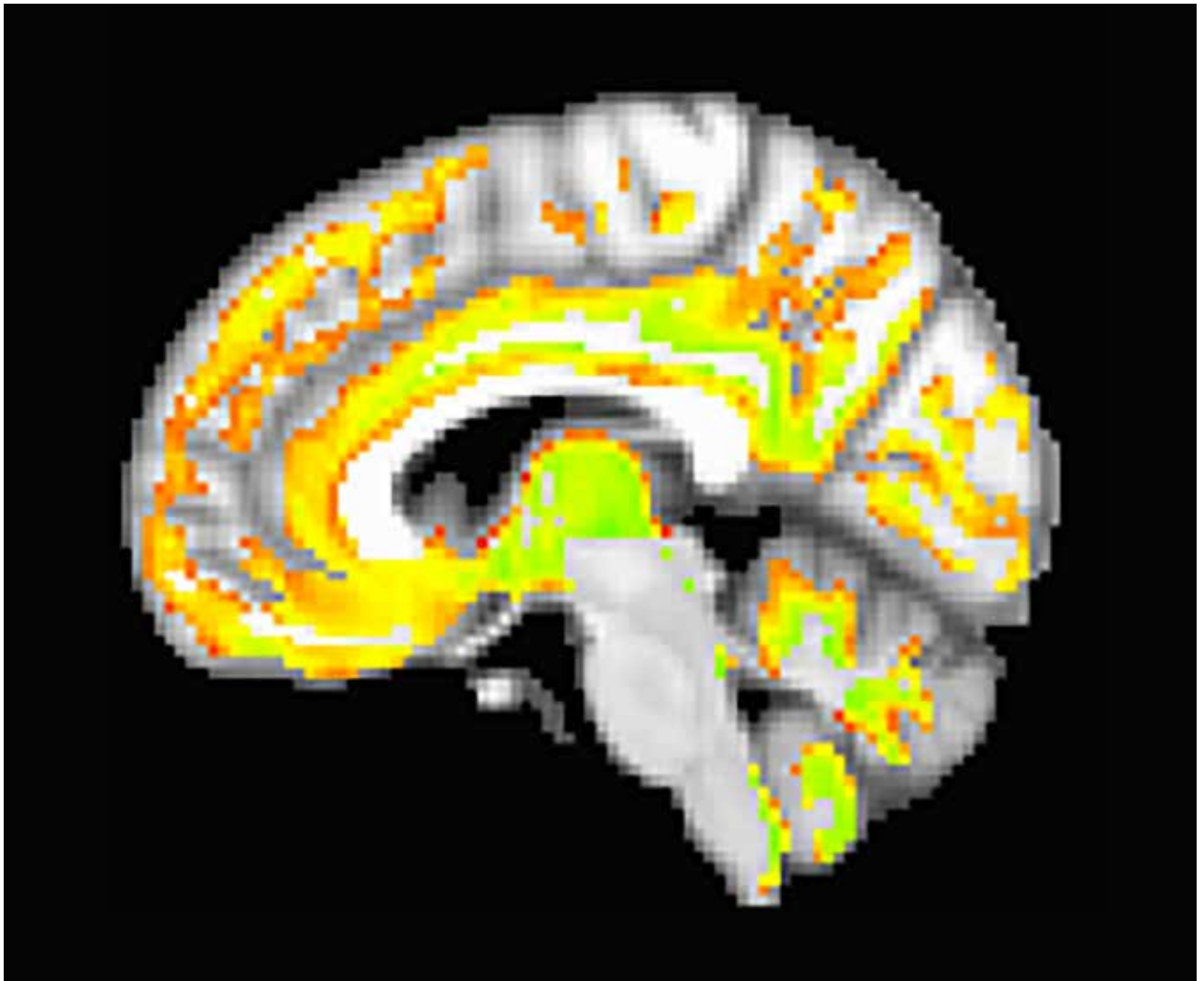
# Modulating Inflammation in the CNS in Major Depression

**M**ajor depressive disorder (MDD) is a leading contributor to the global burden of disease and has been projected by the World Health Organization 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. Secondly, 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.



Statistical map showing average voxel-wise free-water parameter as a function of brain region.

There are several secondary objectives of our study. Recent genome-wide association studies on very large samples of depressed and non-depressed persons have identified ~100 genome-wide-significant single-nucleotide polymorphisms associated with depression. These effects can be summed into a single polygenic risk score (PRS) for depression.

In an independent replication cohort, persons with high PRS (top tenth percentile) were found to be two times more likely to have a history of depression than persons with a low PRS (bottom tenth percentile). This finding makes it possible to separate individuals into four groups of interest: persons at high genetic risk for depression that have developed depression (HI-PRS depression); people with high genetic risk for depression that have not developed this disorder (HI-PRS healthy); persons at low genetic risk for depression that developed depression, nonetheless (LO-PRS depression); and those with a low genetic risk for depression that have not developed depression (LO-PRS healthy).

We would like to further our mechanistic understanding of high-gene load MDD. Recent work indicates that familial depression could be associated more with metabolic disturbance. One marker of metabolic imbalance is fatty liver. Using the whole-body imaging sequence available at CMIV, we have scanned both depressed and healthy persons and, in collabora-

tion with Magnus Borga and Anette Karlson, will estimate liver fat levels from these data. We predict that depressed persons at elevated genetic risk will exceed all other groups in liver fat levels. We are currently analyzing these data to determine if this is the case. ◀

**MRI** **Neurology** **No Method Development**

### *Project information*

#### **PROJECT NAME**

Modulating Inflammation in the Central Nervous System in Major Depression via Inflammatory Cytokine Blockade

#### **PROJECT LEADER**

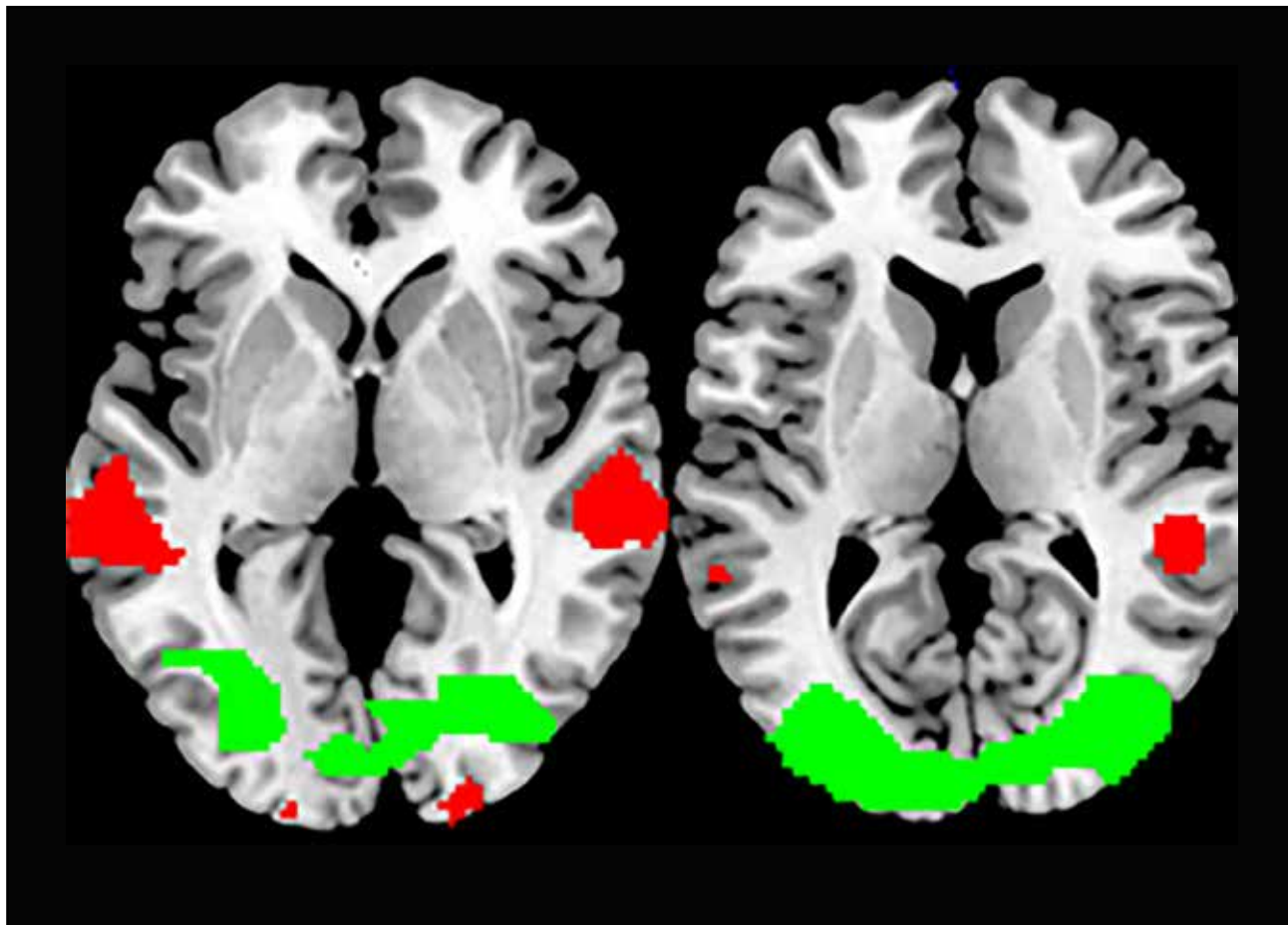
Paul Hamilton, Center for Social and Affective Neuroscience; Department of Clinical and Experimental Medicine

#### **MAIN PROJECT PARTICIPANTS**

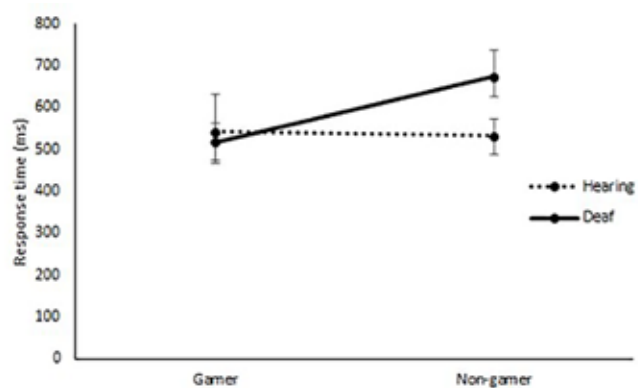
Markus Heilig, Martin Samuelsson, Sandra Boda, Elisabeth Paul, Åsa Axén

#### **GRANTS**

The Swedish Medical Research Council



**Figure 1.** Significant activation pertaining to effects of resolution. Red indicates clear > degraded and green degraded > clear. All activations  $p_{fwe} < .05$ . (Reproduced from Andin et al., 2019, SNL).



**Figure 2.** Significant interaction between group (Deaf or Hearing) and video gaming experience (Gamer or Non-gamer) on behavioural performance (response time, in ms) in a visual attention task. (Reproduced from Holmer et al., 2020, Frontiers in Psychology).



# Working Memory in Visual Noise

**I**n the present study, we are investigating the effect of poor visual resolution on working memory for sign language as well as the effects of video gaming on cognition. The study includes data from 16 deaf early signers (DES) and 22 hearing non-signers (HNS), who performed a working memory (WM) task based on high- and low-resolution signs during functional Magnetic Resonance Imaging (fMRI) as well as a set of other cognitive tasks off-line. We also collected data on the participants' video gaming habits.

Behavioural data show that WM performance decreases with both increasing load and decreasing stimulus resolution. Whole brain fMRI analysis showed increasing activation of the fronto-parietal WM network as load increased, and an effect of stimulus degradation was found in temporal and occipital brain regions. This result suggests that load and stimulus resolution for visual material is supported by different neural mechanisms. This differs from findings on auditory material, where an overlapping neural mechanism has been proposed. We also found stronger activation in auditory cortex for deaf signers compared to hearing non-signers, as well as stronger connectivity from this region to frontal and occipital regions, supporting the notion of cross-modal reorganization of auditory cortex for deaf individuals. These results are currently under consideration for publication.

Recently published is an article reporting behavioural data indicating better visuospatial attention in deaf participants, who are video gamers compared to those who are non-gamers. However, there was no evidence of an effect of gaming experience in the brain imaging data. ◀

**MRI** **Neurology** **No Method Development**

## *Project information*

### **PROJECT NAME**

Working Memory in Visual Noise

### **PROJECT LEADER**

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

### **MAIN PROJECT PARTICIPANTS**

Josefine Andin, Emil Holmer, Krister Schönström

### **GRANTS**

Swedish Research Council 2016–2020

### **KEY PUBLICATIONS**

Holmer E, Rudner M, Schönström K, Andin J. (2020).

Evidence of an effect of gaming experience on visuospatial attention in deaf but not in hearing individuals. *Front. Psychol.* 11:534741. doi: 10.3389/fpsyg.2020.534741.

Andin J, Holmer E, Rudner M. (2019). The role of auditory cortex in WM for sign language. 5th conference on Cognitive Hearing Science for Communication, June 9–12, 2019, Linköping, Sweden.

Holmer E, Andin J, Rudner M. (2019). Cross-modal plasticity in secondary auditory cortex. 11th Annual Meeting of the Society for the Neurobiology of Language, August 20–22, Helsinki, Finland.

# Detection and Neurological Effects of Manganese

**M**anganese (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.

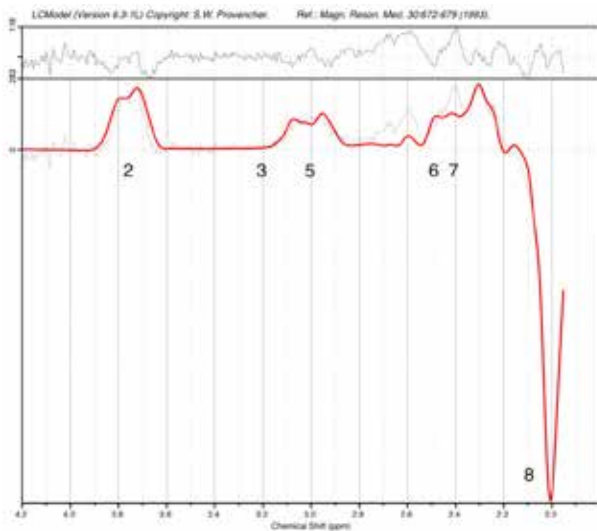
Manganese can pass the barriers that protect the brain and accumulate in specific areas of the brain, e.g. the basal ganglia. Welders examined with MRI have previously shown accumulation of manganese in the brain. When exposure is terminated, manganese is only gradually excreted and the concentration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

Workers that in their profession are exposed to high levels of manganese in the air ( $> 1 \text{ mg/m}^3$ ) 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 influ-

ence on motor and cognitive functions, increased tremor and an increased frequency of neuropsychiatric symptoms among groups of manganese exposed workers at significantly lower exposure levels than  $1 \text{ mg/m}^3$ .

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. ◀



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(CH<sub>3</sub>)<sub>3</sub>]; **5**, GABA+ [-4CH<sub>2</sub>-]; **6**, tNA [-3CH<sub>2</sub>-]; **7**, Glx [-4CH<sub>2</sub>-]; **8**, tNA [-2CH<sub>3</sub>]. Abbreviations: Glx, glutamate+glutamine; GABA+,  $\gamma$ -Aminobutyric acid [+macromolecule signal]; tNA, total N-acetylaspartate (NAA + NAAG).

**MRI** **Neurology** **Acquisition** **Imaging Biomarkers**

### *Project information*

#### **PROJECT NAME**

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

#### **PROJECT LEADER**

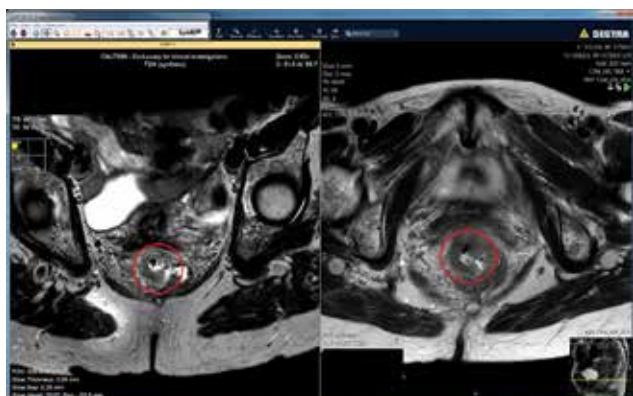
Peter Lundberg, Department of Health, Medicine and Caring Sciences, Division of Diagnostics and Specialist Medicine

#### **MAIN PROJECT PARTICIPANTS**

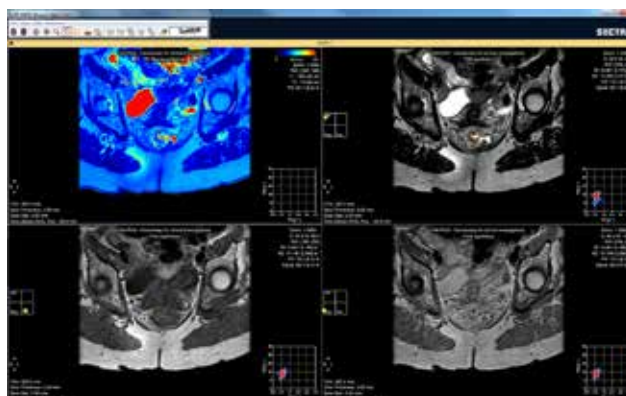
Anders Tisell, Sofie Tapper, Ida Blystad, Per Thunberg, Karin Åberg, Göran Lidén, Karine Elihn, Gunilla Wastensson, Bernt Bergström, Louise Fornander, Göte Mölleby

#### **GRANTS**

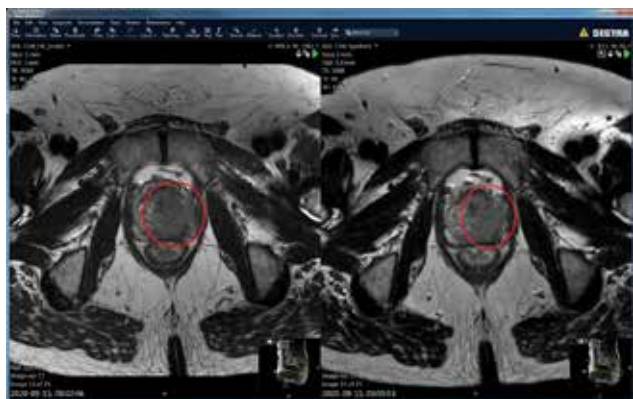
FORTE



Comparison of image quality of T2 weighted images obtained by the original MR sequence (to the right) and the synthetic T2 weighted image with the same TR and TE as the clinical sequence (to the left). The circle shows the rectal cancer.



Synthetic MRI acquisition of a rectal cancer with a quantitative T2 map (upper left), T2 weighted images (upper right), T1 weighted images (lower left) and PD weighted images (lower right). The tumour was outlined with a freehand ROI tool. The quantitative information of these ROIs is shown as R1/R2 plots.



Comparison of image quality of T2 weighted images obtained by the original MR sequence (to the left) and the synthetic T2 weighted image with the same TR and TE as the clinical sequence (to the right). The circle shows the prostate cancer (PI-RADS 5).



Synthetic MRI acquisition of a prostate cancer with a quantitative T2 map (upper left), T2 weighted images (upper right), T1 weighted images (lower left) and PD weighted images (lower right). The tumour was outlined with a freehand ROI tool. The quantitative information of these ROIs is shown as R1/R2 plots.



# Abdominal Synthetic MRI

**B** **ackground:** Synthetic MRI is a new method for producing MRI images, where T1, T2 and PD weighted images can be calculated from a single MRI acquisition, instead of 3 different acquisitions as made today. The method also provides the opportunity to quantify T1, T2 and PD relaxation times, which are tissue-specific parameters that theoretically can be used to distinguish different tissues in the body. Thus, with this technology it is possible to differentiate quantitatively between tissues (tissue characterization) and pathology (healthy or diseased tissue).

In this project we want to investigate whether synthetic MRI can increase the detection ability for certain cancers within the abdomen; whether synthetic MRI can be used to increase the confidence of treatment results after various chemotherapies and local treatments (RF and TACE treatments), and whether synthetic MRI can increase the ability to distinguish between scar tissue and cancer tissue.

## Hypothesis

Quantitative MRI scans provide added value in the detection, follow-up, treatment planning and evaluation of cancers and other diseases within the abdomen and the rest of the body.

## Method

A quantitative sequence of 7 minutes will be added to standard clinical examinations (MR cervix, MR prostate and MR rectum). In the MRI rectum follow up, we will also plan for another MRI examination including a quantitative sequence just before surgery. The quantitative information from tumour and plain tissue will be correlated with different clinical parameters, as well as probability assessments of tumor disease (i.e., PI-RADS, Li-RADS).

## Knowledge gains

If the quantitative information from synthetic MRI sequences is stable and reliable, this information can possibly be used in

radiation planning, prediction of treatment results, detection and segmentation of MRI images and more secure separation of healthy tissue from pathological. ◀

MRI Oncology Gastrointestinal Acquisition  
Imaging Biomarkers

## Project information

### PROJECT NAME

Abdominal Synthetic MRI; implementation of Synthetic MRI in the abdomen

### PROJECT LEADER

Mischa Woisetschläger, Department of Health, Medicine and Caring Sciences, Division of Diagnostics and Specialist Medicine

### MAIN PROJECT PARTICIPANTS

Nils Dahlström, Marcel Warntjes, Bengt Norén, Wolf Bartholomä

### GRANTS

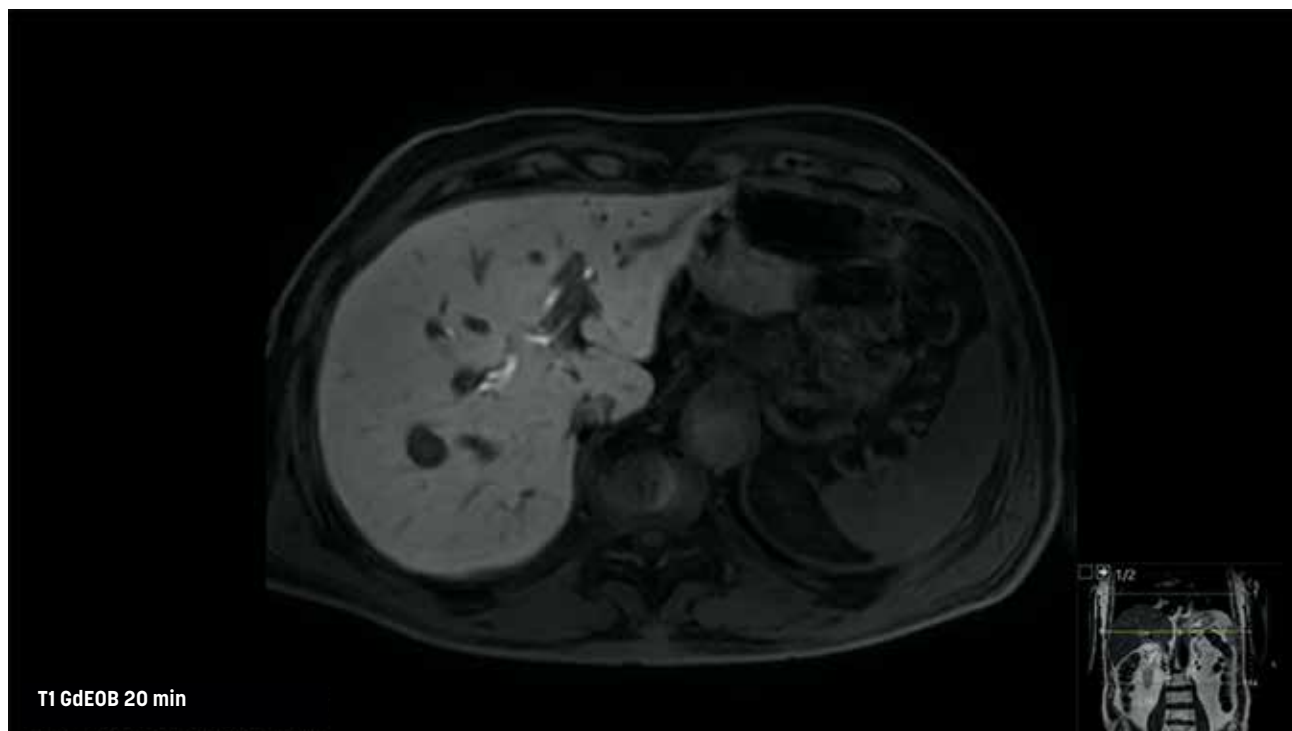
LFoU  
Forsknings- och stipendieförvaltningen

### KEY PUBLICATIONS

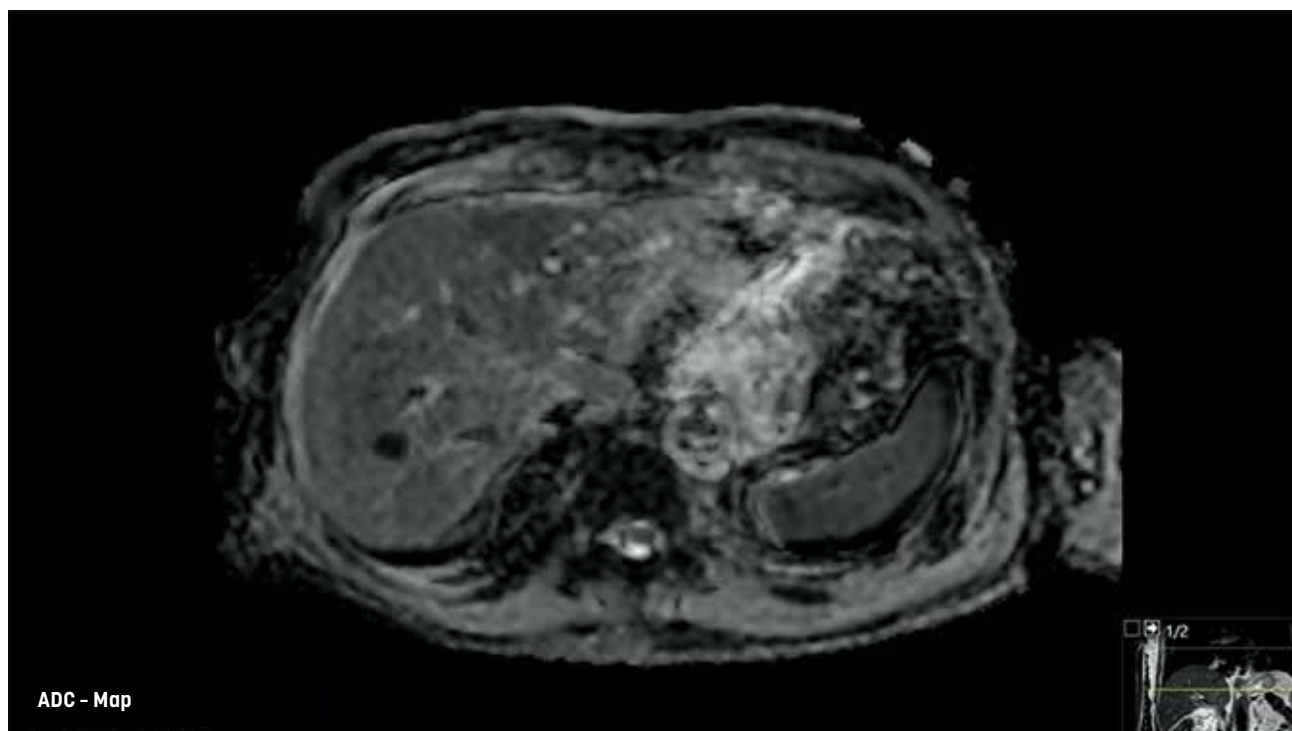
Warntjes JBM, Dahlqvist O, Lundberg P.  
Novel method for rapid, simultaneous T1, T2\*, and proton density quantification. *Magn Reson Med.* 2007;57(3):528–37.

Blystad I, Warntjes JBM, Smedby O, Lundberg P, Larsson E-M, Tisell A (2017).  
Quantitative MRI for analysis of peritumoral edema in malignant gliomas. *PLoS ONE* 12(5): e0177135. <https://doi.org/10.1371/journal.pone.0177135>.

Kumar NM, Fritz B, Stern SE, Warntjes JBM, Chuah YML, Fritz J.  
Synthetic MRI of the Knee: Phantom Validation and Comparison with Conventional MRI, *Radiology* 2018; 289:465–477.



A metastasis from colorectal cancer is seen here in the right liver lobe in a T1-weighted image acquired 20 minutes after i.v. injection of the liver-specific contrast agent Gd-EOB-DTPA (Primovist®, Eovist®). Normal liver tissue and biliary ducts have high signal (light grey and white), whereas the metastasis has very low signal (black or dark grey) since it has no uptake of the contrast agent.



A metastasis from colorectal cancer is seen here in the right liver lobe in an Apparent Diffusion Coefficient (ADC) map as a round area homogeneously markedly darker than the normal liver tissue.

# Optimizing Hepatobiliary Contrast in Liver Imaging

**C**olorectal cancer is the third most common form of cancer worldwide. Though mortality has been relatively stable in the last decade, significant improvements have been achieved in terms of long-term survival. Key to improved survival is the detection of metastatic disease as early and completely as possible. In colorectal cancer, the by far most common site of metastatic disease is the liver, and the best method to detect metastases in this organ is MRI with hepatobiliary contrast media. However, the complexity of the examination, long scanning times, challenging interpretation and overall high costs involved have severely limited the use of this modality in cancer patients and restricted it mainly to radiology departments of major hospitals or university hospitals.

We aim to show that a shortened version of the regular MRI protocol with liver specific contrast can preserve the same level of sensitivity for metastases as the complete protocol while slashing down complexity and scanning times. In camera time is reduced from 60–75 minutes to 12–15 minutes and most of the technical challenges in acquisition will be eliminated. This will enable more patients to be evaluated with MR without the need for more equipment. It will also open the examination for acquisition at minor hospitals that normally would refrain from using the more complex protocol, further increasing capacity.

As the shortened protocol is focused on detection (sensitivity) rather than differential diagnosis (specificity), a drop in specificity is expected and will be measured. However, in real life, clinical decision making happens always in the context of all available examinations, including priors, patient history and clinical data.

It is the aim of the next part of the project to study how a

shortened protocol will affect the clinical decision making and treatment process of cancer patients. The patients will be presented in a simulated multidisciplinary team meeting, using all relevant clinical data and prior examinations. It will evaluate if clinical management of the patient will actually differ when using either a complete or a shortened protocol and if implementation of such a protocol can have a negative effect on patient treatment in form of e.g., unnecessary delays and additional imaging.

Finally, economic impact of using a more expensive contrast media – the only monetary factor as of now that cannot be reduced – will be evaluated. In the last part, we will study if large scale introduction of such a method would be a financially viable and sustainable option for the public health service. ◀

**MRI** **Gastrointestinal** **Visualization**

## *Project information*

### **PROJECT NAME**

Optimizing the Use of Hepatobiliary Contrast in Metastatic Liver Disease (LiverMet)

### **PROJECT LEADER**

Nils Dahlström, Department of Health, Medicine and Caring Sciences, Division of Diagnostics and Specialist Medicine

### **MAIN PROJECT PARTICIPANTS**

Wolf Claus Bartholomä, Peter Lundberg, Per Sandström, Nils Dahlström, Mischa Woisetschläger, Lars Valter, Johan Kilberg, Martin Henriksson, Anders Persson, Bergthor Björnsson

# 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 transplantation may be the only available treatment. Patients with malignant liver tumors are increasingly surgically treated, removing the part(s) of the liver with tumors. Measuring the expected liver volume that remains after resection has become standard procedure. To improve treatment planning, adding an evaluation of liver function to the liver volume measurements is desired.

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 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 and also to 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 our other liver projects. In 2018, the project began further exploration and testing of new algorithms for automatic segmentation. ◀

**MRI** **Gastrointestinal** **AI/Data analytics** **Visualization**

## *Project information*

### **PROJECT NAME**

Semiautomatic Liver Volume Determination and Segmentation

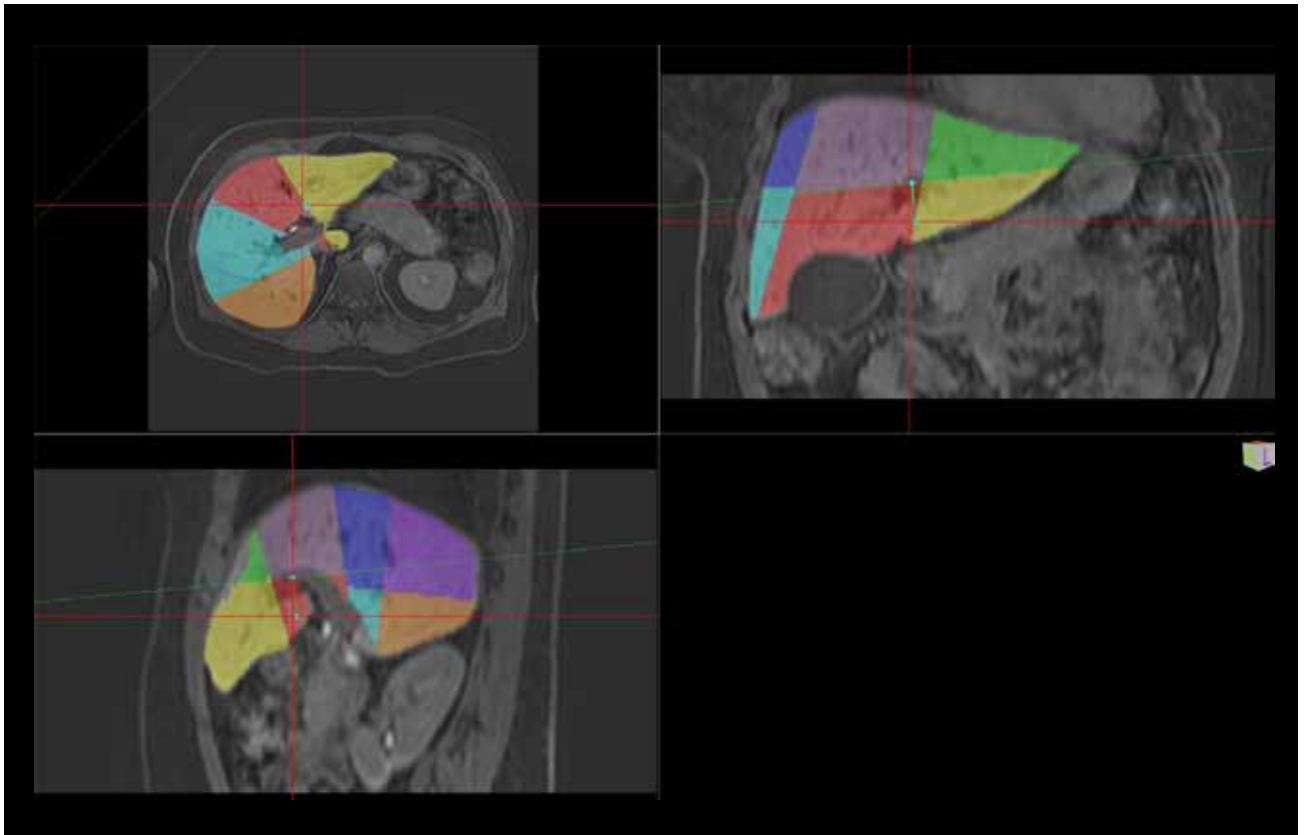
### **PROJECT LEADER**

Nils Dahlström, Department of Health, Medicine and Caring Sciences, Division of Diagnostics and Specialist Medicine

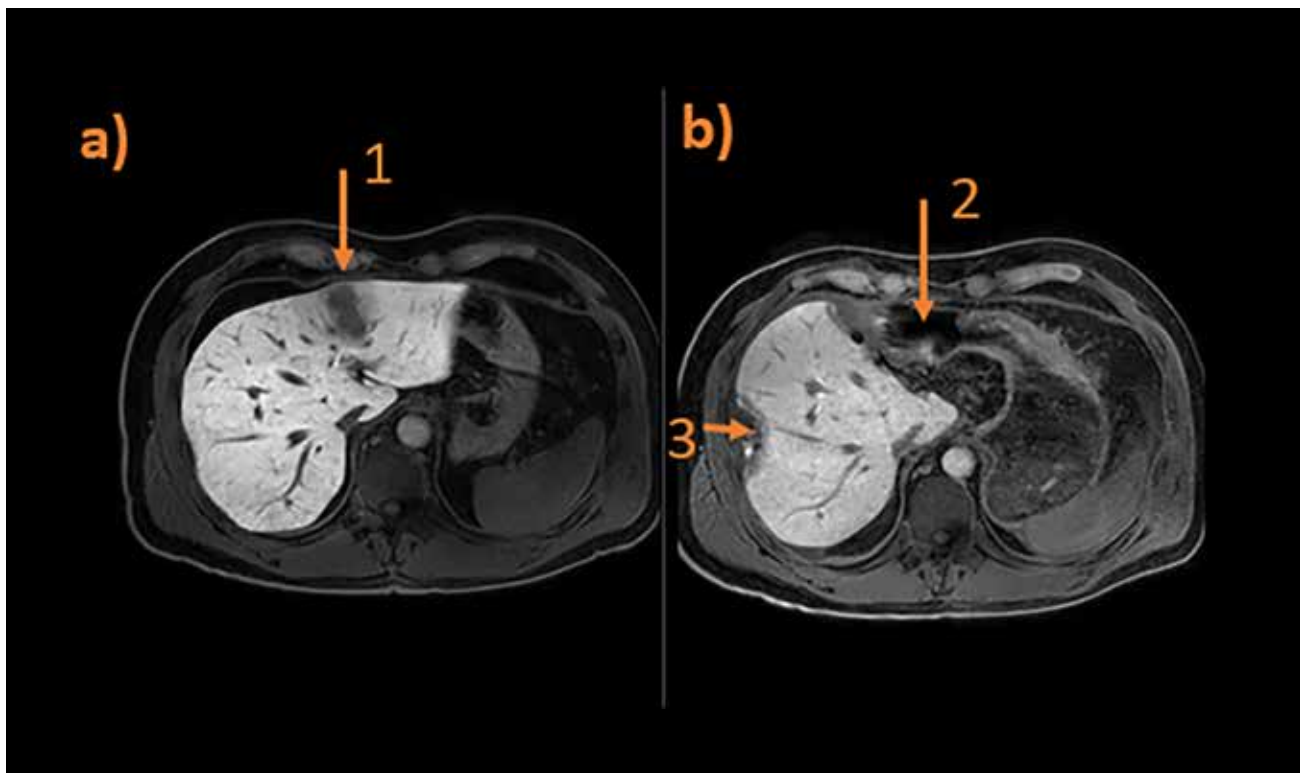
### **MAIN PROJECT PARTICIPANTS**

Mikael Forsgren, Chunliang Wang, Amir Razavi, Markus Karlsson, Peter Lundberg, Ola Persson, Petr Vorel





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).



Example of DCE-MRI images 20 minutes after bolus gadoxetate injection for both pre- and post resective surgery, for the same patient. a) Pre-surgery image, with visible metastasis at 1). b) Post-surgery image. Resection of the left liver lobule is shown at 2), and a small local resection at 3). Also, at 3) a small accumulation of gadoxetate is seen due to biliary leakage. [Simonsson, unpublished].

# Liver Function Evaluation

**T**he 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 for 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 are 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. ◀

**MRI** **Gastrointestinal** **Acquisition** **Modeling**  
**Imaging Biomarkers**

## *Project information*

### **PROJECT NAME**

Liver Function Evaluation

### **PROJECT LEADER**

Peter Lundberg, Department of Health, Medicine and Caring Sciences, Division of Diagnostics and Specialist Medicine

### **MAIN PROJECT PARTICIPANTS**

Christian Simonsson, Wolf Bartholomä, Stergios Kechagias, Mattias Ekstedt, Per Sandström, Olof Dahlqvist Leinhard, Nils Dahlström, Mikael Forsgren, Markus Karlsson, Patrik Nasr, Johan Kihlberg, Marcel Warntjes, Gunnar Cedersund, Bengt Norén, Torkel Brismar, Martin Henriksson

### **GRANTS**

VINNOVA 2013–2017  
Swedish Research Council (VR/NT) 2015–2024 (5)  
ALF 2019–2022

### **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.

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

# Assessment of Hepatic Function in Health and Disease

**T**he long-term purpose of this project is to achieve the procedural means for a thorough understanding of the complex both short and long time-scale events involved in liver disease, especially in the early stages. The project will also strive to devise a both comprehensive and non-invasive method for quantification.

Major aims of the project are to allow the early detection of liver inflammation and fibrosis as proxies for chronic liver disease, and also to be able to understand the underpinnings of the consequences of fibrosis and fat storage on up-stream events including portal hypertension. Portal hypertension is clinically highly significant and early signs are therefore of importance. Quantitative measurement of hepatic blood flow would be useful in the understanding of disease progression in the cirrhotic liver, particularly the early development of fibrosis and inflammation, since the development of liver fibrosis and lipid accumulation constrict the blood flow to the liver.

The project is divided into two separate phases, the first being a developmental phase involving different protocols and healthy research subjects, and the second involving clinical patients. The research will in the early phase mainly focus on the challenges of developing, implementing and validating the technologies for measurements of dynamic characteristics of disease including restrictions of flow. Four-dimensional flow (4D-Flow) MRI is an emerging method for quantitative evaluation of hemodynamics in the liver and abdomen, however, it is limited to be used in clinical setting due to the long acquisition time. Compressed sensing (cs) is a method for image acquisition acceleration that is gaining in popularity in abdominal imaging. ◀

MRI Gastrointestinal Acquisition Modeling Visualization  
Imaging Biomarkers

## *Project information*

### PROJECT NAME

Comprehensive Assessment of Hepatic Function in Health and Disease, Techniques for early disease detection and tissue characterization – HEALD

### PROJECT LEADER

Peter Lundberg, Department of Health, Medicine and Caring Sciences, Division of Diagnostics and Specialist Medicine

### MAIN PROJECT PARTICIPANTS

Stergios Kechagias, Mattias Ekstedt, Nils Dahlström, Markus Karlsson, Bengt Norén, Jens Tellman, Christian Simonsson, Frederik Testud, Ralph Sinkus, Marcel Warntjes, Magnus Borga

### GRANTS

Swedish Research Council  
ALF 2019–2022

### KEY PUBLICATIONS

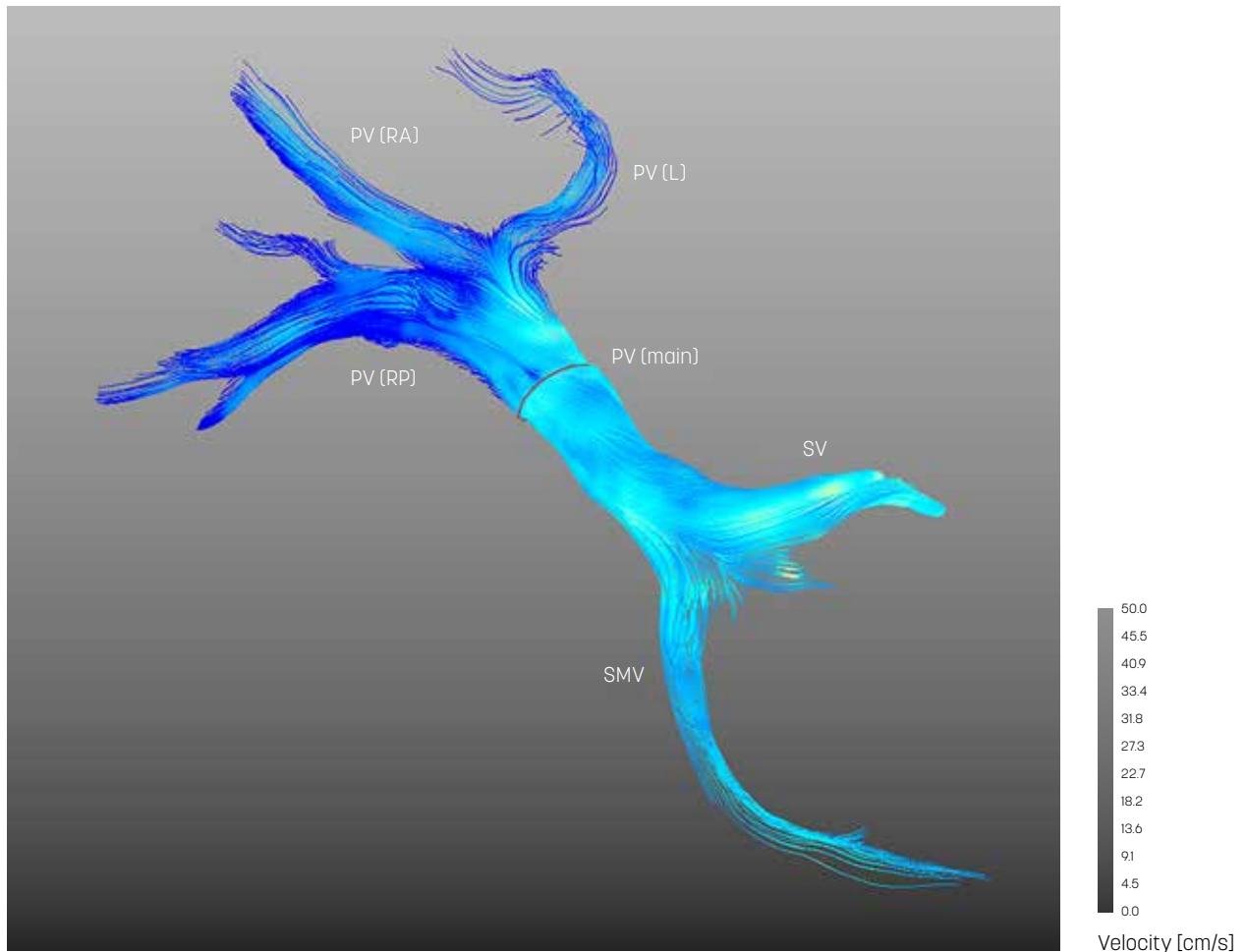
Forsgren MF, Nasr P, Karlsson M, Dahlström N, Noren B, Ignatova S, Sinkus R, Cedersund G, Dahlqvist Leinhard O, Ekstedt M, Kechagias S, Lundberg P (2020).

Biomarkers of liver fibrosis: prospective comparison of multimodal magnetic resonance, serum algorithms and transient elastography. *Scan J Gastroenterology*.

Karlsson M, Tellman J, Testud F, Jin N, Dahlström N, Lundberg P (2020).

Feasibility of 4D-Flow MRI of the Liver using Pencil Beam Navigator for Respiratory Gating and Compressed Sensing, ISMRM (Paris, France).





**MR-measurements of blood flow in the portal system at 3 T using 4D-flow MRI streamlines visualization**

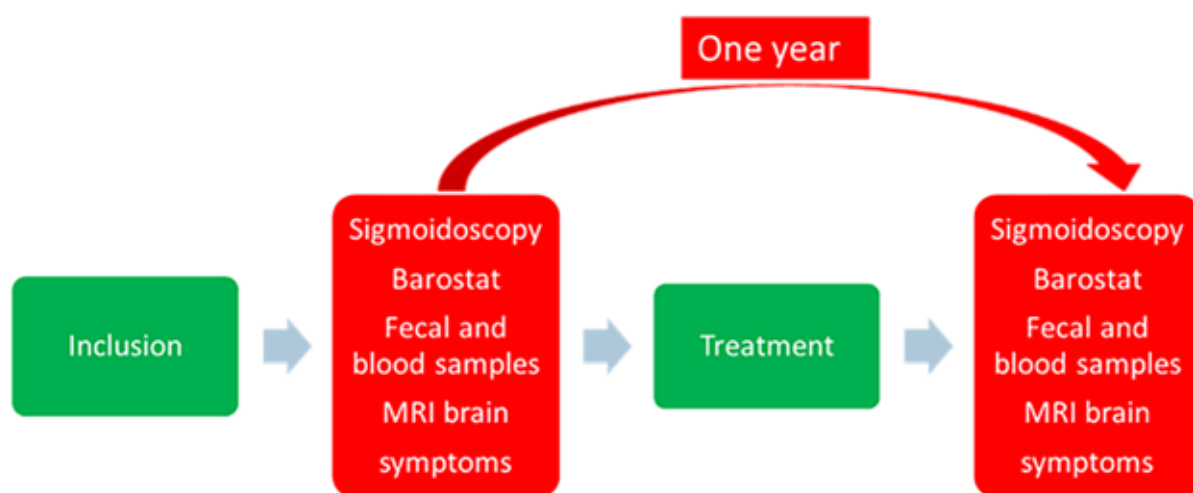
The Portal Vein transports blood from the gastrointestinal tract, the spleen and the pancreas and consists of the Main Portal Vein, here denoted PV [ main], which inside the liver divides into the following major branches: PV [RA]: Right Anterior branch, PV [RP]: Right Posterior branch and PV [L]: Left branch. The two major tributaries to the Main Portal Vein are the Superior Mesenteric Vein (SMV) and the Splenic Vein (SV), seen in the lower right corner. Colour signifies the local blood velocity, here showing a lowering of the velocity as the blood travels from the SMV and SV into the liver.

# Neuroplasticity in Irritable Bowel Syndrome

**T**he present project is a longitudinal intervention study to determine the direction of brain-gut interactions in Irritable bowel syndrome (IBS). We want to understand if and how brain alterations in IBS are changing together with symptom relief or alternately if brain alterations persist despite change in symptoms. By performing this study, we will also be able to understand whether peripheral alterations in the gut change in relation to symptom relief, and whether this change is, or is not, reflected by central alterations. During the latest years our study group has contributed with several important findings to the IBS brain-gut research by performing cross sectional and case-control studies.

This longitudinal study is the next important step to evaluate cause-effect relationships of brain-gut alterations in IBS. IBS is a chronic pain disorder characterized by abdominal pain and disturbed bowel function, often accompanied by extraintestinal symptoms such as anxiety, depression or chronic fatigue. IBS is a disorder of disturbed bidirectional communication between the brain and the gut, referred to as gut-brain axis alterations.

Based on the findings of our latest study evaluating multiple factors along the brain-gut axis in IBS and healthy controls we have designed the present project. Using functional Magnetic Resonance Imaging (fMRI), structural MRI, and MR spectroscopy, we were able to identify altered brain function and structure in IBS patients. Alterations in brain function and structure were also related to both symptoms and colonic mucosal barrier integrity. We have been able to find a relationship between microbiota, symptoms and brain function in the IBS patients and altered neurotransmitter concentration in insula and medial prefrontal cortex, two regions important for symptom generation in IBS. Altogether our recent findings, in agreement with those of other research groups, strongly suggest the occurrence of neuroplastic brain alterations in IBS. Now the next step is to understand whether and how the brain alterations found in IBS are affected by a change in symptoms or whether these alterations are persisting despite changes in symptoms. For this we will perform a longitudinal study with the aim to assess brain structure and function in relation to change in symptoms. ◀



The concept of the project.

**MRI** **Gastrointestinal**

*Project information*

**PROJECT NAME**

Neuroplasticity in Irritable Bowel Syndrome. A longitudinal follow-up study of gut-brain axis alterations

**PROJECT LEADER**

Susanna Walter, Department of Biomedical and Clinical Sciences, Division of Inflammation and Infection

**MAIN PROJECT PARTICIPANTS**

Maria Engström, Peter Lundberg, Nawroz Barazanji, Paul Hamilton, Åsa Keita

**KEY PUBLICATIONS**

Witt ST, Bednarska O, Keita ÅV, Icenhour A, Jones MP, 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: Clinical*. 2019;21:101602.

Icenhour A, Tapper S, Bednarska O, Witt ST, Tisell A, Lundberg P, Elsenbruch S, Walter S. Elucidating the putative link between pre-frontal neurotransmission, functional connectivity, and affective symptoms in irritable bowel syndrome. *Sci Rep*. 2019 Sep 19;9(1).

Bednarska O, Icenhour A, Tapper S, Witt ST, Tisell A, Lundberg P, Elsenbruch S, Engström M, Walter S. Reduced excitatory neurotransmitter levels in anterior insulae are associated with abdominal pain in irritable bowel syndrome. *Pain*. 2019 Sep;160(9):2004–2012.

**GRANTS**

ALF

# MR Mammography

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

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

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

Despite the wide use of 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 and 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 endpoint is whether the treatment will reduce the risk for breast cancer. ◀

**MRI** **Oncology** **Acquisition** **Modeling** **Imaging Biomarkers**

## *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 Health, Medicine and Caring Sciences, Division of Diagnostics and Specialist Medicine

### **MAIN PROJECT PARTICIPANTS**

Charlotta Dabrosin, Anette Karlsson, Ieva Tomkeviciene, Mikael Forsgren, Johan Kihlberg, Maria Kristoffersen Wiberg, Magnus Borga, Marcel Warntjes, Olof Dahlqvist Leinhard, Pantelis Gialias, Anna Rzepecka

### **GRANTS**

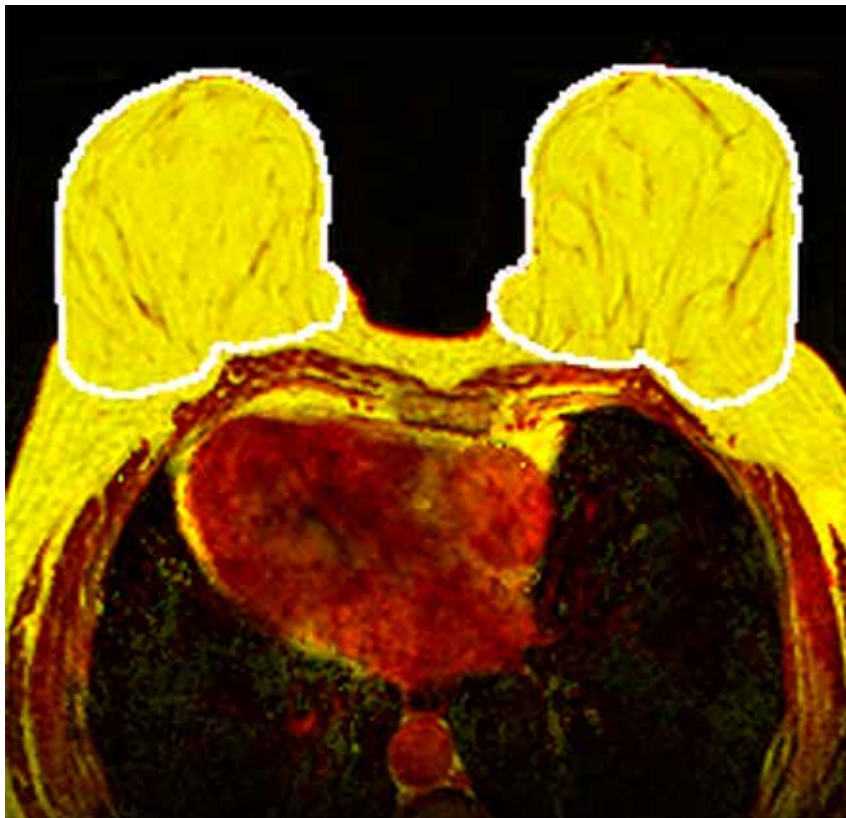
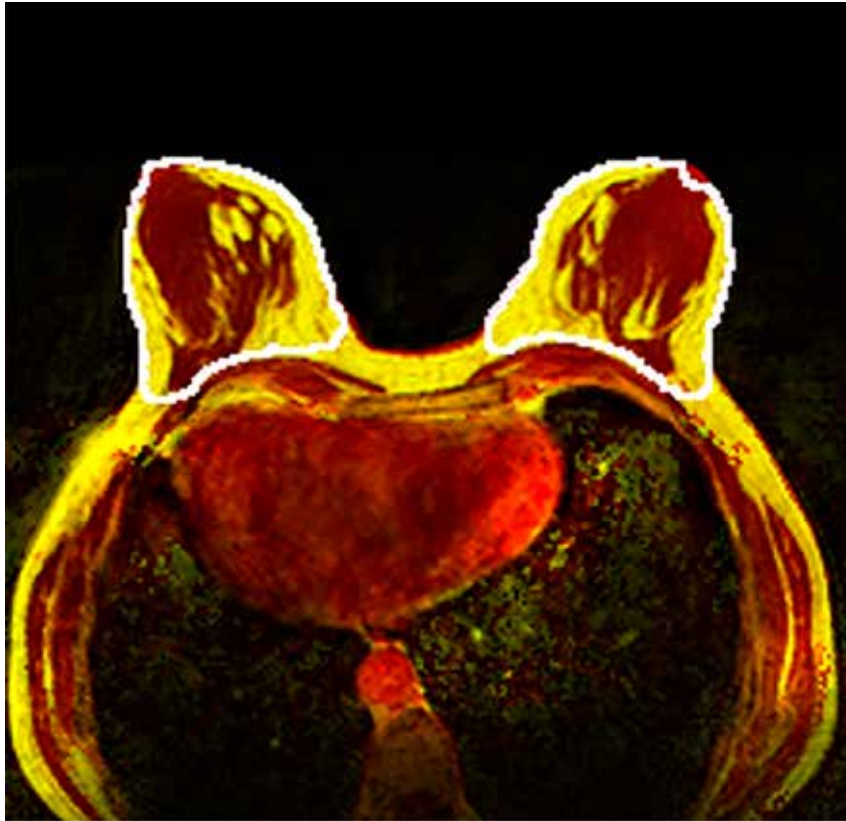
LiU-Cancer  
The Swedish Cancer Society

### **KEY PUBLICATIONS**

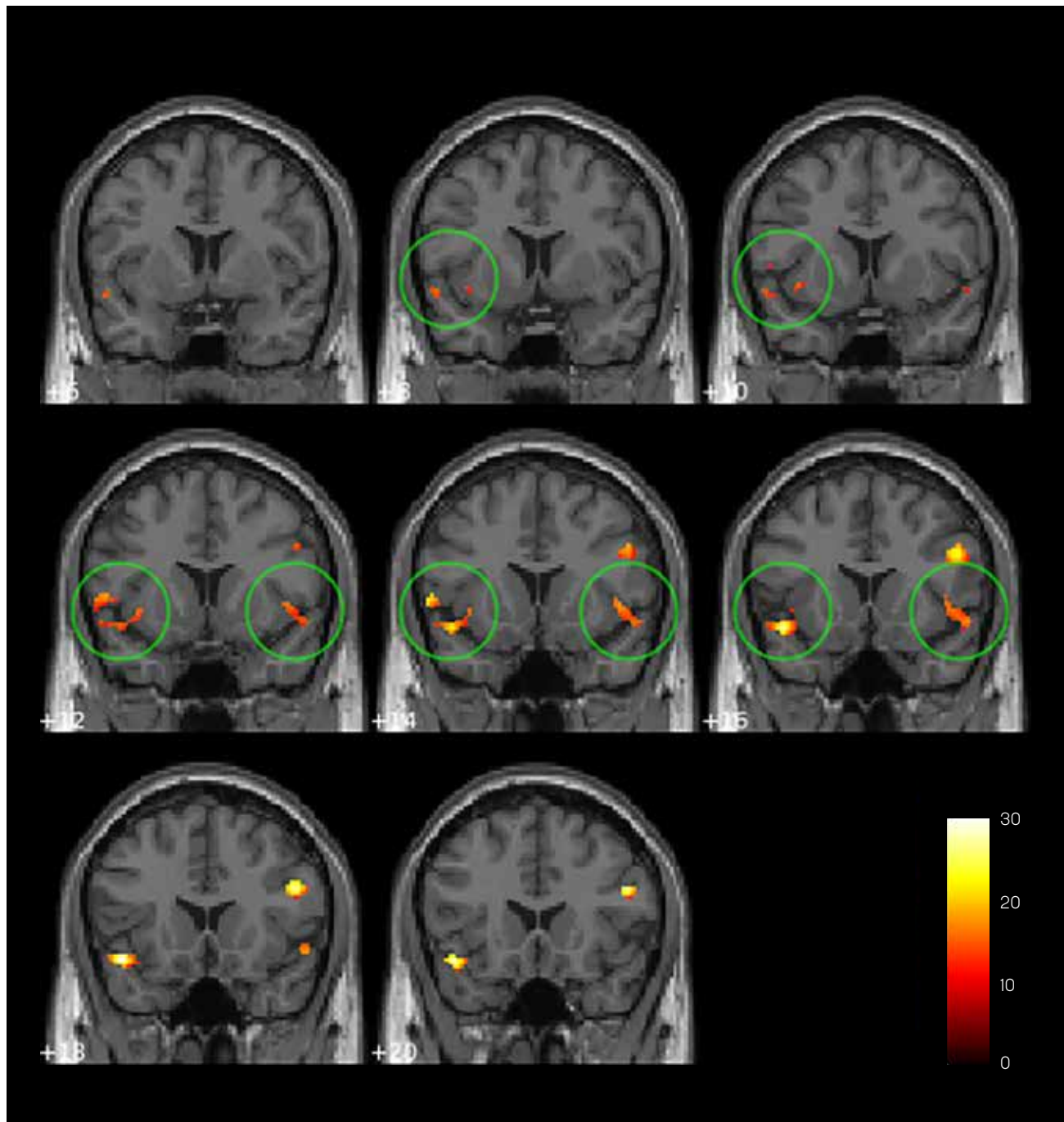
Abrahamsson A, Rzepecka A, Romu T, Borga M, Dahlqvist Leinhard O, Lundberg P, Kihlberg J, Dabrosin C.

“Dense breast tissue in postmenopausal women is associated with a pro-inflammatory microenvironment in vivo”, *Oncoimmunology*, 5(10), 2016.





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



**Legend:** Patients with fibromyalgia who reported a high level of pain show a stronger coupling between an attentional network and the insula shown within the green rings. The insula did also show changed connectivity of the insula in patients with chronic widespread pain and may give key insights in brain alterations related to long-standing pain perception.

# Pain Mechanisms in Widespread Pain

**C**hronic widespread pain (CWP) including fibromyalgia (FM) is characterized by generalized musculoskeletal pain and is often associated with symptoms such as psychological distress, insomnia, fatigue, and cognitive difficulties. CWP affects not only patients but also their families and society, leading to significant suffering and high socioeconomic burden. Peripheral and central nervous system mechanisms are believed to contribute to the clinical picture in CWP, but an understanding of the activated pain mechanisms is mainly lacking.

In the first part of this project concerning CWP we have investigated the function (connectivity) of some of the networks in the brain with functional magnetic resonance imaging (fMRI) i.e. the default mode network (DMN) and the salience network (SN). An important result was that the connectivity within the DMN was decreased and connectivity within the SN was increased for CWP. The anterior insula is part of the SN and plays a key role in switching between internal- and external-oriented tasks. Thus, the insula has a reflective role and can switch between monitoring subjective feelings such as emotions and paying attention to external events.

In a second on-going part of the project the networks in the brain of fibromyalgia patients and healthy controls are investigated. In addition, clinical characteristics (e.g., pain intensity, psychological distress, quality of life etc.), fitness level, pain sensitivity and biochemical alterations in blood, muscles and fat tissues are investigated. The right intraparietal sulcus (IPS) node of the Central executive network (CEN) showed a higher level of connectivity strength with right insula in FM with higher pain intensity compared to controls. More anxiety symptoms in FM correlated with higher levels of connectivity strength between the ventromedial prefrontal cortex DMN node and right sensorimotor cortex. These findings support the theory of altered insular connectivity in FM and suggest altered IPS connectivity in FM.

An important research question in the ongoing analyses is if there exist associations between peripheral biochemical tissue alterations and alterations in the brain of FM.

The results from this project will be clinically important both with respect to assessment and when designing and choosing interventions for these patients. ◀

**MRI** **Neurology** **Musculoskeletal** **Acquisition**  
**Imaging Biomarkers**

## Project information

### PROJECT NAME

Pain mechanisms in chronic widespread pain including fibromyalgia

### PROJECT LEADER

Björn Gerdle, Department of Health, Medicine and Caring Sciences, Division of Prevention, Rehabilitation and Community Medicine

### MAIN PROJECT PARTICIPANTS

Eva Lund, Peter Lundberg, Bijar Ghafouri, Helene van Ettinger-Veenstra, Håkan Olausson, Rebecca Boehme, Rikard K. Wicksell, Maria Engström, Ann Bengtsson, Mikael Forsgren, Olof Dahlqvist Leinhard

### GRANTS

Swedish Research Council  
ALF, Region Östergötland  
ForSS

### KEY PUBLICATIONS

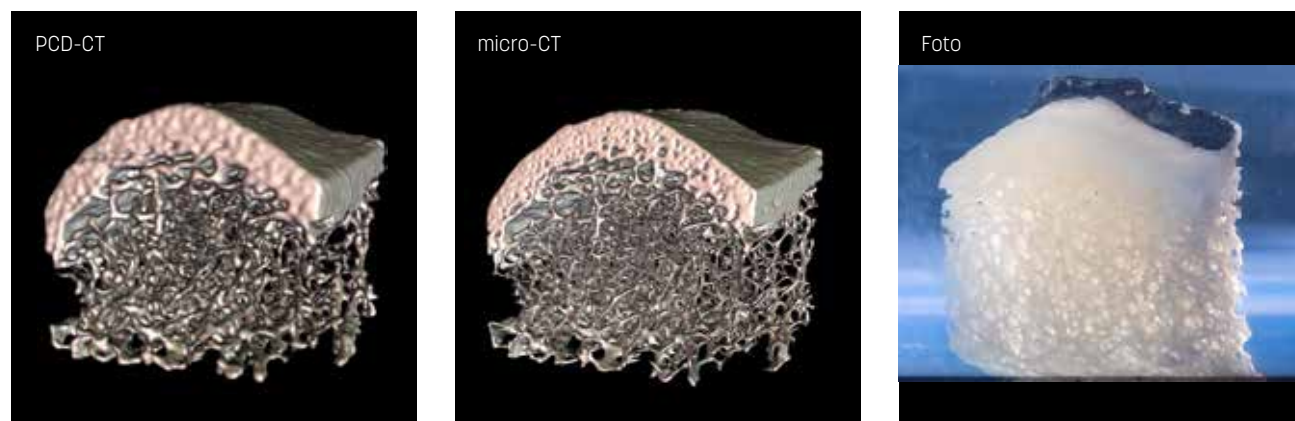
van Ettinger-Veenstra H, Lundberg P, Alföldi P, Södermark M, Graven-Nielsen T, Sjörns A, Engström M, Gerdle B.  
Chronic Widespread Pain patients show disrupted cortical connectivity in Default Mode and Salience Networks, modulated by pain sensitivity. *J Pain Res* 2019;12:1,743–1,755.

Boehme R, van Ettinger-Veenstra H, Olausson H, Gerdle B, Nagi SS.

Anhedonia to Gentle Touch in Fibromyalgia: Normal Sensory Processing but Abnormal Evaluation. *Brain Sci.* 2020 May 18;10(5):306. doi: 10.3390/brainsci10050306. PMID: 32443443; PMCID: PMC7288027.

van Ettinger-Veenstra H, Boehme R, Ghafouri B, Olausson H, Wicksell RK, Gerdle B.

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3D images from a bone specimen, PCDCT micro-CT, a foto, CBCT, MSCT.

# Bone Structure Analyses for Reducing Future Osteoporotic Fractures

**P**atients suffering from osteoporosis have an increased risk of fractures. When studying osteoporosis, the amount of calcium in bone is measured. This bone mineral density (BMD) is lower in osteoporotic bone. Research have shown that bone microstructure, seems to be more important for its strength than the reduced calcium content.

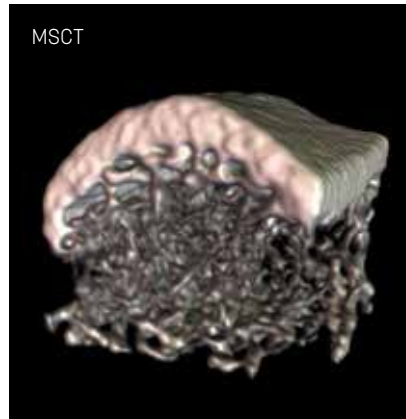
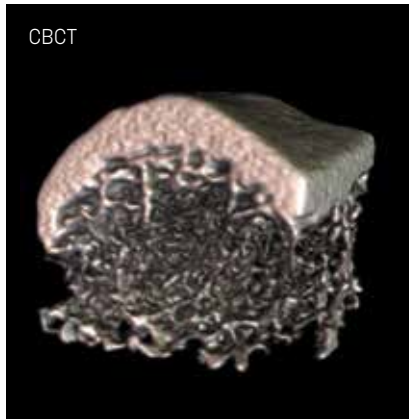
The internal bone microstructure consists of a network of thin bone structures called trabeculae. This network of trabeculae can be measured by different parameters like their thicknesses, number, free ends and distance between them. Earlier, the 3D microstructure of humans could be studied only

by microscopy and by micro-computed tomography (micro-CT) of specimens removed from the body.

This project aims to study this 3D structure in living humans, by using methods available in a radiological department, in particular different types of CT methods. Since the trabeculae often are less than 0.1 mm thick, the limited resolution of the radiological methods may be a problem. We have focused on examinations on CT devices with possibilities of imaging at high resolution and on developing new image processing techniques for as accurate measurements as possible using these image data sets.

Data from dental cone beam CT (CBCT) shows very strong cor-





relations for bone microstructure when compared to micro-CT and results from the research are published in a number of publications. Most recently, a manuscript in collaboration with University of Iowa was published in the journal *Medical Physics*.

Another CT device with high resolution is photon counting detector (PCD) CT. This is a very novel technique available only in 2–3 radiology departments around the world. One of the devices is installed at CMIV. This technique is very promising since it allows high resolution of central body parts like the hip and vertebrae where osteoporotic fractures are common. All other devices, so far, have been able to image bone microstructure only in the peripheral skeleton like wrist and forearm. Studies on bone microstructure on this PCD-CT device have started just recently and show promising results.

A clinical study on patients visiting the Department of Endocrinology at Linköping University for osteoporosis examinations is ongoing. CBCT data of forearm and mandible is compared to dual energy X-ray absorptiometry (DXA) data.

On the segmented CT-data sets, we also analyse bone strength by finite element modeling (FEM), a computational method that requires long time even on very fast computers. Our segmented data, presented in previous studies, correlates well with results from FEM analyses.

In the future, we hope that our methods will be useful in particular in early detection of osteoporosis. With better tools to measure the structure of the 3D bone network, it will be possible to diagnose osteoporosis at an earlier stage. We hope for a diagnosis already at the time for the first fracture, which will result in reducing the number of future painful fractures. ◀

Computed Tomography Musculoskeletal Acquisition  
Visualization

### *Project information*

#### **PROJECT NAME**

Bone microstructure and strength derived from imaging data from different CT devices: relation to osteoporosis and fractures

#### **PROJECT LEADER**

Eva Klintström, Department of Health, Medicine and Caring Sciences, Division of Diagnostics and Specialist Medicine

#### **MAIN PROJECT PARTICIPANTS**

Örjan Smedby, Rodrigo Moreno, Benjamin Klintström, Mischa Woisetschläger

#### **KEY PUBLICATIONS**

Klintström E, Smedby Ö, Moreno M, Brismar TB.

Trabecular bone structure parameters from 3D image processing of clinical multi-slice and cone-beam computed tomography data. *Skeletal Radiology*, 2014 Vol. 43, nr 2, 197–204.

Klintström E, Klintström B, Pahr D, Brismar TB, Smedby Ö, Moreno M. Direct Estimation of Human Trabecular Bone Stiffness Using Cone-Beam Computed Tomography. *PLoS ONE*, Vol. 11, nr 8 2016.

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# CT-MOCAP: Visualization of Skeletal Joint Movement

**T**here are many tools available for the orthopedic doctor to help with the diagnoses, treatment, and overall care of their patients. Often imaging, like for example computed tomography (CT) or magnetic resonance imaging (MRI), can assist in understanding the underlying cause of the problems. However, orthopedic problems most often involve issues related to a restriction or pain during movement. Standard CT or MRI merely show a static image of the skeletal or soft tissues. In some cases, these still images are not sufficient to understand the clinical problem presented by the patient. Currently, there are systems that can show movement of the skeletal and soft tissues during a short time frame. One method is 4D CT. With this method a 3D image is taken over time (the 4th dimension). However, there are some major drawbacks with these systems. For example, the high levels of radiation, limited time frame and movement range of motion. It would be of incredible added benefit if, by some means, we could combine standard clinical imaging with the well-established motion capture methodology. The capture of whole-body movements has been done as long back as the 1980's both in the scientific field as well as in the movie making industry. There are different systems that can be used but in general, multiple cameras are used to track predetermined points (markers) on the subject's body. Using this method, many clinically relevant daily activities can be measured without any restrictions.

In the current project we are aiming to combine the standard CT images taken as part of the standard clinical care and combining them with the information from the motion capture system. By combining these two applications we could generate a visualization of the patients' skeleton movements while performing daily clinically relevant movements.

In a collaboration with industrial leading partners in both

medical imaging and motion capture we have developed an application that can combine information from both systems to provide a visualization of the skeletal movements. Initial application at the hip and knee joints have proven to have added clinical benefits. However, optimization of this method is still needed. In addition to optimizing and simplifying the methodology, we need to focus on minimizing errors. For example, the errors introduced because our skin moves relative to our bones (soft tissue artifacts). Using a large dataset from patients with suspected femoroacetabular impingement, we aim to understand the size of the error and the effective methods to reduce these errors. Moreover, the clinical benefits of this system will be studied to help validation of this methodology. ◀

Computed Tomography Musculoskeletal Visualization

## *Project information*

### **PROJECT NAME**

CT-MOCAP: A novel method to visualize joint movement by means of combining computed tomography with motion capture

### **PROJECT LEADER**

Hans Tropp, Department of Biomedical and Clinical Sciences, Division of Surgery, Orthopedics and Oncology

### **MAIN PROJECT PARTICIPANTS**

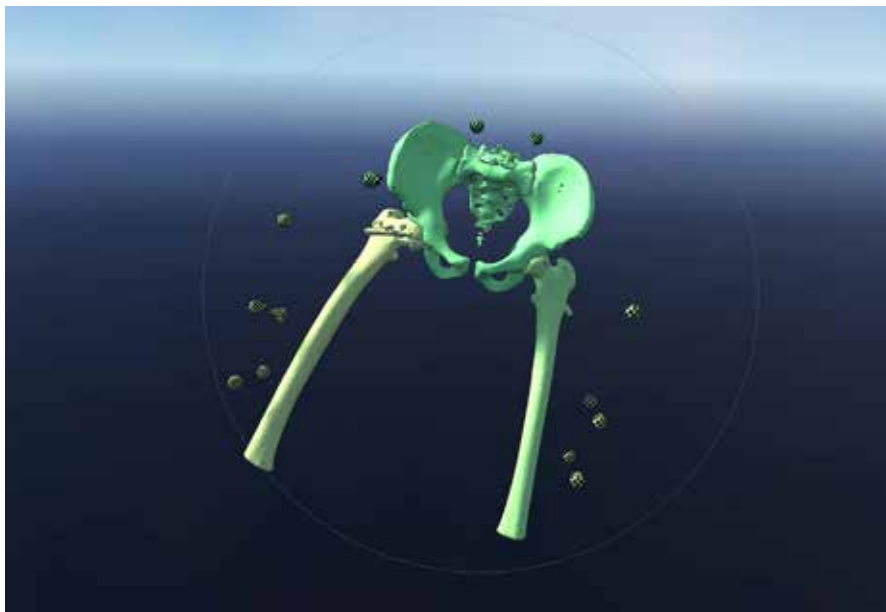
Marcus Malmqvist, Daphne Wezenberg

### **GRANTS**

Vinnova  
FORSS



The first application for CT-Mocap is femuroacetabular impingement of the hip joint with limited motion resulting from certain types of underlying morphological abnormalities in the femoral head-neck region and/or acetabulum.



Motion analysis combining patient specific low-dose CT images with traditional motion capture techniques.

# The NACOX-Study

**A**nterior cruciate ligament (ACL) injury in the knee joint can result in joint instability, decreased functional performance, reduced physical activity and quality of life. The most important long-term consequence is the increased risk for posttraumatic osteoarthritis (PTOA). The underlying mechanisms behind PTOA are not well understood but altered biological processes due to injury and joint bleeding as well as concomitant structural injuries to the cartilage and the subchondral bone have been suggested to be of relevance. Despite the development of new treatment techniques and extensive research, the complex and multifaceted nature of ACL injury and its consequences are yet to be fully understood.

The overall aim of the NACOX study is to evaluate the natural corollaries and recovery after an ACL injury. There are five main study objectives:

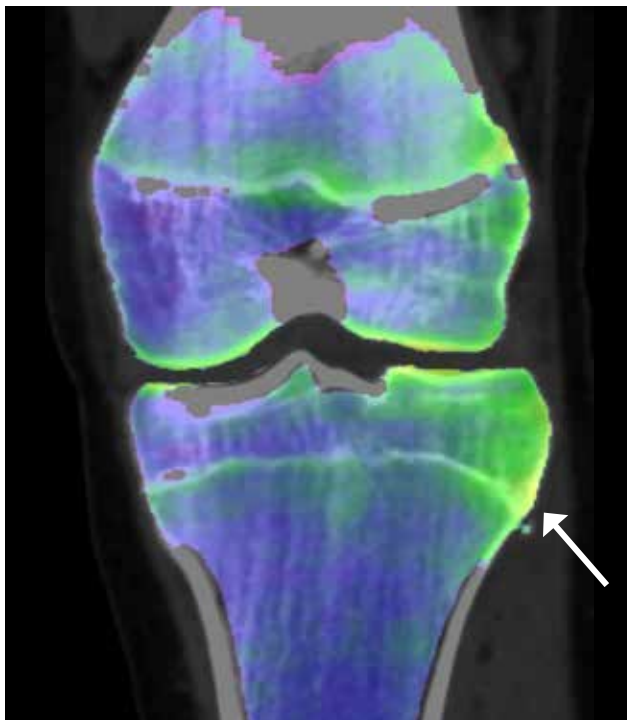
1. To assess biological, psychological and social factors and their relationships to the natural corollaries and recovery after acute ACL injury
2. To evaluate the choice of treatment after acute ACL injury (i.e., ACL reconstruction, ACLR or non-ACL reconstruction, non-ACLR)
3. To evaluate return to sport after acute ACL injury
4. To study knee problems in the short and long term after acute ACL injury
5. To identify proxies (biomarkers and structural risk factors) for

early detection of symptomatic and radiographic osteoarthritis

The NACOX study is a multi-centre prospective cohort study of patients with acute ACL injury. At seven sites in Sweden, we have included 275 patients aged 15–40 years, within 6 weeks after primary ACL injury. Patients complete questionnaires at multiple occasions over the 3 years following injury or the 3 years following ACL reconstruction (for participants who have surgical treatment). In addition, a subgroup of 131 patients is followed with extensive imaging modalities, biological samples and clinical examinations.

The study is ongoing and several analyses with specific interest on imaging have been done. Example:

- Diagnostic accuracy of dual energy CT (DECT) for detection of bone marrow lesions in the injured knee using MRI as reference method. Bone marrow lesions can be a telltale sign of a more severe injury in the bone and is usually demonstrated with MRI, but our results show that DECT also can detect these lesions.
- Ongoing quantitative MRT analysis of cartilage matrix organization, as measured by T2 relaxation time, of the tibiofemoral joint cartilage after acute anterior cruciate ligament injury, in both the injured and contralateral non-injured knee.
- Ongoing methodological development for analyses of posterior tibial slope. The association between the magnitude of the slope and patient-reported symptoms, such as experienced knee instability, will then be analysed. ◀



DECT virtual non-calcium image with color overlay displaying the bone marrow lesion (arrow).



MRI PD fat saturated image displaying good correlation with DECT image concerning bone marrow lesion (arrow).

Computed Tomography | MRI | Musculoskeletal | Acquisition | Visualization | Imaging Biomarkers



## Project information

### PROJECT NAME

NACOX – Natural Corollaries and Recovery after Acute Anterior Cruciate Ligament Injury

### PROJECT LEADER

Joanna Kvist, Department of Health, Medicine and Caring Science, Division of Prevention, Rehabilitation and Community Medicine

### MAIN PROJECT PARTICIPANTS

Håkan Gauffin, Hanna Tigerstrand Grevnerts, Bashir Tajik Edwardsson, Anders Persson, Ann-Sofi Björkman, Kati Laukkanen, Martin Englund, Richard Frobell, Miika Nieminen, Victor Casula, Seppo Koskinen, Rolf Scheiderbauer

### GRANTS

Swedish Medical Research Council 2015–2020  
Swedish Research Council for Sport Science 2017–2021  
Medical Research Council of Southeast Sweden 2020  
ALF Grants Region Östergötland 2018–2020

### KEY PUBLICATIONS

Kvist J, Gauffin H, Tigerstrand Grevnerts H, Ardern C, Hägglund M, Ståhlman A, Frobell R.

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Björkman AS, Koskinen SK, Lindblom M, et al. Diagnostic accuracy of dual-energy CT for detection of bone marrow lesions in the subacutely injured knee with MRI as reference method. *Acta Radiol* 2020;61(6):749–59. doi: 10.1177/0284185119877343.

Fomin S, Gauffin H, Kvist J. Short-term recovery of physical activity and knee function after an acute knee injury. *BMJ Open Sport & Exercise Medicine* 2020;6:e000950. doi: 10.1136/bmjsem-2020-000950.



MR scan of a patient with an Achilles tendon rupture.

A) A sagittal view of the intact tendon (Left image) and the injured tendon (right image).

B) An axial image of the triceps surae muscles. There is a clear atrophy on the injured side (left) compared to the intact side (right).



# Muscle Adaptation after Achilles Tendon Rupture

**T**endon disorders are common. Annually more than 15 million musculoskeletal injuries worldwide involve tendons or ligaments. This results in a high socioeconomical burden. The Achilles tendon is the most frequent tendon to rupture and this usually occur during sports. The incidence is rising, probably due to a high number of older adults participating in high-demand sports. Rehabilitation after a tendon rupture is long and demanding. It is also a major challenge as patients often lack muscle force and only 30% of these patients return to their pre-injury sports level, which is troubling. These patients are often 30–40 years old and should have many years of active sporting left. Despite improved rehabilitation regimens persistent deficits remain.

Lack of complete recovery in muscle strength after tendon rupture is commonly accepted as the principal mechanism for incomplete recovery. However, this permanent physical dysfunction can be related to A) tendon elongation or B) a change in material properties of the tendon, or C) an inability of the muscle cell to adapt to the new tendon length.

We will perform a case-control study to investigate if tendon elongation is the cause for poor function in non-surgically treated Achilles tendon ruptures. There are two questions that we want to answer with the case-control study. 1) is tendon elongation the principal mechanism behind poor function after an Achilles tendon rupture? 2) is this linked to muscle specific effects? Our working hypothesis is that poor function is related to substantial tendon elongation and this results in a smaller

soleus muscle. Bilateral Magnetic Resonance Imaging (MRI) will be used to measure tendon length and tendon diameter on both legs (see figure). Furthermore, the volume of each calf muscle will be measured, as well as fatty infiltration in each muscle to assess if the amount of atrophy in any of the muscles differ between the groups. The objective with our research is to seek novel mechanistic and molecular insights into the connection between the adaptation of the tendon and muscle tissue, which we hypothesize plays a large role in the recovery after tendon injuries. ◀

**MRI** Musculoskeletal

## *Project information*

### **PROJECT NAME**

Muscle adaptation after Achilles tendon rupture

### **PROJECT LEADER**

Pernilla Eliasson, Department of Biomedical and Clinical Sciences, Division of Surgery, Orthopedics and Oncology

### **MAIN PROJECT PARTICIPANTS**

Andreas Meunier

### **GRANTS**

The Swedish Society of Medicine 2020–2022  
Region Östergötland 2020–2021

# SCAPIS

**S**CAPIS is a collaborative project between six Swedish universities. We randomly invited 30,000 individuals from the general population living in six Swedish university cities (Gothenburg, Linköping, Malmö/Lund, Stockholm, Umeå and Uppsala), aged 50–64 years.

In Linköping we included 5,058 study participants between 2015 and 2018 with a participation rate of 58%.

In addition to determining the traditional cardiovascular risk factors, the participants underwent extensive imaging, including non-contrast and contrast-enhanced computed tomography (CT) coronary angiography; CT scanning of the abdomen for the quantification of visceral and subcutaneous adipose tissue, liver fat; and ultrasound analysis for carotid artery atherosclerosis.

In addition to the core study protocol, we have in SCAPIS-Linköping added several optional investigations as home blood pressure recordings (7 days), measurements of stress exposure by cortisol levels in hair, echocardiography, microcirculatory function by integrated laser Doppler flowmetry and diffuse reflectance spectroscopy in a fiberoptic probe for skin, and determination of pulse wave velocity as a surrogate marker for arterial stiffness.

In a recent publication we showed that calcification in the coronary arteries was present in 39.5% and carotid plaque in 56.0%. In men, coronary artery calcium score (CACS) >0 ranged from 40.7% to 65.9% and presence of carotid plaques from 54.5% to 72.8% in the age group 50–54 and 60–65 years, respectively. In women, the corresponding difference was from 17.1% to 38.9% and from 41.0% to 58.4%.

Currently, we are investigating the prerequisites for performing a re-investigation of the SCAPIS-Linköping cohort starting in 2023.

In 2021, we will start planning and exploring the possibilities for a physical follow-up and a re-examination of the cohort. A physical re-examination will be costly and thus the aims and methods chosen must be thoroughly scrutinized to ensure that the important research questions raised may be properly addressed if the re-examination is performed.

The re-examination will most likely follow the baseline protocol and include a fasting blood sample for both immediate analysis and stored in a biobank for later analyses, anthropometry, blood pressure, accelerometry, dynamic spirometry, imaging of carotid arteries with ultrasound and imaging of heart (including coronary arteries), lungs and fat depots with computed tomography. ◀

Computed Tomography    Ultrasound    Cardiovascular  
Metabolism    No Method Development

## Project information

### PROJECT NAME

Swedish CARdioPulmonary bioImage Study (SCAPIS) in Linköping

### PROJECT LEADER

Carl-Johan Östgren, Department of Health, Medicine and Caring Sciences, Division of Prevention, Rehabilitation and Community Medicine

### MAIN PROJECT PARTICIPANTS

Jan Engvall, Eva Swahn, Anders Persson, Fredrik Nyström, Carl-Johan Carlhäll, Lena Jonasson, Charlotte Brage, Karin Festin, Tomas Annerholm

### GRANTS

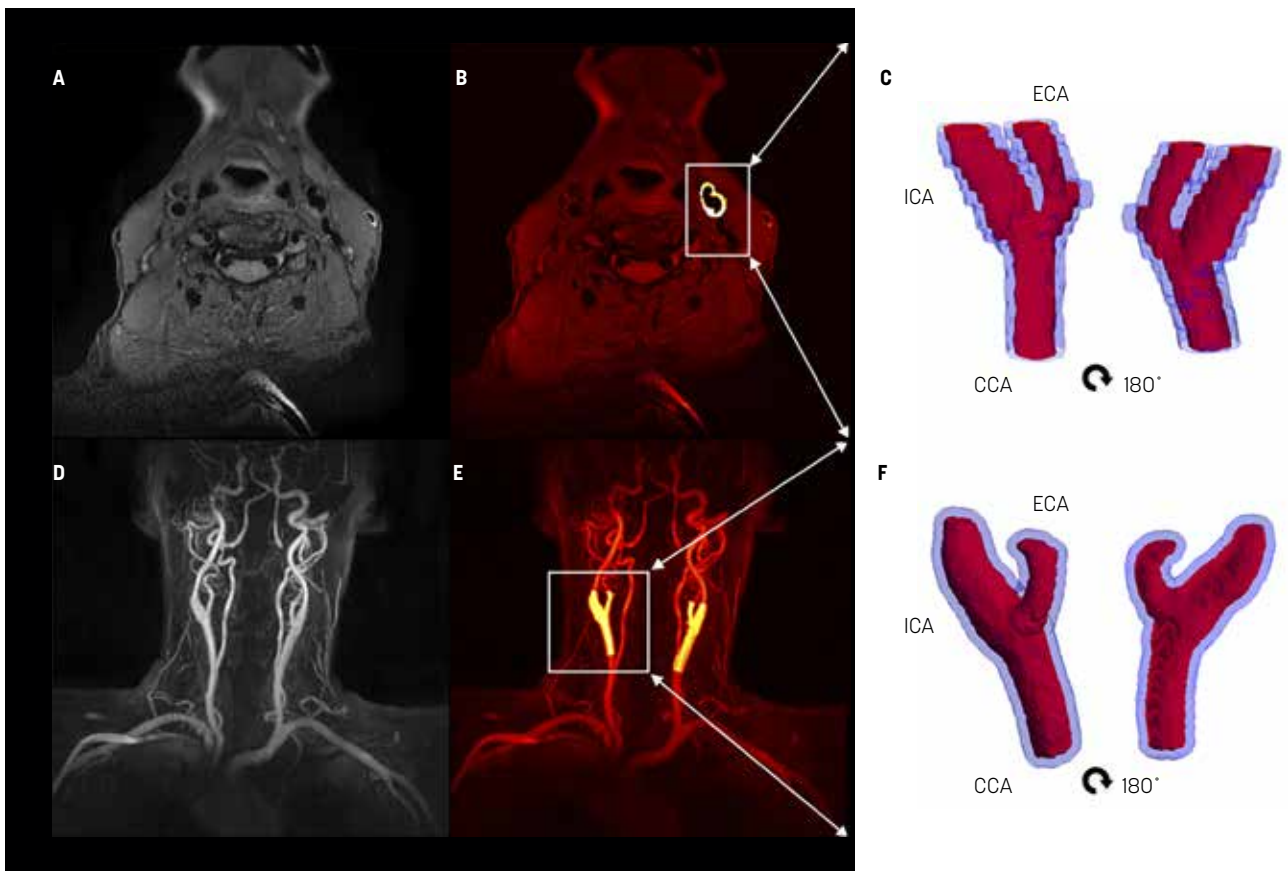
The Swedish Heart-Lung Foundation

### KEY PUBLICATIONS

Östgren CJ, Söderberg S, Festin K, et al. Systematic Coronary Risk Evaluation estimated risk and prevalent subclinical atherosclerosis in coronary and carotid arteries: A population-based cohort analysis from the Swedish Cardiopulmonary Bioimage Study [published online ahead of print, 2020 Mar 3]. *Eur J Prev Cardiol*. 2020;2047487320909300. doi:10.1177/2047487320909300

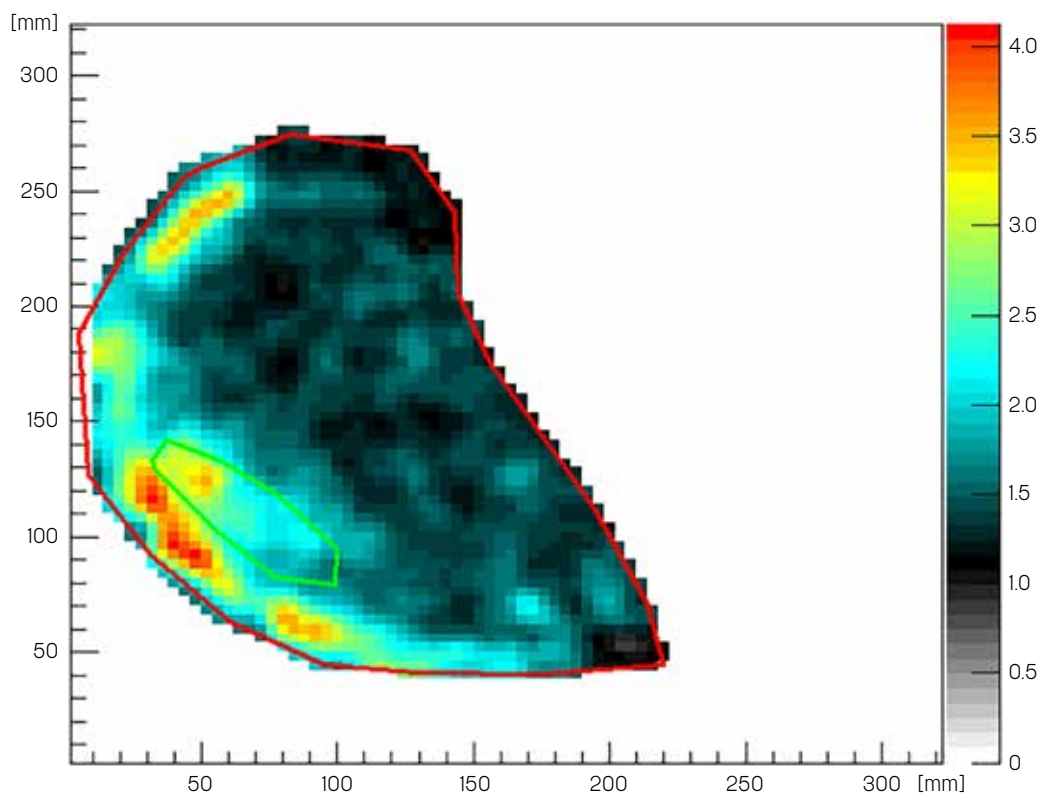
Malinovsky A, Zhou X, Bake B, Bergström G, Blomberg A, Brisman J, Caidahl K, Engström G, Eriksson MJ, Frölich A, Janson C, Jansson K, Vikgren J, Lindberg A, Linder R, Mannila M, Persson HL, Sköld CM, Torén K, Östgren CJ, Wollmer P, Engvall JE. Assessment of Global Lung Function Initiative (GLI) Reference Equations for Diffusing Capacity in Relation to Respiratory Burden in the Swedish CARdioPulmonary BioImage Study (SCAPIS). *Eur Respir J*. 2020 Apr 27;1901995. doi: 10.1183/13993003.01995-2019. Online ahead of print. *Eur Respir J*. 2020. PMID: 32341107.

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Manual segmentation of a carotid bifurcation using T1w data (top row), and example automated segmentation using CE-MRA data (bottom row). Left panels depict a mid-stack slice from T1w imaging (A), and a maximum intensity projection of CE-MRA data (D). Center panels (B, E) depict the same images with segmentation overlays. Right panels (C, F) show 3D visualizations of the segmentations, with the vessel's lumen depicted in red and the vessel wall in blue. CCA: Common Carotid Artery. ICA: Internal Carotid Artery. ECA: External Carotid Artery.

Ziegler M, Good E, Engvall J, Warntjes M, de Muinck E, Dyverfeldt P. Towards Automated Quantification of Vessel Wall Composition using MRI. *J Magn Reson Imaging* 2020; In Press, available online.



Magnetic resonance elastography (MRE) of the liver at 56 Hz. MRE is a technology that combines MRI imaging with low-frequency vibrations to create a visual map (an elastogram) illustrating hepatic stiffness. There is a strong correlation between MRE-measured hepatic stiffness and the stage of hepatic fibrosis at histology.

# Scapis-HEALTH

**S**wedish Cardio Pulmonary bioImage Study (SCAPIS), is a large-scale national population study initiated by The Swedish Heart-Lung Foundation and supported by the Wallenberg Foundation. The study is led 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 were examined in the study. Of these 5,000 were examined in Linköping. The participants' lungs and cardiovascular system were examined with computed tomography and ultrasound. All the collected data were 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 measurements.

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 3–4 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 were recruited from the SCAPIS cohort. In total 46 persons with T2DM (as reported in SCAPIS forms) and 46 matched control subjects without T2DM.

There are several manuscripts in preparation. ◀

MRI	Cardiovascular	Musculoskeletal	Gastrointestinal
Metabolism	Acquisition	Visualization	Imaging Biomarkers

## Project information

### PROJECT NAME

Scapis-HEALTH

### PROJECT LEADER

Carl-Johan Carlhäll, Department of Health, Medicine and Caring Sciences, Division of Diagnostics and Specialist Medicine

### MAIN PROJECT PARTICIPANTS

Peter Lundberg, Tino Ebbers, Olof Dahlqvist Leinhard, Jan Engvall, Carl Johan Östgren, Eva Swahn, Mattias Ekstedt

### GRANTS

KAW

The Swedish Heart-Lung Foundation

The Swedish Research Council

### 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.

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# Diffuse Myocardial Fibrosis

**A**pproximately 1,800 aortic valve implantations are performed every year in Sweden, the majority due to aortic valve stenosis. Symptoms and/or impairment of left ventricular function are indications for surgery. However, symptoms and ventricular dysfunction occur late in the natural history of aortic valve stenosis. Irreversible impairment of left ventricular function (LVF) is believed to be related to diffuse myocardial fibrosis, which develops during disease progression as the heart compensates and develops hypertrophy. Regional fibrosis is known to cause impaired LVF after myocardial infarction, but data are scarce on how diffuse fibrosis affects cardiac performance and aerobic exercise capacity.

The overall purpose of the project is to improve patient management by generating knowledge on how diffuse myocardial fibrosis affects cardiac function and physical capacity over time, and how fibrosis is affected by surgical intervention. The specific hypotheses for the present project are that cardiac magnetic resonance imaging (CMR) gives a valid representation of diffuse myocardial fibrosis and compared to endomyocardial biopsy, fibrosis has a prognostic value for post-operative heart function and aerobic exercise capacity.

The preliminary results showed that our novel automated assessment support for diastolic function proved to be consistent for the analysis of a larger group of patients with aortic stenosis pre- and postoperatively. The algorithm is freely available for researchers and clinicians online.

Analyses of a subgroup of CMR examinations pre- and post-operatively indicate that changes in myocardial relaxation times and thus changes in tissue characteristics can be observed already within the first 3 months after aortic valve implantation. The significant changes from preoperative examinations to the follow up may be interpreted as a reduction of interstitial fibrosis in the left ventricular wall.

This study has a unique design, where we adapt and develop new technology (both for research purposes and clinical use) within echocardiography, cardiopulmonary exercise testing and CMR. We also perform myocardial biopsy in the same patients, making it possible to gain new insights into the functional con-

sequences of fibrosis, the effects of valve surgery, and ultimately, optimize pre- and post-operative treatment for patients with aortic stenosis. ◀

**MRI** **Cardiovascular** **No Method Development**

## *Project information*

### **PROJECT NAME**

Diffuse Myocardial Fibrosis: Functional Consequences for Cardiac and Overall Function in Patients with Aortic Stenosis

### **PROJECT LEADER**

Eva Tamas, Department of Health, Medicine and Caring Sciences, Division of Diagnostics and Specialist Medicine

### **MAIN PROJECT PARTICIPANTS**

Erica Holmberg, Jan Engvall, Johan Kihlberg, Eva Nylander, Sofia Kvernby, Tino Ebbers

### **GRANTS**

ALF  
Region Östergötland

### **KEY PUBLICATIONS**

Tamás É, Nylander E.

Decision support for assessment of left ventricular diastolic function. *Physiol Rep*. 2018 Aug;6(16): e13815. doi: 10.14814/phy2.13815.

Kvernby S, Warntjes M, Carlhall C, Engvall J, Ebbers T. Clinical feasibility of 3D-QALAS - Single breath-hold 3D myocardial T1- and T2-mapping. *Magn Reson Imaging*. 2017 May;38:13–20. doi: 10.1016/j.mri.2016.12.014. Epub 2016 Dec 18. PMID: 2799874.

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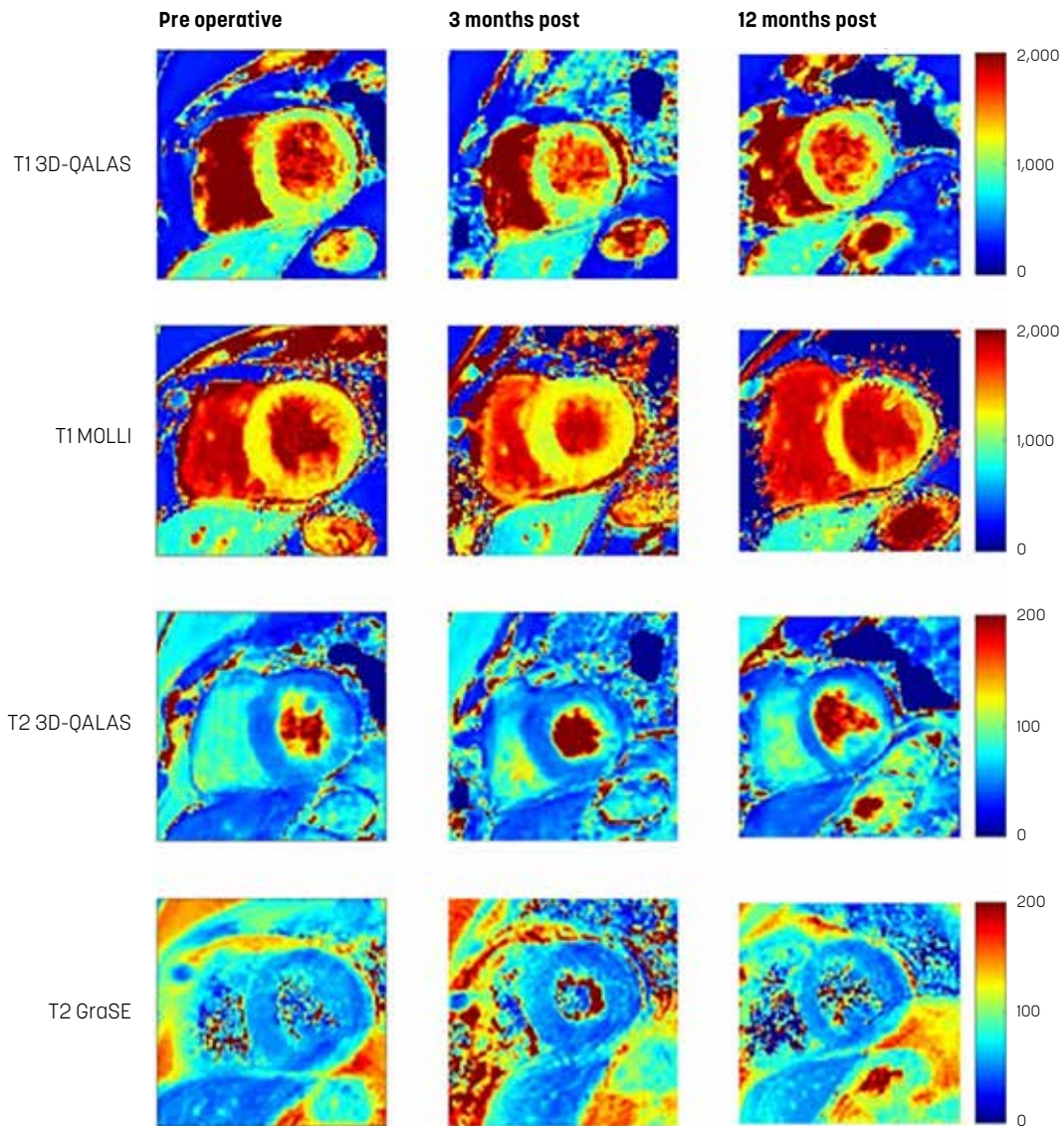


Illustration of mid-ventricular maps with 3D-QALAS, MOLLI and GraSE in a patient with severe aortic stenosis. The T1 and T2 relaxation times maps are acquired at three different time points: before, 3 and 12 months after surgery.

Kvernby et al.: Myocardial Relaxation Times After AVR

# Myocardial Perfusion by MRI without Contrast Media

**I**shemic heart disease is the most common cause of death in the western world. The disease is characterized by an impaired blood supply to the heart muscle caused by inadequate perfusion into the tissue. Perfusion of blood brings oxygen and nutrients into the tissue and washes out waste products.

Perfusion in the myocardium can be measured with several different techniques, the most common being scintigraphy, Position Emission Tomography (PET) and Magnetic Resonance Imaging (MRI). MRI has the advantage of not involving ionizing radiation. Contrast agents are, however, still necessary and involves a risk of side effects.

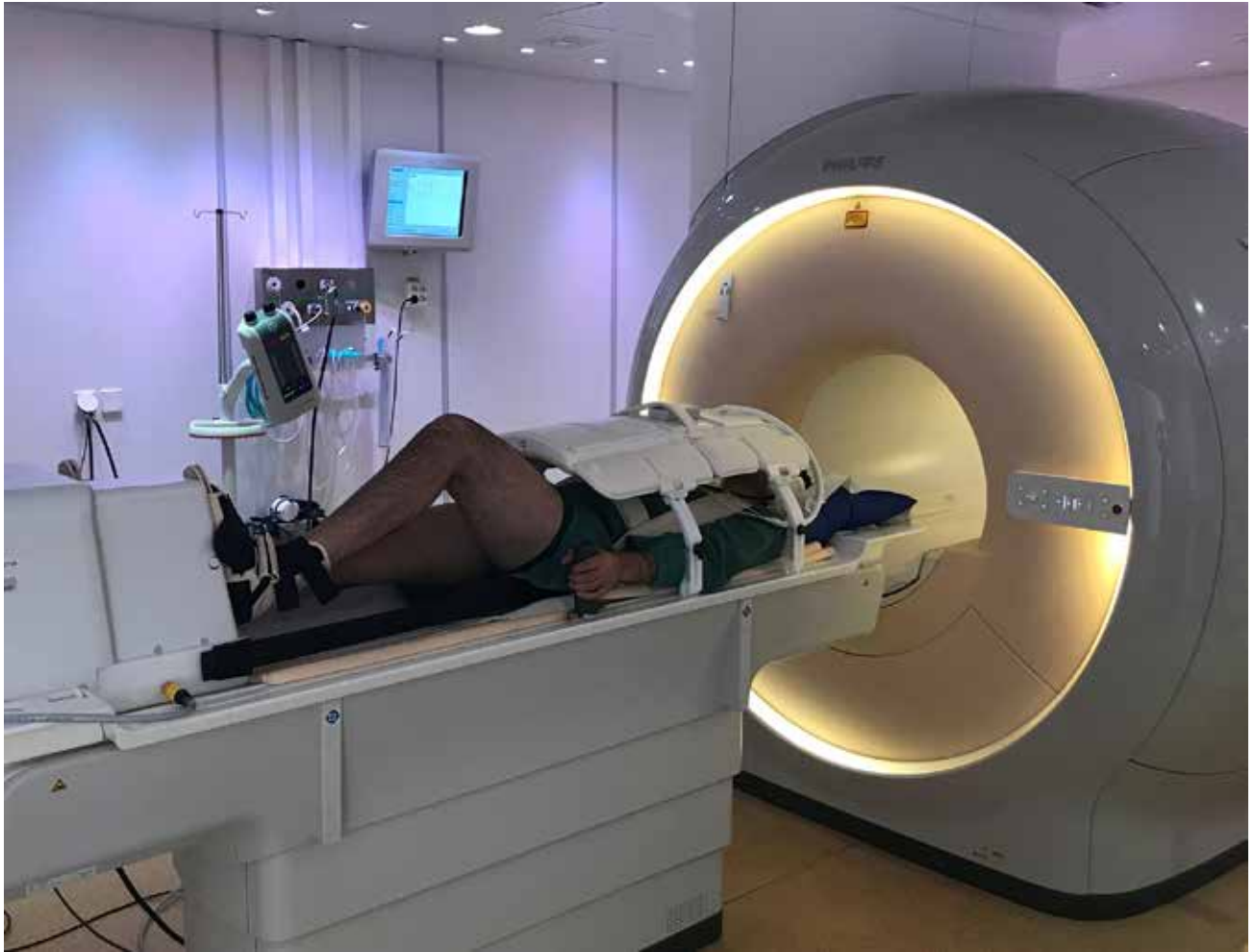
Arterial Spin Labeling (ASL) is a non-invasive MRI technique where the water protons of the arterial blood are magnetically labeled and used as an endogenous tracer. This technique has so far been used for measuring perfusion in the brain. However, performing ASL in the myocardium has several challenges due to movement and extensive blood flow around the myocardium.

After adjusting the ASL sequence into the cardiac context and to the available MRI-scanner, ten healthy volunteers were scanned using an advanced image acceleration technique called compressed sense. Acquiring the images in systole provided

an increased area of analyzable myocardium compared to the diastolic period of the heart cycle. This first study demonstrates the robustness of the ASL sequence.

In order to detect myocardial ischemia in patients, both rest and stress perfusion imaging is required. The second study in this project aimed to scan another 10 healthy volunteers during rest and exercise stress. The exercise set up used an in-bore ergometer with a step function, Figure 1. From the acquired images myocardial blood flow (MBF) was estimated and temporal signal-to-noise ratio (tSNR) was calculated. Example of perfusion maps for three subjects during rest and stress are shown in Figure 2 with considerably increased perfusion during stress compared to rest and overall good image quality. The mean heart rate during the stress scan was  $84 \pm 14$  bpm, significantly higher than during rest ( $63 \pm 11$  bpm) ( $p < 0.01$ ). The group mean MBF was also significantly higher during stress ( $2.8 \pm 0.9$  ml/g/min) compared to rest ( $1.2 \pm 0.6$  ml/g/min) ( $p < 0.01$ ). However, the tSNR was significantly lower during stress ( $7.4 \pm 3.8$ ) than rest ( $12.4 \pm 5.1$ ) ( $p < 0.01$ ).

This ASL technique appears robust and may offer an attractive approach for myocardial perfusion assessment during stress without the use of contrast agents or pharmacological stress. ◀



Step ergometer used for the exercise test. Exercise was performed in the scanner bore between breath holds when stress images were acquired.

**MRI** Cardiovascular

## Project information

### PROJECT NAME

Myocardial Perfusion by MRI without Contrast Media

### PROJECT LEADER

Johan Kihlberg, Department of Health, Medicine and Caring Sciences, Division of Diagnostics and Specialist Medicine

### MAIN PROJECT PARTICIPANTS

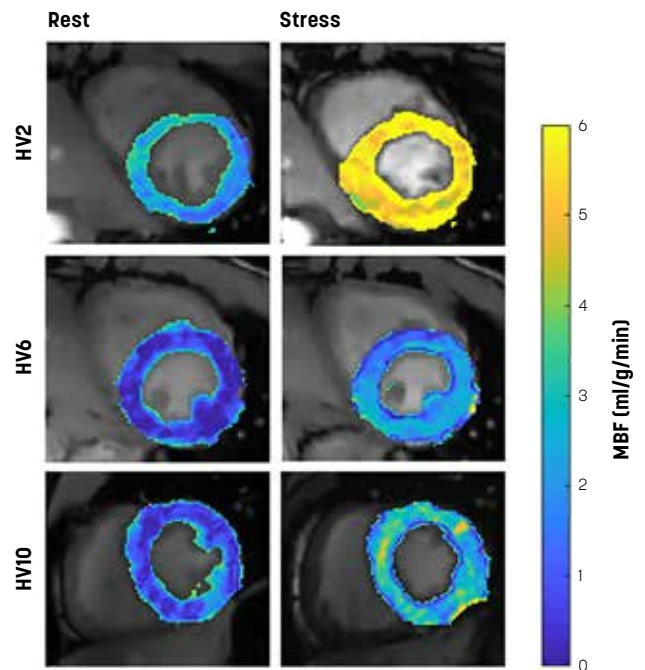
Markus Henningsson, Carl-Johan Carlhäll, Tino Ebbers

### GRANTS

Region Östergötland

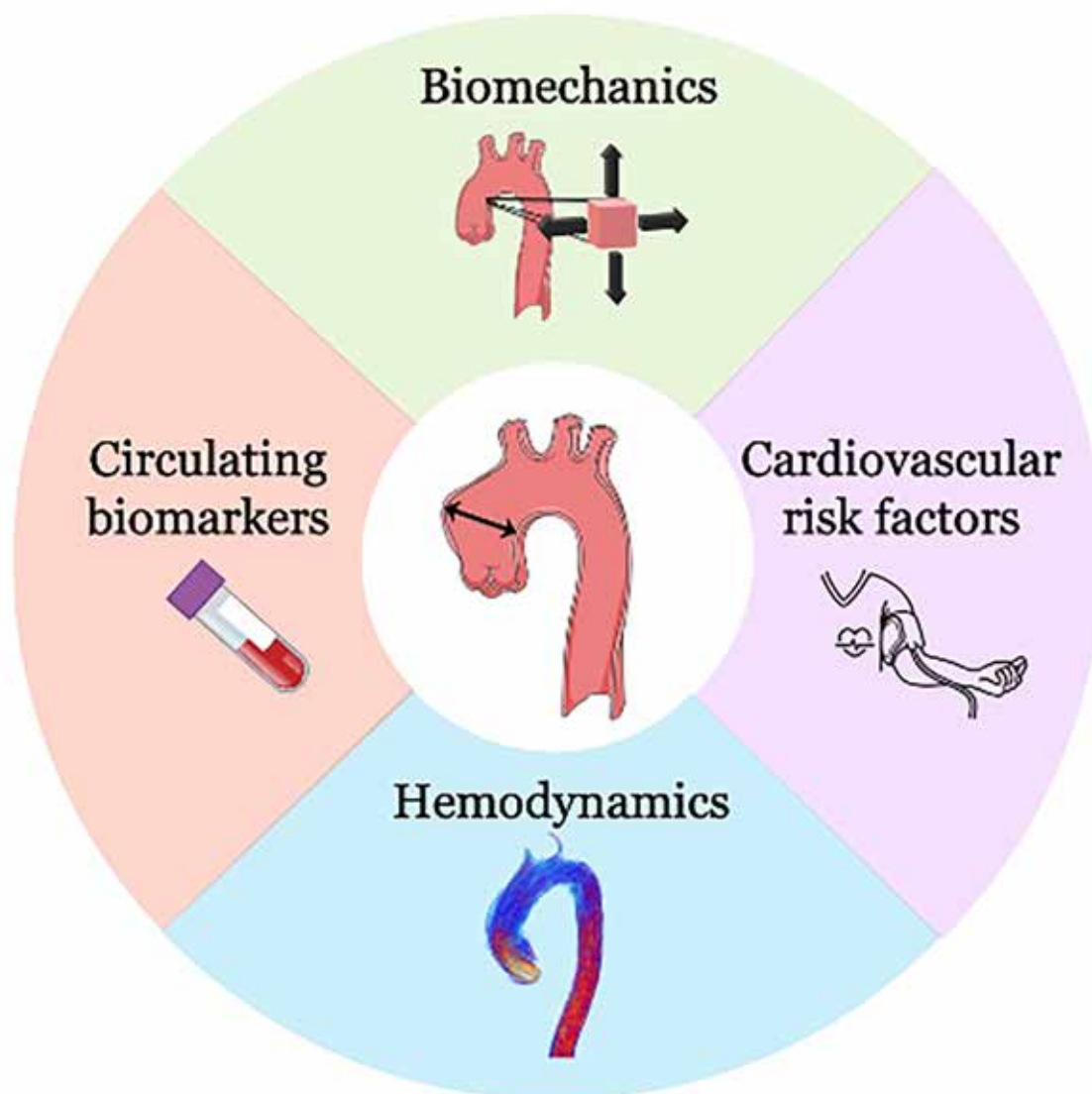
### KEY PUBLICATIONS

Henningsson M, Carlhäll CJ, Kihlberg J. Myocardial arterial spin labeling in systole and diastole using flow-sensitive alternating inversion recovery with parallel imaging and compressed sensing. *NMR in Biomedicine* (2020): e4436.



Example perfusion images for three healthy volunteers (HV2, 6 and 10) during rest and stress. Increased heart rate and myocardial blood flow (MBF) is observed during the stress test compared to rest.





**Project overview.** The overall purpose of the AscA project is to improve the characterization and risk-stratification of mild to moderate ascending aortic (AA) dilation. This will be achieved by a thorough analysis of cardiovascular risk factors and a comprehensive investigation the potential role of several novel hemodynamics, biomechanics and circulating markers in a unique cohort of individuals with mild to moderate AA dilation and age- and sex-matched controls. Annual follow-up measurements of AA diameter will provide data on growth rates and allow us to explore novel predictors of growth.



# Ascending Aortic Dilation

**A**scending aortic (AA) dilation is an increasingly diagnosed but poorly understood disease with asymptomatic progression and fatal end points such as dissection and rupture. Risk-stratification relies almost exclusively on surveillance of the lumen diameter, but it is well known that growth rate and risk of complications of AA dilation are not fully revealed by AA diameter.

The overall goal of this project is to identify new risk factors for AA dilation. The project challenges the current clinical paradigm which relies on AA diameter to risk stratify AA dilation. We hypothesize that hemodynamics, biomechanics and circulating markers can provide added value for the characterization and risk stratification of mild to moderate AA dilation and growth.

The project is divided into three aims. In Aim 1, AA diameter, a wide variety of cardiovascular risk factors and the burden of atherosclerosis will be measured and compared in all individuals with mild to moderate AA dilation (cases) and in age- and sex-matched controls with normal AA diameter in SCAPIS Linköping. In Aim 2, we will utilize, adapt and develop advanced methods to study the hemodynamics and biomechanics of the AA using magnetic resonance imaging (MRI) and apply these methods in all cases and controls. This comprehensive MRI study will be complemented by a panel of circulating markers. Relationships between AA dilation, hemodynamics and biomechanics, and circulating markers will be explored in a cross-sectional design. The AA diameter in cases will be measured annually during a 5-year period and the AA diameter in controls will be measured twice. In Aim 3, the impact of cardiovascular risk factors and atherosclerosis, hemodynamics

and biomechanics, and circulating markers on AA growth rate will be determined.

AA diameter is a blunt and insufficient measure to appropriately risk-stratify AA dilation. By mapping the characteristics of AA dilation, this project addresses important gaps in our clinical understanding of the disease. By using advanced MRI of hemodynamics and biomechanics as well as circulating biomarkers, the project has the potential to provide novel insights into the mechanisms of AA dilation and growth. By improving our understanding of AA dilation and exploring new measures to discriminate between cases and controls as well as to predict growth, this project may lead to new ways to risk-stratify patients with AA dilation. ◀

MRI   Ultrasound   Cardiovascular   Acquisition  
AI/Data analytics   Imaging Biomarkers

## *Project information*

### **PROJECT NAME**

Unraveling the mystery of ascending aortic dilation using advanced imaging and circulating biomarkers

### **PROJECT LEADER**

Petter Dyverfeldt, Department of Health, Medicine and Caring Sciences, Division of Diagnostics and Specialist Medicine

### **MAIN PROJECT PARTICIPANTS**

Chiara Trenti, Magnus Ziegler, Lena Jonasson, Eva Swahn

# Assessment of Cardiovascular Blood Flow

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

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

Despite the primacy of flow, cardiac diagnostics still rely almost exclusively on tools focused on morphological assessment. Flow characteristics are often assumed rather than measured directly. Suitable non-invasive tools for characterizing and measuring flow dynamics are needed to push our medical effectiveness to the next level.

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

The project makes use of 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, which was pioneered at CMIV, reveals blood flow patterns in the heart and the large vessels. By combining this approach with modelling approaches, more knowledge can be obtained from the measured data about the cardiovascular system under different conditions.

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, in-

terventional, and surgical therapies, and promoting exploration of new avenues for management of cardiac disorders can facilitate treatment of cardiovascular patients with higher quality and lower costs. ◀

MRI Cardiovascular Acquisition Modeling  
AI/Data analytics Simulation

## Project information

### PROJECT NAME

Assessment of Cardiovascular Blood Flow Using 4D flow MRI and Physiological Modelling

### PROJECT LEADER

Tino Ebbers, Department of Health, Medicine and Caring Sciences, Division of Diagnostics and Specialist Medicine

### MAIN PROJECT PARTICIPANTS

Carl-Johan Carlhäll, Jan Engvall, Petter Dyverfeldt, Gunnar Cedersund, Mariana Bustamante, Federica Viola, Kajsa Tunedal

### GRANTS

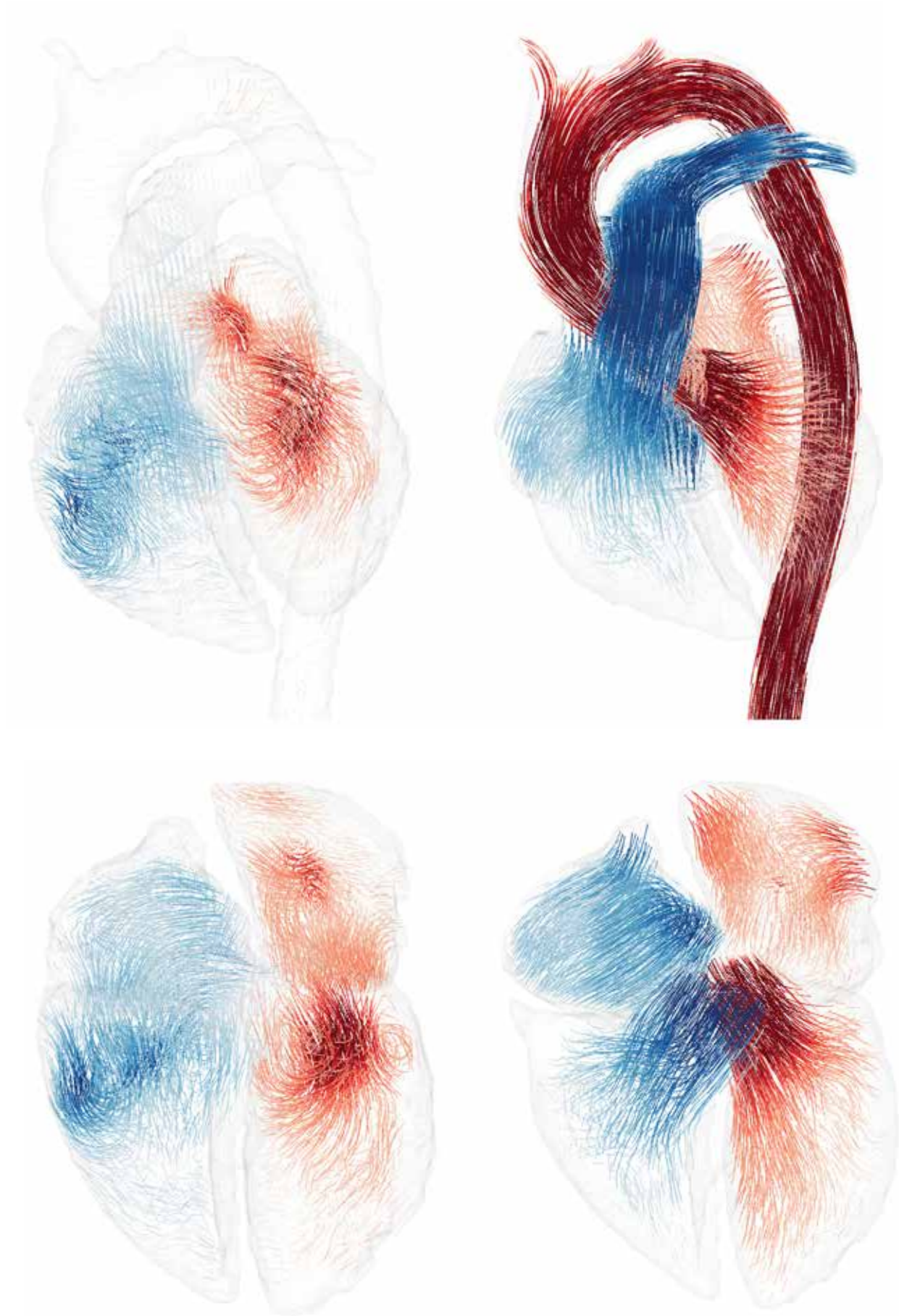
Swedish Research Council 2019–2022

### KEY PUBLICATIONS

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Garg P, Swift AJ, Zhong L, Carlhäll CJ, Ebbers T, Westenberg J, Hope MD, Bucciarelli-Ducci C, Bax JJ, Myerson SG. Assessment of mitral valve regurgitation by cardiovascular magnetic resonance imaging, *Nature Reviews Cardiology*, 1–15, 2019.



Blood flow in the left (red) and right (blue) side of the heart during left ventricular filling (left) and ejection (right). Segmentation of the blood pool (gray) are created automatically using atlas-based segmentations.

# 4D Flow CT

**A**dvanced 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.

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 as well as improved management of cardiac diseases.

Even though many forms of functional imaging data and modelling approaches are currently available, a gap persists between modelling and experimental research. This project has 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, 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.

The results show that the 4D Flow CT method can produce blood-flow patterns that are qualitatively and quantitatively similar to the current reference standard 4D Flow MRI, but at higher resolution. The high resolution also allows the simulated data to reveal processes that could not be studied before, like the coagulation of blood or the occurrence of turbulence in the blood flow.

One clinical application that is explored is in atrial fibrillation. These patients have an increased risk of blood clots 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 clots are forming. The goal is that the information from this model may be used to identify patients at risk.

The simulation-based approach potentially allows for studies of what-if scenarios where different treatment options can be explored. This is challenging, as the heart is complex and adapts

to changes in demand and constrains. A model is a simplified version of reality and there has to be a balance in the amount of details included and clinically usability. ◀

Computed Tomography MRI Cardiovascular Acquisition  
Modeling Simulation

## 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 Health, Medicine and Caring Sciences, Division of Diagnostics and Specialist Medicine

### MAIN PROJECT PARTICIPANTS

Anders Persson, Matts Karlsson, Carl-Johan Carlhäll, Lilian Henriksson, Sophia Beeck, André Da Luz Moreira, Faisal Zaman

### GRANTS

Swedish Heart Lung Foundation 2019–2021  
Visual Sweden / MeDigiT 2019–2021

### KEY PUBLICATIONS

Lantz J, Gupta V, Henriksson L, Karlsson M, Persson A, Carlhäll CJ, 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.

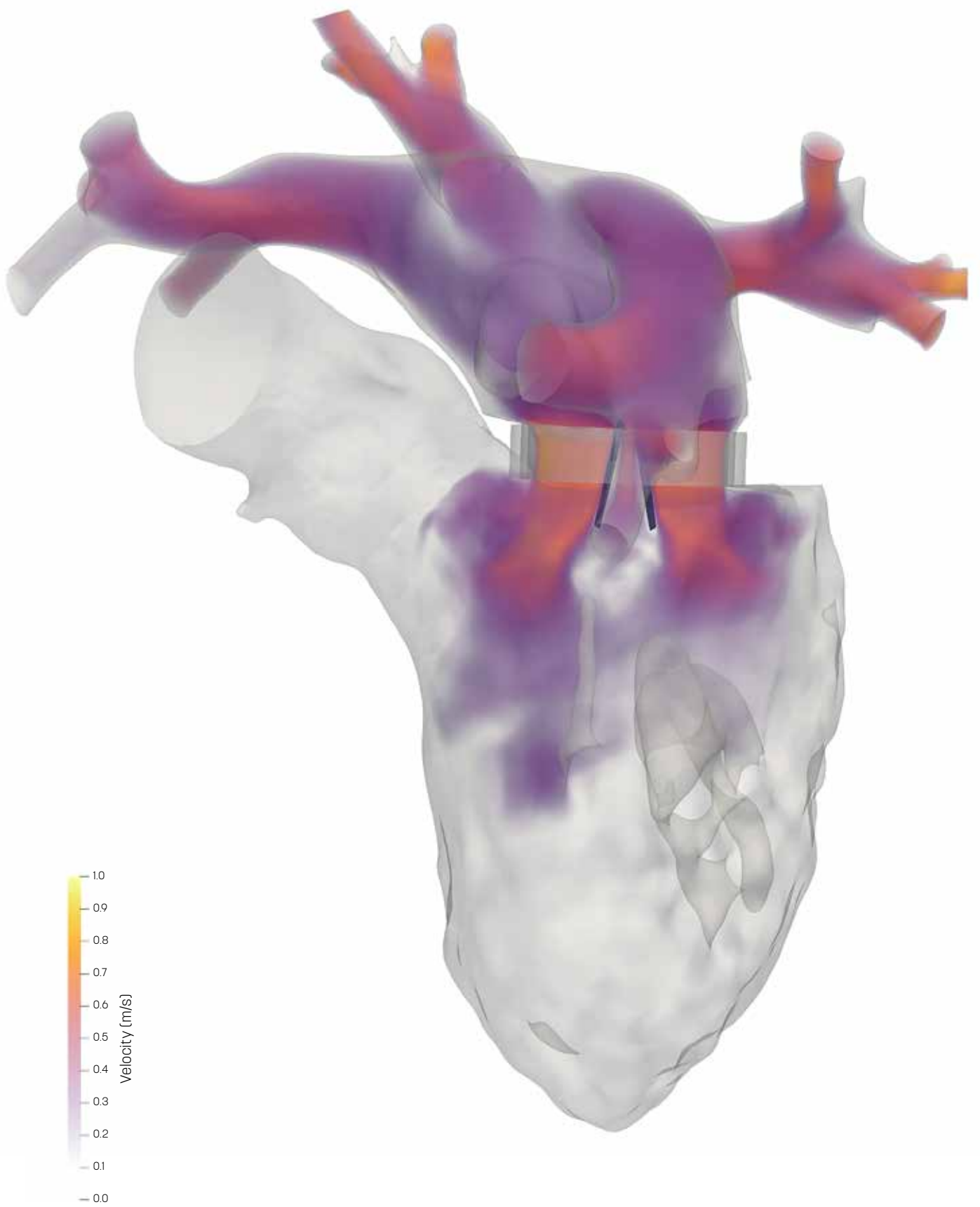
Lantz J, Gupta V, Henriksson L, Karlsson M, Persson A, Carlhäll CJ, Ebbers T.

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).





Virtually valve surgery by simulation of blood flow in the heart of a patient in which the competent native mitral valve is virtually replaced by a prosthetic mechanical valve.







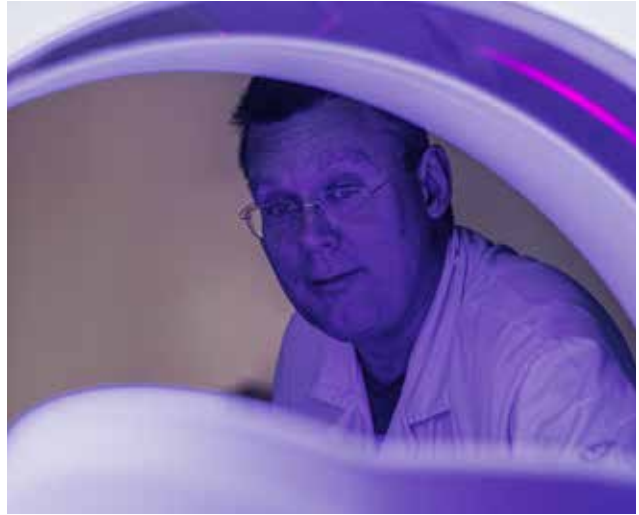
# The Project Path through CMIV

The Project Path through CMIV – a presentation of all the instances and key personnel that a research project passes at CMIV.





Håkan Gustafsson



Petter Quick



Lilian Henriksson



Jennie Kempfi, Biomedical Analyst at the Department of Physiology and Christer Holm.



Henrik Ekman



Marcelo Pereira Martins



Mona Cederholm



Martin Norling de Brun and Tobias Ekholm

# The Project Path through CMIV

Over the years since CMIV first was founded we have continued to grow. For every year there are more and more researchers who want to be affiliated. And with them new research projects start and the opportunity for translational research increases.

In order to meet the needs of all researchers our core staff have increased.

By the end of 2019, we finally knew that we had a deputy director coming. In March we welcomed Håkan Gustafsson, who now could lift off some burden from our director Anders Persson's shoulders. Håkan defended his thesis at CMIV in 2008 and his research area is in quantification and visualization of oxygen pressure and reactive species (e.g., superoxide radicals), oxidative stress and inflammation. He now works half-time as AI coordinator at the Region Östergötland and half-time as deputy director.

Håkan is the chairman of the scientific council and also leads the relatively recently established group of modality managers. He is the convener of the reg-

ular MR and CT research meetings open to all affiliated researchers.

All research projects that desire to use our modalities will be assigned one of our modality managers.

Petter Quick is in charge of our CT Force. Petter is also an application specialist at Siemens and a great resource when it comes to CT.

For the new Photon Counting Detector CT our research nurse Lilian Henriksson is the manager. She is also a PhD student, enrolled in CMIV Research School and always ready to give a helping hand.

The lion's share of all research at CMIV is performed on our MR-scanners.

Christer Holm is the manager of our 1.5T Philips MR, which is the most used MR scanner for cardiovascular projects. Christer has long and valuable experience of working with MR.

Henrik Ekman is in charge of the 3T Philips MR, former application specialist at Philips and a great asset.

Marcelo Pereira Martins is the manager of our 3T Siemens MR. He is also working close together with the neuro-

surgeons with the newly installed intra-operative MR at the Neurosurgical Clinic. Our Siemens MR scanner is the one most used for fMRI projects.

To start doing research at CMIV the PI has to be affiliated. After that there is an application form to fill in, in order to help us be as prepared as possible to help with the research desired.

The project application passes through the scientific council and when approved the assigned modality manager invites the research group to a start-up meeting.

At the start-up meeting our key resource when it comes to optimizing the use of the MR scanners, Mona Cederholm, attends as well. She is managing all our MR bookings.

With the large amount of data that is produced at CMIV there is a great need of IT support. For that we have increased our IT personnel and are now pleased to have welcomed both Martin Norling de Brun and Tobias Ekholm during the fall. They work hard with our IT infrastructure to make it run as smooth as possible. ◀





Azad Najjar, Sophia Beeck, Per Widholm, Robin Kämpe, Martin Lindvall, Deneb Boito, Marco Domenico Cirillo, Chiara Trenti and Milda Pocevičiute participating in a virtual PhD Seminar.



A person is seen from the side, sitting at a desk in a dimly lit room. They are looking at a laptop screen. The room has a blueish tint, likely from the laptop screen and ambient lighting. There are some shelves and equipment in the background.

# 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 25 PhD students admitted to the research school. Here a selection of them presents their research.

# fMRI Methods for Brain Tumour Treatment

**F**unctional 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 gray matter, one of the two main tissues types of the brain. Gray matter is found in the outer layers of the brain and is where brain processing takes place. However,

the brain is also composed of white matter, which constitutes around 50% of the brain mass, and serves to connect gray matter regions. This tissue has until recently been neglected in fMRI studies, due to questions about the mechanism by which the relevant signals are generated in this tissue, as well as the weakness of these signals in comparison to those generated in gray matter. Nevertheless, the developing consensus is that these

signals are meaningful, so the attention has to shift to the development of methods to address their weakness.

In our work we developed an improved method for detecting these signals that relies on knowledge of their spatial shape in white matter. Since white matter is made of long axonal strands, it has a very directed structure, and recent studies have shown that the fMRI signal in white matter follows this structure. To incorporate this knowledge into a standard fMRI processing pipeline, we devised a novel filtering approach informed by diffusion-weighted MRI, a modality that encodes the direction of the neuronal axons at every point in the brain. We evaluated our filtering approach on carefully constructed simulated data, as well as on real fMRI data from 100 subjects. Our results show that our method is capable of detecting very subtle activations that conventional methods cannot detect.

Recent advances in the study of fMRI in white matter can provide new ways of characterizing the brain and diagnosing diseases. Our work incorporates several of these advances, and we believe it can be helpful in reaching this goal. ◀

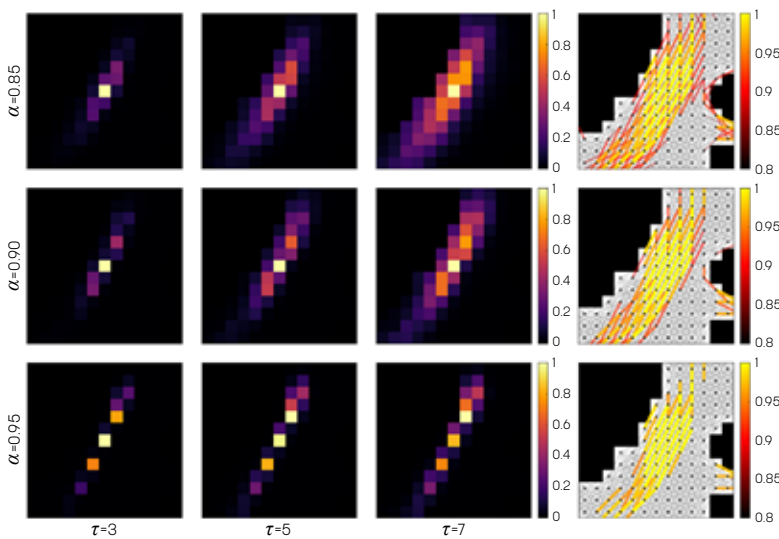
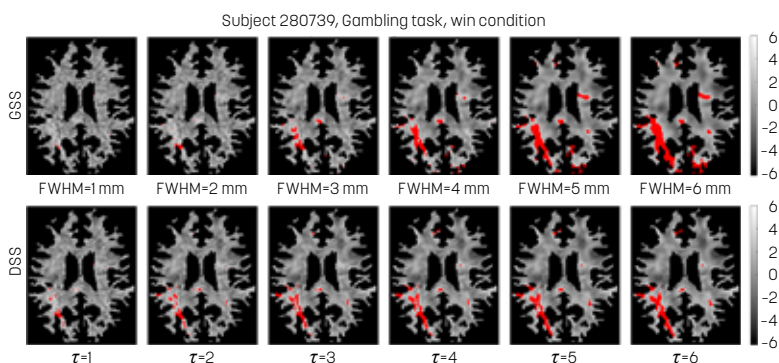


Illustration of the range of shapes that filters can take with the proposed method. While conventional fMRI analyses rely on isotropic (i.e., round) filters, our approach enables the definition of very slender filters that closely follow the orientation of neuronal axons.



Example of white matter activations detected with conventional methods (top) and the proposed method (bottom). Conventional methods result in blob-like detections and are incapable of separating signals from distinct but adjacent sources. On the other hand, our approach results in filters that adapt to the orientation of the signal and is capable of finding much subtler detections (lines, dots). In this figure, our method detects two separate parallel elongated activations on the bottom left of the brain, whereas these appear joined together for the conventional approach.

## PROJECT INFORMATION

### Supervisors

Anders Eklund, Evren Özarslan, Ida Blystad, Hamid Behjat

### Project

Methods for analyzing fMRI data – with applications to brain tumour treatment

### Short CV

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

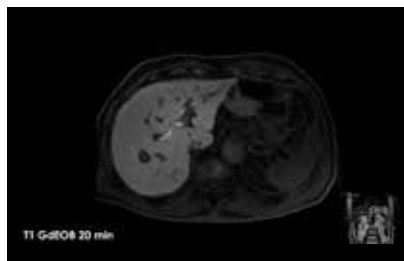
# Optimizing Hepatobiliary Contrast in Liver Imaging

Colorectal cancer is the third most common form of cancer worldwide. Though mortality has been relatively stable in the last decade, significant improvements have been achieved in terms of long-term survival. Key to improved survival is the detection of metastatic disease as early and completely as possible. In colorectal cancer, the most common site of metastatic disease is the liver, and the best method to detect metastases in this organ is MRI with hepatobiliary contrast media. However, the method is underutilized due to high cost, complexity and challenging interpretation.

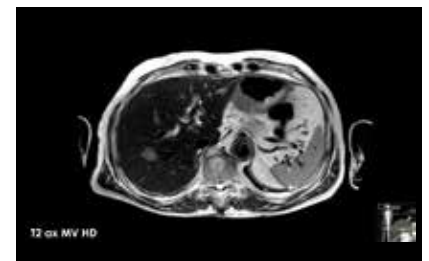
We aim to show that a shortened version of the regular MRI protocol with liver specific contrast can preserve comparable levels of sensitivity for metastases to the complete protocol while reducing complexity and scanning times. This will enable more patients to be evaluated without the need for more equipment and open the examination for acquisition at minor hospitals that normally would avoid these complex examinations.

Due to the nature of the shortened protocol, a drop in specificity is expected and will be measured. However, in real life, clinical decision-making never happens in isolation and always in the context of all available information and clinical data.

It is the aim of the next part of the project to study how a shortened protocol will affect the clinical decision making and treatment process of cancer patients. The patients will be presented in a simulated multidisciplinary team meeting, using all relevant clinical data and pri-



A T2-weighted image in the transversal plane showing the right liver lobe with a metastasis (marked with a dashed circle). The metastasis is well demarcated and is brighter than the surrounding liver tissue.



The metastasis is seen here in a T1-weighted image acquired 20 minutes after i.v. injection of the liver-specific contrast agent Gd-EOB-DTPA (Primovist®, Eovist®). Normal liver tissue and biliary ducts have high signal (light grey and white), whereas the metastasis has very low signal (black or dark grey) since it has no uptake of the contrast agent.

or examinations to evaluate if and how clinical management of the patient will actually differ when using a shortened rather than the complete protocol.

Finally, economic impact of using a more expensive contrast media – the only

monetary factor as of now that cannot be reduced – will be evaluated. In the last part, we will study if large scale introduction of such a method would be a financially viable and sustainable option for the public health service. ◀

## PROJECT INFORMATION

### Supervisors

Peter Lundberg, Nils Dahlström, Per Sandström, Mischa Woisetschläger

### Project

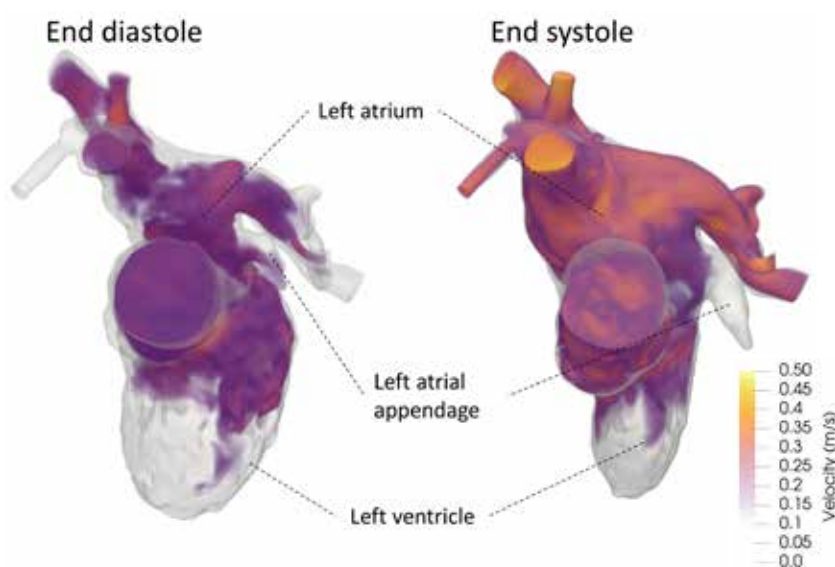
Optimizing the Use of Hepatobiliary Contrast in Metastatic Liver Disease (LiverMet)

### Short CV

Medical degree, Medical School, Justus-Liebig University, Gießen, Germany, 2002  
 Radiologist, Department of Radiology, University Hospital, Linköping, Sweden, 2010  
 Consultant Radiologist, Department of Radiology, University Hospital, Linköping, Sweden 2014–present



# Cardiac Blood Flow During Atrial Fibrillation Therapy



**A**trial fibrillation (AF) is a very common disease of the heart. It is characterized by an irregular contraction of the atria of the heart. This changed motion can lead to blood coagulation, which can cause stroke or myocardial infarction. In this project, we want to understand how the motion of the left atrium influences the blood flow and how the blood flow is changed in patients with atrial fibrillation.

We focus especially on a structure in the left atrium called left atrial appendage (LAA). The shape of left atrial appendage differs between people, but there are also differences in the contraction patterns.

There are two techniques to measure the geometry and motion of the heart in people: Computed tomography (CT) and magnetic resonance imaging (MRI). With MRI it is possible to directly measure the blood velocity in the heart

Blood flow in the left heart at end diastole and end systole, calculated based on time resolved CT images.

(4D flow MRI), however, the resolution of the images is relatively low, and it is difficult to measure low speeds. CT on the other hand produces images with a high resolution but does not provide direct velocity information and it exposes the patient to radiation. With the use of modern computers, we can calculate the velocity of blood inside the heart based on the high-resolution CT images. This way, we can also calculate the blood flow in regions where the blood speed is low and the risk for blood coagulation is high.

In the current stage of the project, we focus on improving the preprocessing of the data and decreasing the computation time in order to be able to apply the technique in a larger cohort of patients. This will allow us to study the relations between the blood flow in the left atrium and the risk of stroke. This information might lead to improved patient selection and therapy of atrial fibrillation. ◀

## PROJECT INFORMATION

### Supervisors

Tino Ebbers, Carl-Johan Carlhäll, Matts Karlson, Anders Persson

### Project

Simulation of time-resolved, three-dimensional cardiac blood flow from Computed Tomography (4D flow CT)

### Short CV

PhD student Linköping University, since November 2019

Research engineer at Linköping University, August 2018–October 2019

Master of Science, Mechanical Engineering, RWTH Aachen, Germany, October 2016–June 2018

Bachelor of Science, Mechanical Engineering, RWTH Aachen, Germany, October 2012–September 2016



# Spectral CT for the Musculoskeletal System

**M**agnetic resonance imaging (MRI) has been the modality of choice for imaging of soft tissues such as muscles, ligaments, and menisci as well as cartilage because of its unparalleled soft tissue contrast. The drawback is that it is usually less available, the cost is relatively high, and patients must be able to lie still to avoid reduced image quality due to motion. Metal implants and cardiac pacemakers can make MRI contraindicated or reduce image quality significantly.

Computer tomography (CT), on the other hand, is readily available, cheaper, and fast. To the present its usefulness in musculoskeletal imaging has been mostly limited to fracture detection. Soft tissue contrast between different tissues is low meaning many abnormalities cannot be visualized. CT also imposes radiation whereas MRI does not.

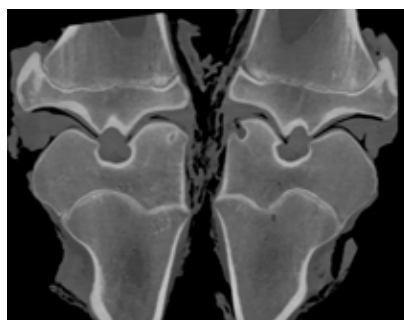
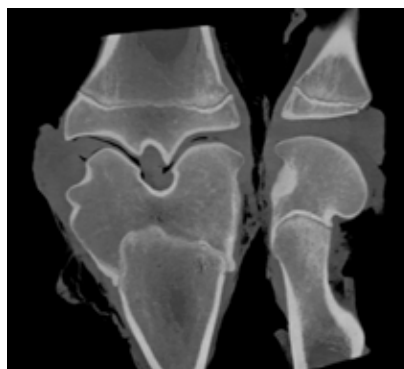
Therefore, new types of CT scanners are being developed e.g., the Photon-Counting-Detector-based CT (PCD-CT). Such a research machine has recently been installed at CMIV as one of very few whole-body PCD-CT in the world. It differs from conventional CT in that the x-ray photons are no longer converted to visible light before generating an electrical signal. Instead the incoming photon directly generates the electrical impulse. This increases the spatial resolution, reduces image noise and radiation dose. Also, the PCD-CT has the potential to discriminate different types of tissue as well as to remove certain elements from the image, such as calcium in bone, to visualize previously hidden information.

The BoCaSt project aims at developing imaging for the musculoskeletal system and more specifically visualizing ligaments and cartilage in the knee joint using the PCD-CT. First this will be done on animal tissue followed by human studies. Other uses within the musculoskeletal system would be maintaining details while markedly reducing radiation dose as well as improving imaging of bone ad-

ja cent to metal implants, such as screws and prostheses, which now is obscured by metal artefacts.

The possible capabilities and advantages of this machine are thrilling. As this is one of very few machines of that

kind in the world and with the research environment provided by the CMIV we possess an ideal position to bring imaging into the future with decreased radiation, higher precision, and revelation of previously hidden information. ◀



Images of the knee joint from a cow specimen obtained with the Photon Counting Detector CT.



3D reconstructed images of the skeleton of a chicken specimen obtained with the Photon Counting Detector CT.

## PROJECT INFORMATION

### Supervisors

Anders Persson, Seppo K Koskinen, Håkan Gauffin, Alexandr Malusek

### Project

Bone Cartilage Soft Tissue Photon Counting (BoCaSt)

### Short CV

Doctor of Medicine (MD), Linköping University, 2010

Resident in Radiology, Radiology Department at Linköping University Hospital, 2012–2020

Radiologist, Radiology Department at Linköping University Hospital, 2020–  
PhD student, 2020

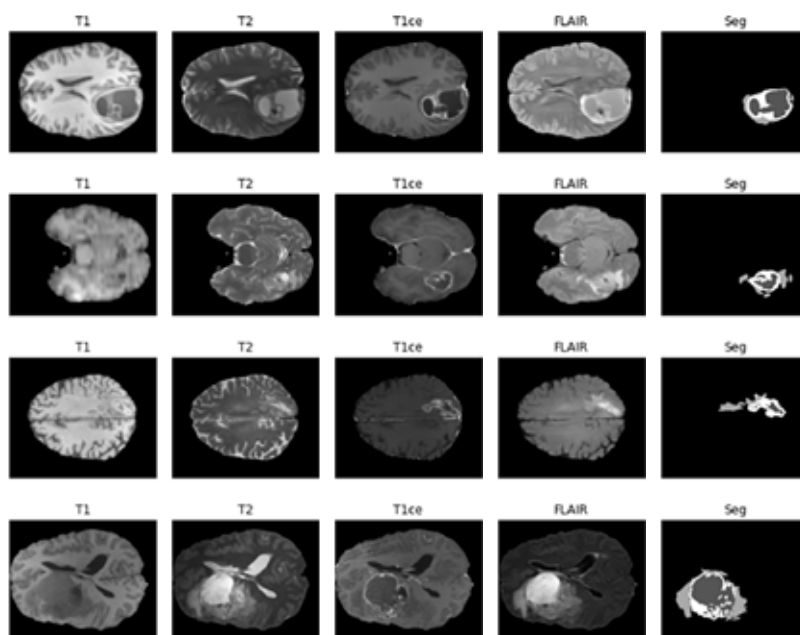
# Deep Learning for Image Segmentation

**M**y research focuses on medical image segmentation using artificial intelligence, deep learning to be specific. Segmentation is important for many medical applications, since the type of treatment often depends on how big a brain tumor is, or how large a burn wound is. Despite this fact, image segmentation is often performed manually by a medical doctor, but manual segmentation is very time consuming, especially in 3D. It is therefore of interest to develop automatic segmentation algorithms, that can save time for medical doctors.

In my most recent work, I started doing image segmentation in 3D to segment brain tumors from multi-channel MR images, see figure. I developed a Generative Adversarial Network (GAN), which is a network composed by two convolutional neural networks (CNN:s), called generator and discriminator, respectively. The first CNN generates the brain tumor segmentation, whereas the second certifies that the generated image looks like a realistic segmentation. Moreover, I also focused on image augmentation, which is a technique used to increase

the size of the available image dataset. Often, in medicine the number of images provided for research is not sufficient to train a deep network.

Image augmentation transformations such as rotation, flipping, elastic deformations, brightness changes, etc., are therefore essential to give to the network more images to train with, and also to avoid under and over-fitting. I therefore investigated which kind of image augmentation techniques that are useful for 3D brain tumor image segmentation, using the Brain Tumor Segmentation (Brats) 2020 challenge dataset. Even though the Brats dataset contains training data from 369 brain tumor patients, we show that augmentation can significantly improve the segmentation accuracy. ◀



Four training examples in the Brats 2020 dataset. From left to right: T1W, T2W, T1w with contrast, T2W FLAIR, ground-truth segmentations. Peritumoral edema (ED), necrotic and non-enhancing tumor core (NCR/NET), and GD-enhancing tumor (ET) are highlighted in silver, dark grey and white respectively.

## PROJECT INFORMATION

### Supervisors

Anders Eklund, Göran Salerud, Ida Blystad

### Project

Methods in Neuroimaging

### Short CV

Bachelor's degree in Information Technology at the University of Padova, Italy, 2013  
Master's degree in Bioengineering at the University of Padova, Italy, 2016  
PhD student in Biomedical Engineering at Linköping University, Sweden (ongoing)

# <sup>18</sup>F-FDG Uptake in Carotid Plaques, Using PET/MRI

**Background:** Death in cardiovascular disease is often caused by the rupture of atherosclerotic plaques resulting in a heart attack or stroke. Plaques with a high content of fat and blood (caused by bleedings inside plaque)

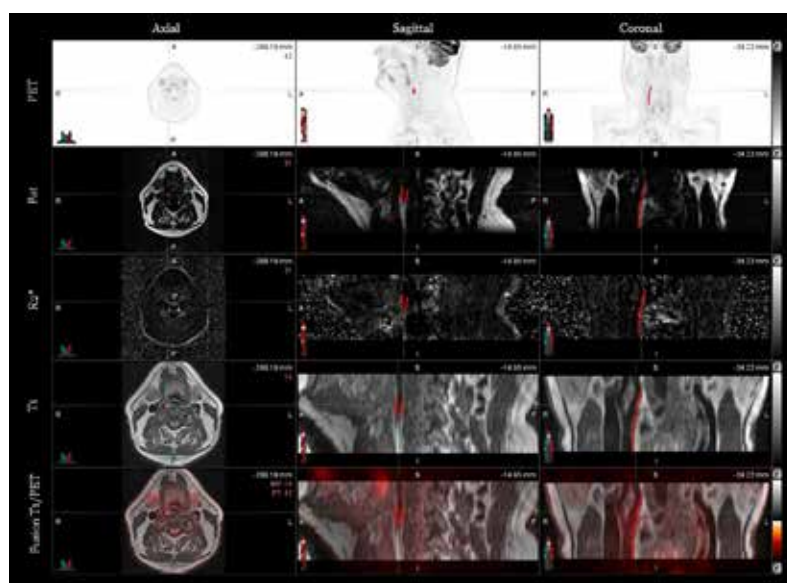
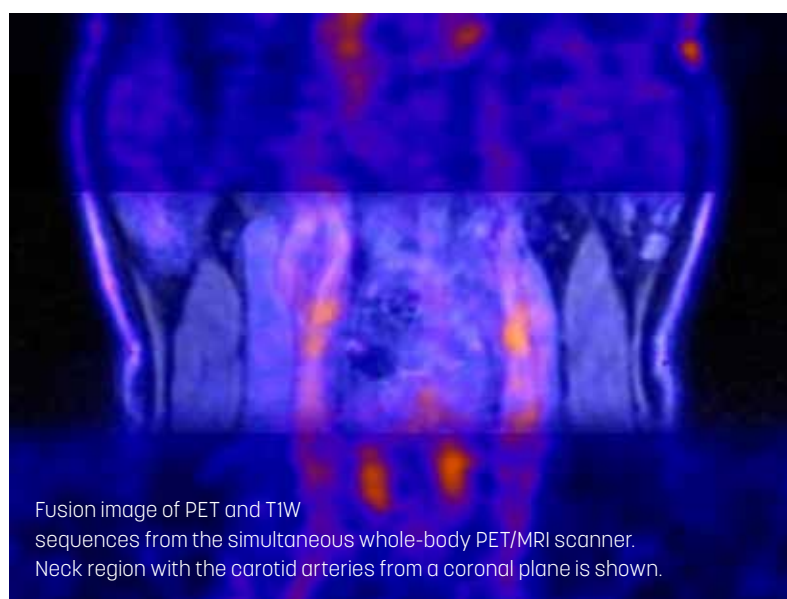
are known to be especially vulnerable and it is also known that inflammation is a process that accelerates the plaque towards rupture. However, no-one has previously assessed the quantitative relationships between plaque inflammation and

plaque components like fat and blood.

**Aim:** Since this is not previously done, we wanted to explore a new method for investigating the quantitative relationship between fat and blood inside carotid plaques and inflammation in the same plaques. To this end we used a simultaneous whole-body PET/MRI scanner that has the possibility to generate both MRI and PET images at the same time. This current study is a pilot study.

**Methods:** Twelve patients with high-grade carotid artery stenosis were enrolled in the study. The extent of fat and blood was quantified from a previously validated but new quantitative magnetic resonance imaging (MRI) technique, in a stand-alone MRI scanner. PET/MRI was used to measure <sup>18</sup>F-FDG uptake (a measure for inflammation) in the plaques alongside T1W sequences for anatomical bearings. The different images were then synchronized to generate localized plaque data both for inflammation and for plaque components.

**Results and conclusion:** It was possible to access reliable and quantitative data from the carotid plaques using our method. The plaques were heterogeneous with respect to their volumes and composition. The results we received did not indicate any linear relationships between FDG, fat and blood. However, this pilot study was not powered for statistically significant correlations and for a thorough analysis of the interdependence of these plaque characteristics a larger and adequately powered study would need to be done. ◀



The figure illustrates the segmentation and fusion methodology applied in the current study. Segmented carotid plaque is shown in red. Axial, coronal and sagittal planes are automatically aligned for PET, fat, R2\* and T1W images.

## PROJECT INFORMATION

### Supervisors

Ebo de Muinck, Petter Dyverfeldt

### Project

CARMA-PET Study

### Short CV

Degree of Master of Science in Medicine. Medical School, Linköping University, 2012

Resident physician in cardiology and internal medicine, Department of Cardiology, Region Östergötland, 2015–present

# Improving the Accuracy of Coronary CT Angiography

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 making it possible to see plaques in the vessel wall. CCTA has a high sensitivity for detection of coronary stenoses whilst the specificity is lower due to a tendency to overestimate the stenosis degree.

As a result patients sometimes end up being unnecessarily sent for further evaluation with invasive coronary angiography. Coronary angiography is considered to be the reference method for stenosis evaluation when the Fractional Flow Reserve (FFR) i.e., pressure drop caused by the stenosis is measured.

## PROJECT INFORMATION

### Supervisors

Anders Persson, Jan Engvall, Tino Ebbers, Mischa Woisetschlager

### Project

Measurement of the Transluminal Attenuation Gradient (TAG)

### Short CV

Radiology nurse, 2005

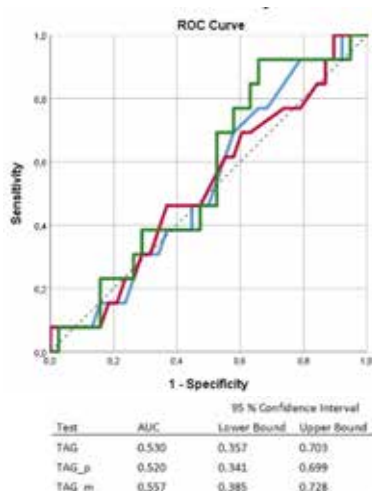
Master's degree, 2013

CT Research nurse, 2015

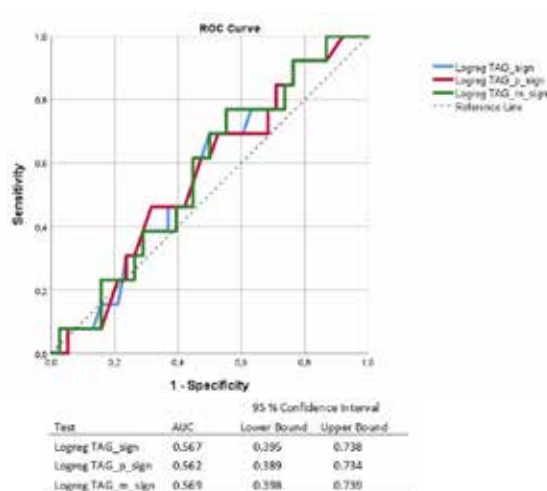
A method for improving the accuracy of CCTA is highly sought after. Measurement of the transmural attenuation gradient (TAG) has been proposed as an alternative to other existing methods i.e.,

CT perfusion and CT FFR. The theory behind TAG is that the contrast attenuation in the vessel reflects the flow of contrast through that vessel.

By measuring the attenuation at small



**Figure 1.** Receiver operating characteristic curves for the diagnostic accuracy of semi-automatic TAG including attenuation measurements of the entire ostium around the centerline and manually measured TAG using fractional flow reserve (FFR) measurements  $\leq 0.80$  as reference.



**Figure 2.** Receiver operating characteristic curves for the diagnostic accuracy of probability values derived by logistic regression between the coronary CT angiography (CCTA) assessment and semi-automatic TAG including attenuation measurements of the entire ostium TAG in a 3x3 pixel patch around the centerline and manually measured TAG using fractional flow reserve (FFR) measurements  $\leq 0.80$  as reference.



## Fibrosis and Heart Function in Aortic Stenosis

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. 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. The purpose of this project was to evaluate the incremental value of three types of TAG in high pitch spiral CCTA with invasive FFR measurements as reference. TAG was measured using two semiautomatic and one manual method. A receiver operating characteristic (ROC) analysis was made to determine the usefulness of TAG alone as well as TAG combined with CCTA for detection of significant coronary artery stenoses defined by an invasive FFR value  $RO.80$ .

A total of 51 coronary vessels in 37 patients were included in this retrospective study. Hemodynamically significant stenoses were found in 13 vessels according to FFR. The ROC analysis TAG alone resulted in area under a curve (AUC) of 0.530 and 0.520 for the semi-automatic TAG and 0.557 for the manual TAG (Figure 1). TAG and CCTA combined resulted in AUC:s of 0.567, 0.562 for semi-automatic TAG and 0.569 for the manual TAG (Figure 2). The results from our study showed no incremental value of TAG measured in single heartbeat CCTA in determining the severity of coronary artery stenosis degrees.

We believe that TAG, at least in the present form, should not be used as an alternative to CT perfusion and CT-FFR. ◀

**A**ortic stenosis (AS) has a prevalence of 12% at the age of 75 and increases along with the elderly population. The only treatment for severe aortic stenosis is prosthetic implantation, aortic valve replacement (AVR). Intraoperative risk is low, but studies have shown the presence of focal myocardial fibrosis in approximately one fifth of the patients undergoing AVR. Focal fibrosis is known to cause impaired left ventricular function (LVF) and shorten survival. AS causes pressure overload in the left ventricle (LV). Compensatory mechanisms include concentric hypertrophy and diffuse interstitial fibrosis. In literature there is little information available on how the diffuse fibrosis (DF) affects LVF and whether these changes are reversible over time. Cardiac magnetic resonance tomography (CMR) is a promising way to image the diffuse fibrosis, but the optimal CMR method for clinical use has not been established yet. The aim of the doctoral thesis is to demonstrate the presence of diffuse my-

ocardial fibrosis and to investigate how it affects cardiac function before and after surgical intervention.

60 patients with severe aortic stenosis are included in the study. Preoperatively, 3 and 12 months postoperatively, patients undergo CMR to image the diffuse fibrosis and evaluate the left ventricle remodelling. Echocardiography examination is also performed to evaluate the LV function and remodelling. Inclusion is finished but we are awaiting the last follow ups. We have started the image processing and data extraction from the examinations performed.

Present guidelines recommend AVR when symptoms or LV dysfunction is present. The risk of permanent scarring is imminent. There is a need to develop non-invasive diagnostic tool for better understanding the heart's adaptation to AS both before and after surgery. This project has the potential to improve cardiac imaging techniques of patients with aortic valve disease. ◀

### PROJECT INFORMATION

#### Supervisors

Éva Tamás, Jan Engvall, Eva Nylander, Hans Granfeldt, Tino Ebbers

#### Project

Diffuse myocardial fibrosis and heart function in patients with aortic stenosis

#### Short CV

Medical degree, 2009

Licensed physician, 2011

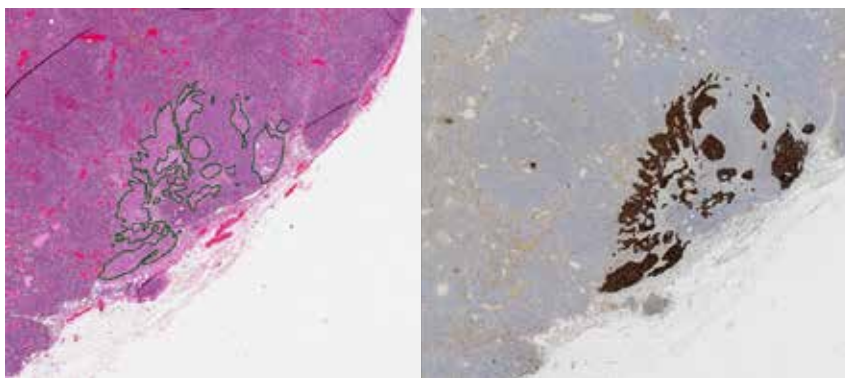
Specialist in cardiothoracic surgery, 2018

Physician at the Thoracic Clinic, the University Hospital, Linköping, 2011–ongoing

# Deep Learning as an Aid for the Pathologist in Cancer Diagnostics

Clinical pathology is essential for diagnosing cancer. Today, the demands on pathology increases with more requests of parameters and analyses, and at the same time there is a shortage of pathologists. The introduction of digital pathology opens up opportunities of novel workflows and potentially enhanced diagnostics. Digital pathology means that histopathological glass slides are scanned with a high-resolution glass slide scanner, and the pathologist analyses the slides directly on a computer screen rather than using a microscope. At the pathology department in Linköping they have been scanning all the histopathological glass slides since 2011, making over 2 million digital slides stored in the digital archive. To fully reach the potential of digitized pathology, the next step is the introduction of image analysis, that potentially could lead to more efficient and accurate diagnostics. Today computational pathology research groups develop image analysis tools based on machine learning algorithms. The field is moving towards more complex analysis options, applying so called deep convolutional neural networks, also called deep learning. Studies with deep learning image analysis have been performed on digitized histopathology cases, e.g., for detecting prostate cancer and lymph node metastases.

In this project we aim to develop and evaluate algorithm-based tools to aid pathologists in diagnosing and staging cancer. Important questions are: How accurate are algorithms at detecting cancer cells on digitized histopathology material? How can we transfer image analysis algorithms to clinical settings?



Example of annotated metastasis (stained with hematoxylin and eosin respectively immunohistochemical stain).

We initially focus on evaluating an algorithm for detecting lymph node metastases in breast cancer cases. The algorithm is developed and trained at Radboud University Medical Center in Nijmegen in the Netherlands. An important step is to be able to transfer or generalize the algorithm to material from another setting. During 2019, a large dataset of digitized histopathological slides of axillary lymph nodes from breast cancer cases was collected, anonymized, and transferred from the clinical digital archive to a research environment simi-

lar to the clinical working environment (AIDA PACS). The dataset is published on the AIDA Datahub. Lymph nodes with metastases are detailed annotated by a pathologist (resident) with help from an immunohistochemical stain that indicates breast cancer cells. The algorithm will then be evaluated and the consistency with the pathologist annotations but also with already reported findings. Inconsistent results will be re-examined. Further actions will be studying steps towards implementing an algorithm-based tool in a clinical setting. ◀

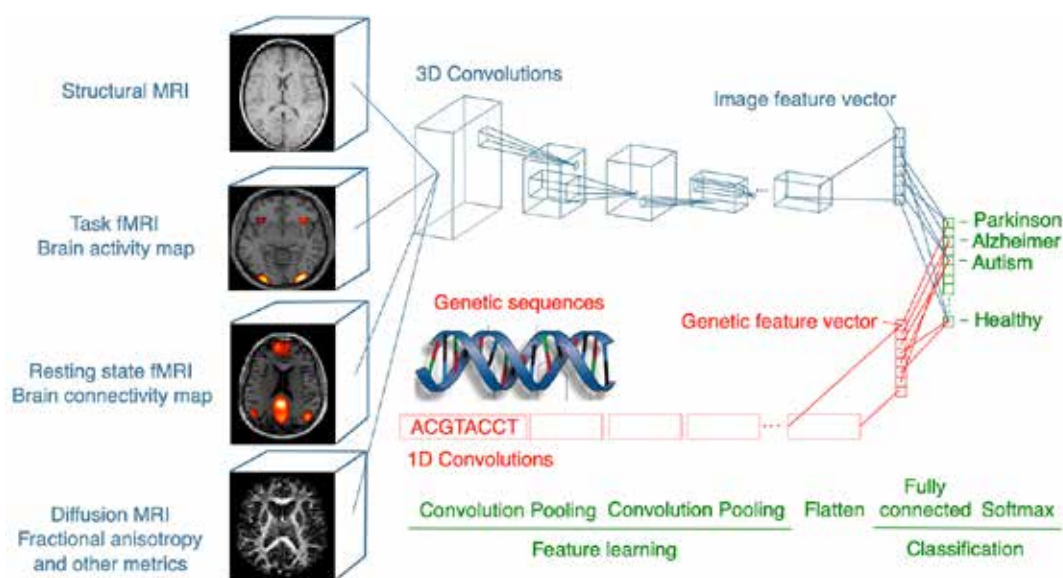
## PROJECT INFORMATION

### Supervisors

Jeroen van der Laak, Darren Treanor, Claes Lundström

### Short CV

Residency in Clinical Pathology, Linköping University Hospital, 2016–present  
Medical degree, Lund University, 2013



Imaging data and genetic data can be combined in a deep neural network, by deriving an image feature vector and a genetic feature vector that are then combined prior to the final dense layers.

## Neuroimaging Genetics

The project aims to develop ways of detecting diseases of the brain in early stages by combining imaging data with genetic information. A combination of new developments in machine learning and the advent of several open brain imaging databases makes it feasible to train machine learning models to predict conditions such as Alzheimer's disease, Autism Spectrum Diseases, Parkinson's disease, Schizophrenia etc.

Magnetic resonance imaging has provided medicine with a method to relatively economically get images superior to X-rays and its newer 3D-version computed tomography, without exposing patients to ionizing radiation. The technology is still advancing, and better images and new sorts of images are being developed all the time. While this project

is not concerned with the acquisition of such images, we do use this material as it is being made available to us.

Genetic sequencing has provided us with an even more exact knowledge not only about the genome of a human, but of the total variability of the genome taken over the entire human population. With this sort of information readily available from free databases and the availability of biochips that cheaply can analyze genetic variations in 10<sup>5</sup>–10<sup>6</sup> positions spread over the entire genome, this is also a very promising source of information.

Machine learning has been advancing by leaps and bounds over the last decade. Driven by both hardware development and the demand from companies for trainable models of everything, from recommending music to producing real-

istic human speech or even imagery. We are trying to put these techniques to use for transforming the different sources of information available to high quality predictions about conditions of the brain. ◀

### PROJECT INFORMATION

#### Supervisors

Anders Eklund, Markus Heilig, Evren Özarslan

#### Short CV

Master of Science, Chemical engineering, Lund University  
 Master of Science, Bioinformatics, Lund University  
 MD, Copenhagen & Lund University

# Deep Learning Applied to Multimodal Datasets in Psychiatry

Among all medical conditions, major depressive disorder (MDD) is a world leader in terms of years of productive life lost due to illness. This loss of productive life is due to a higher risk of suicide for people suffering from depression, but it is also caused by depression's negative effect on work and family relations. Scientists have for a long time tried to understand the underlying brain mechanisms of depression and have made important advances. There are, however, still no good objective biomarkers that can determine if someone has depression or predict whether a patient could benefit from a specific treatment. In this project we want to develop deep learning methods that could help us address these challenges. Our plan is to apply a deep learning algorithm to a large, open repository of structural and functional neuroimaging data from depressed and never-depressed individuals.

This deep learning algorithm can detect patterns that are often undetectable when using more traditional “mass univariate” methods. The algorithm will first be trained and tested using only anatomical data, and next on the neural functional data and, finally, on a combined anatomical plus functional dataset. We can then compare what kind(s) of data result in the best performance of the deep learning network in terms of distinguishing healthy from depressed individuals.

Provided that one or more modalities of neuroimaging data are useful in distinguishing depressed from never-depressed categories, we can advance the theoretical neuroscience of MDD by determining which neural features most inform accurate categorization of disordered and non-disordered subjects.

What region or brain function allows us to tell the difference between a healthy

and depressed individual? A question like this can be addressed by using a different kind of deep learning network: A network that produces artificial brains. Specifically, this generative network will be trained to translate from a healthy brain to a depressed brain. Then, by subtracting the fake depressed brain from the real healthy brain we will be able to tell what the deep learning network

changed in the healthy brain in order to make it look depressed. By applying the same kind of approach, we could, e.g., find the neural differences between depressed individuals, who respond well to a specific treatment and others who did not respond to this treatment.

Applying techniques such as those presented here could strongly advance personalized medicine in psychiatry. ◀



A synthetic 3D image of a brain created with a progressive growing GAN network. Training the algorithm took four days using a 4 Tesla V100 graphics card.

## PROJECT INFORMATION

### Supervisors

Markus Heilig, Anders Eklund, Paul Hamilton

### Project

Deep learning applied to large and small multimodal datasets in psychiatry

### Short CV

Center for Medical Image Science and Visualization (CMIV) and Affective Neuroscience, Part time employee, Linköping University, Research Engineer, 2019–present

Center for Social and Affective Neuroscience (CSAN), Linköping University Research Engineer, 3/2015–present

Department of Medical Radiation Physics, Lund University, Stipend worker, 7/2014–3/2015

Radio Therapy Center, Linköping University Hospital, Medical assistant, summers of 2013–2014

Master of Science (M.Sc) Medical Physics, Lund University, 2014 Licensed Medical Physicist



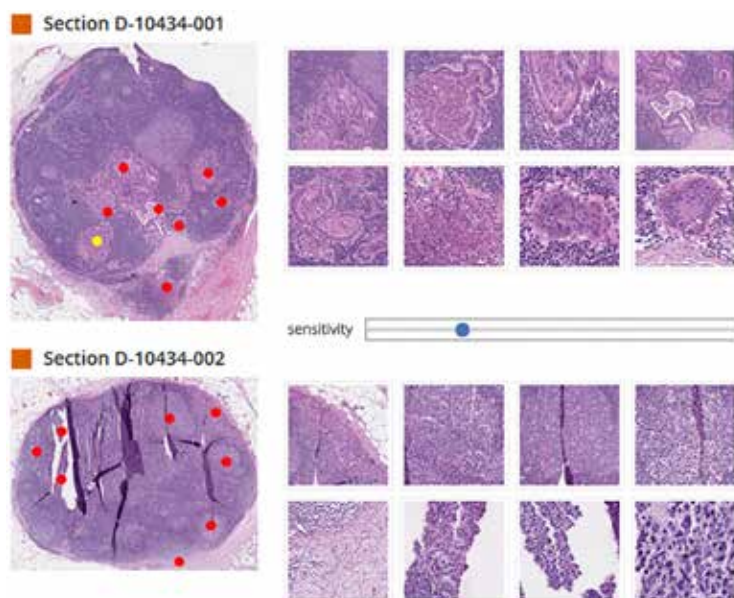
# Human-AI Interaction for Medical Imaging

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.

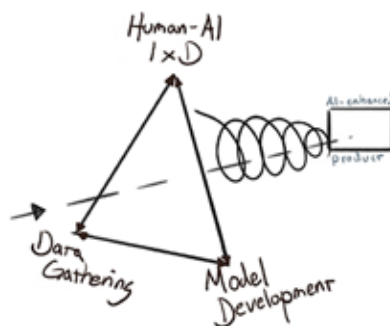
This research project explores the technical and human factors that lead to successful human-machine cooperation when humans interact with narrow artificial intelligence. The research subjects are primarily human computer interaction and technological design. Secondly the research involves medical visualization,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

With roots in constructive design research, projects are 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. ◀



User interface for rapidly staging lymph node sections for metastasis. The pathologist is guided through a ranked list of detection candidates. The sensitivity can be increased if the preliminary results indicate the patient is close to a decision-cutoff. This allows an adaptable pace of work, working fast when possible and slow when needed.



Description of the key elements for an iterative design process for software with predictive capabilities through applying machine learning in the development process.

## PROJECT INFORMATION

### Supervisors

Jonas Löwgren, Claes Lundström, Darren Treanor, Anders Ynnerman

### Project

AIDA Datahub

### Short CV

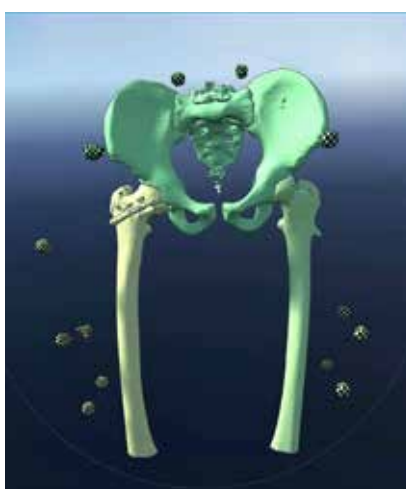
M.Sc, Cognitive Science, Linköping University, Sweden, 2012  
Senior Software Engineer at Sectra

# The Pathomechanism of Idiopathic Scoliosis

Scoliosis is a disorder of the spine characterized by a deformity in three dimensions. While some forms of scoliosis have a known origin, e.g., due to neuromuscular disease or congenital defects, the cause of idiopathic scoliosis remains unknown. Potential factors for disease and deformity progression includes genetics, the musculoskeletal system, the hormonal system and the connective tissues. An established driver for deformity is the so called Heuter-Volkman principle which states that compression forces inhibit skeletal growth and tensile forces stimulate skeletal growth.

The treatment of idiopathic scoliosis varies depending on curve severity. A mild curve may be observed and if there is progression corset treatment may be an option. If the curve progress further, it may be necessary to surgically correct the deformity. The result of physiotherapy is currently conflicting and is under further evaluation in controlled studies.

To increase the understanding on both the pathogenesis of idiopathic scoliosis and the effects of the above treatment methods we want to study the deformity using visualization techniques and biomechanical modelling. To our help we have radiology including computed tomography as well as a motion lab with an optical motion tracking system. Here we use a 10-camera system which registers reflective markers placed on anatomical landmarks on the skin of the patient. This gives us plenty of information on joint kinematics and can be combined with force plates to measure the forces on the ground exerted by the patient. Combining this with biomechanical modeling we can investigate the compressive and shear forces acting on the



Pictured above is a 3D CT scan of the pelvis, femora and tracking markers, each segmented individually. Here shown using specific Unity software to allow for visualization of previously tracked movements.

separate spinal segments during movement, physiotherapy, corset treatment or before and after surgery. Understanding these forces that are acting on the spine may elucidate the pathomechanism of idiopathic scoliosis and clarify the effects of our treatment methods.

We have also developed a novel method,



A 3D CT reconstruction of a scoliotic curve showing the deformity in the frontal, sagittal and axial plane.

“CT-mocap” which essentially is a fusion of optical motion tracking and computed tomography. This allows us to visualize the patient’s own skeletal system during actual movement. We have applied this method to the hip and knee joint and we are currently working on optimizing the method in order to apply it to the spine. ◀

## PROJECT INFORMATION

### Supervisors

Hans Tropp, Ludvig Vavruch, Jörg Schilcher, Allan Abbott, Stefan Lindholm

### Project

Idiopathic scoliosis – pathomechanism and morphology

### Short CV

Medical School, Linköpings University, 2014–2019

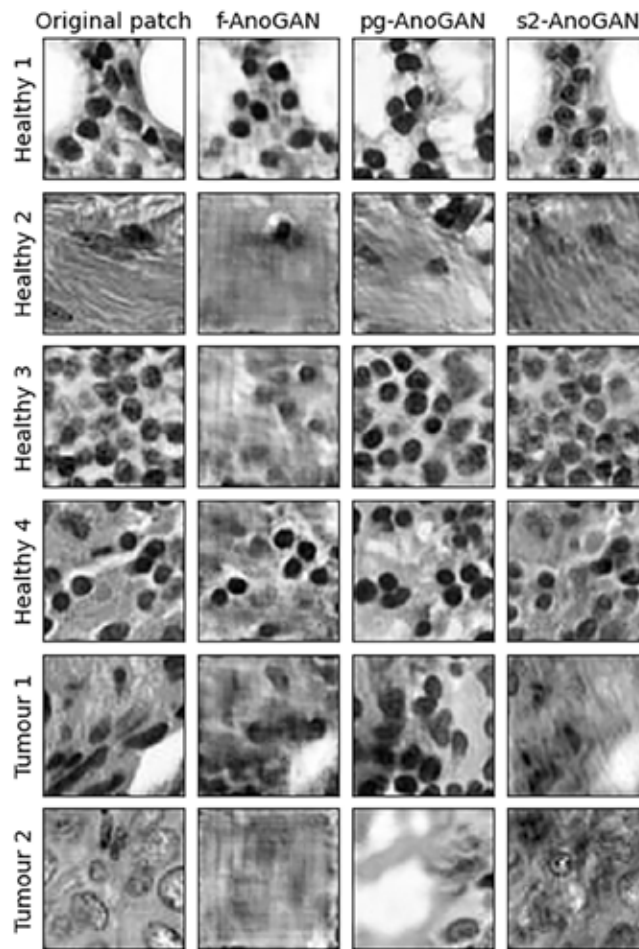
Assistant Physician, Linköping University Hospital, 2020–present

# XAI Applied to Histopathology Image Analysis

Introduction of digital pathology enabled research in Artificial Intelligence (AI) assistance tools for a pathologist. There have been several studies showing that the diagnoses done by pathologists tend to be biased: different doctors provide different assessments of the same patient. Therefore, AI tools combined with a pathologist's expertise could result in a more reliable diagnosis as well as a better-chosen treatment. However, bringing these tools to hospitals has additional challenges. The algorithms should not only have high performance (high accuracy of predictions) but also be transparent, understandable and reliable from a physician's point of view.

This project focuses on the issue of understandability and transparency of the AI tools that are developed for assisting the work of pathologists. In order to do this, the methods of explainable AI (XAI) are explored with the aim to apply them in AI solutions for digital pathology. What is Explainable AI? It is an active research field that aims to provide means of understanding the reasoning behind the predictions, inner workings as well as the limitations of an AI algorithm. For example, in tumour diagnosis, it would provide an insight into why a whole slide image (WSI) has been labelled as containing a "benign tumour". The methods achieve this by creating a heatmap on the original image, generating synthetic visualisations or providing some other scores.

Understanding the limitations of an AI tool is crucial for its safe deployment to clinical practice. What happens if an AI tool encounters some data samples that are significantly different from what it has seen so far? In these scenarios, the algorithm lacks the information to make an informed prediction, and hence, it is unreliable. In our project we developed a method for detecting such anomalous data samples. We trained an AI to recon-



Comparison of four healthy and two tumour histopathology patches (the left column) and their reconstructions by three frameworks: f-AnoGAN, pg-AnoGAN and s2-AnoGAN (ours). All the frameworks fail to reconstruct the unseen tumour patches well which indicates that they may detect anomalies.

struct the images and developed a metric to determine when the reconstruction failed. The failure indicates that the sample is significantly different from all the data that was used in the training. The future work will aim to make AI solutions more transparent by combining XAI with anomalous data detection methods. ◀

## PROJECT INFORMATION

### Supervisors

Claes Lundström, Stina Garvin, Gabriel Eilertsen

### Project

Explainable AI applied to histopathology image analysis

### Short CV

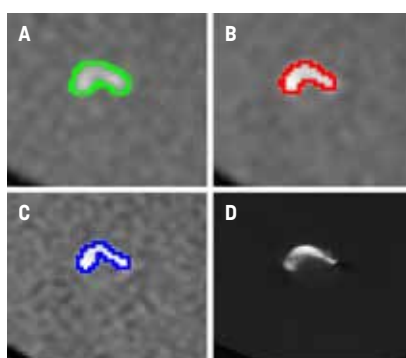
Lancaster University, BSc Hons. Financial Mathematics 2011–2014  
MSc. Statistics and Machine Learning, Linköping University 2017–2019

# Coronary Calcification Quantification using Photon-Counting Detector CT

**C**oronary artery disease (CAD) is the leading cause of death worldwide. The presence of coronary artery calcifications (CAC) is a specific feature of CAD, and the extent of CAC is an important predictor of cardiovascular risk. Computed tomography (CT) is clinically used for CAC imaging, but has a limited spatial resolution (imaging of small details), which may lead to overestimation of CAC estimation- and quantification.

Photon-counting detector-CT (PCD-CT) is an emerging technology, which utilizes detector elements smaller than conventional CT, and can thereby improve the spatial resolution. So far, the PCD-CT technology has exclusively been used for research. The purpose of this study was to compare the accuracy of cadaveric coronary calcification quantification, imaged with both a conventional CT that is commercially available and a research PCD-CT. The study was performed at the Department of Radiology, Mayo Clinic, Rochester, Minnesota, USA.

Coronary specimens were resected from three cadavers and scanned with both conventional CT and PCD-CT. A total of 13 calcifications were included. The scanning- and reconstruction parameters for the conventional CT and PCD-CT were closely matched, using the same radiation dose and a quantitative reconstruction kernel (D50). The PCD-CT images were additionally reconstructed using a sharper kernel (D60), which was not available for the conventional CT. To obtain a standard reference, all calcifications were also scanned with a micro-CT, which has the ability to obtain images with a very high resolution, near histological level of details. All calcifi-



A calcification imaged with computed tomography (CT), photon counting detector (PCD)-CT and micro-CT. The half maximum attenuation thresholds (HMT) are overlaid.

- A.** The HMT for EID-D50 is indicated in green, representing 88 segmented calcified voxels.
- B.** The HMT for PCD-D50 is indicated in red, representing 66 segmented calcified voxels.
- C.** The HMT for PCD-D60 is indicated in blue, representing 55 segmented calcified voxels.
- D.** Corresponding micro-CT image.

cations were segmented using an attenuation-based, half maximum threshold technique. After segmentation, the calcified volumes were compared. Also, the image noise was measured and compared among the conventional CT and PCD-CT image sets.

Most calcifications (12/13) had segmented calcified volumes measurements largest in conventional CT (D50 kernel), followed by PCD-CT (D50 kernel), PCD-CT (D60 kernel) and micro-CT. With matched scanning- and reconstruction parameters, PCD-CT had lower image noise than conventional CT.

The results show that the high-resolution abilities of PCD-CT can provide more accurate CAC quantification than conventional CT, and a sharper kernel could further advance the PCD-CT accuracy. The findings indicate a potential for the PCD-CT to improve CAC estimation and clinical cardiovascular risk estimations. Moreover, with matched prerequisites, the PCD-CT exhibited less noise than conventional CT, which is highly beneficial to optimize clinical reading. ◀

## PROJECT INFORMATION

### Supervisors

Anders Persson, Cynthia McCollough, Shuai Leng

### Project

The study is a cooperative project, and was performed at the Mayo Clinic, Minnesota, USA

### Short CV

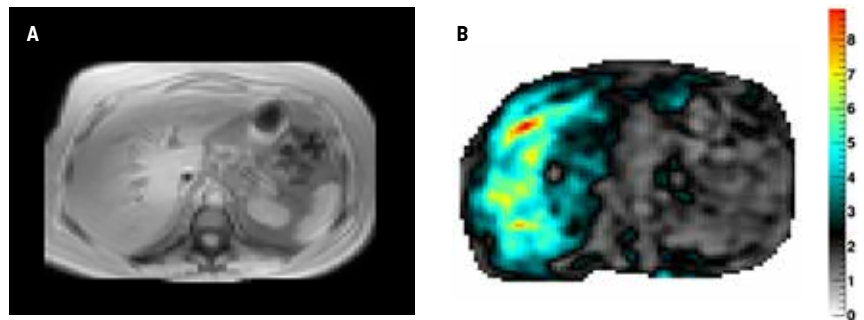
Specialist Medical Radiology, 2008  
PhD, 2020



# Modeling and Multi-Modal MRI – Investigating NAFLD

**O**besity is increasing worldwide and is one of the biggest health risks today. Because of this, one of the most common liver diseases is non-alcoholic fatty liver disease (NAFLD). Fatty liver is not inherently dangerous but can in some cases promote the development of chronic inflammation in the liver, non-alcoholic steatohepatitis (NASH). NASH causes damage in the liver, inducing the formation of scar tissue denoted liver fibrosis and cirrhosis in severe cases. Fibrosis and cirrhosis are non-reversible, and in some cases the only treatment is a liver-transplantation. Because NAFLD is becoming more prevalent it is of importance to increase the understanding of what underlying metabolic changes occur during the disease progression. To limit the development into the more severe conditions, it might be of importance to have precise and non-invasive clinical methods to be able to detect high degrees of inflammation early on.

In my PhD project I am involved in several clinical studies which focuses on collecting NAFLD related data with different MRI methods. In all studies we include 3D magnetic resonance elastography (MRE) for the detection of fibrosis (figure). Recently, there have been studies that indicate that it is possible to measure the degree of hepatic inflammation using MRE. We are aiming to expand upon these studies and investigate if the same methodology can be used to detect inflammation in our own study subjects. Also, to try to better understand the un-



MRE images from a subject in the HIFI study (unpublished). **A.** Magnitude image during MRE sequence, the liver is visible in the left side of the image. **B.** Reconstructed elastogram for 56Hz 3D-MRE showing the liver stiffness (kPa). Higher stiffness correlates to higher degrees of fibrosis. The color gradient shows the differences in stiffness values over the liver.

derlaying metabolic change brought on by the progression of NAFLD we use a system biology approach. Here, I work on constructing mathematical models describing hepatic metabolism and the changes brought on by NAFLD. With the use of the insights from our clinical stud-

ies and the use of NAFLD data from other types of experiments e.g., animal-models and micro physiological systems, we hope to be able to construct mathematical models capable of describing the underlying mechanism of NAFLD and the progression into NASH and fibrosis. ◀

## PROJECT INFORMATION

### Supervisors

Gunnar Cedersund, Peter Lundberg, Mattias Ekstedt, Elin Nyman, Peter Gennemark

### Projects

Liver intrinsic function evaluation (LIFE)

Hepatic inflammation and fibrosis investigation (HIFI)

Heart, adipose tissue, and liver thrust (HEALTH)

Evaluation of prevalence and severity of NAFLD in primary care (EPSONIP)

### Short CV

M.Sc. in Engineering Biology, Linköping University, 2018

# Nonsize Factors in Ascending Aorta Dilation Assessed by Magnetic Resonance Imaging (MRI)

**Background and Aim:** Aneurysmal dilation of the ascending aorta (AA) is an asymptomatic disease that is often not detected until a fatal dissection or rupture occurs. Current guidelines traditionally depend on diameter based criteria for stratification towards surgical intervention. However, size alone is not a sufficient predictor for complications. For example, the majority of patients with ascending aorta dissection present with an aneurysm diameter of < 5.5 cm and thus do not fall within the current guidelines for elective aneurysm surgery. We lack scientific understanding and clinical tools to properly manage individuals with mild to moderate AA dilation.

The main objective of this study is to investigate if asymptomatic ascending aorta dilation is related to alterations

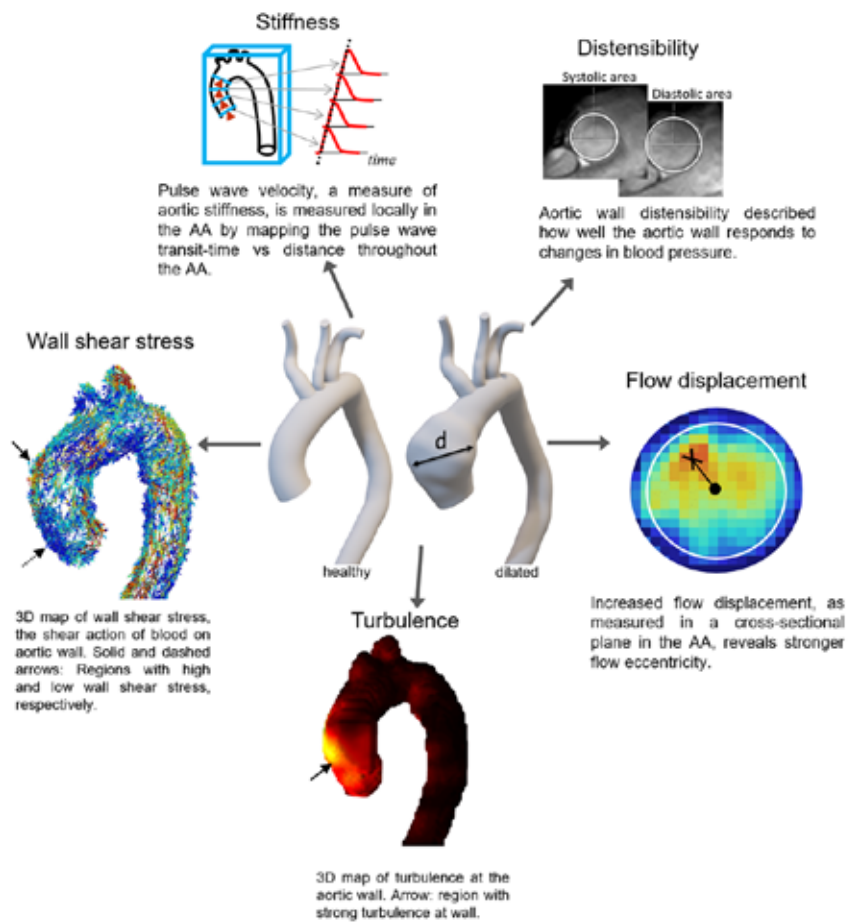


Figure 1. Project overview. Main quantitative parameters that are computed from CMR images.

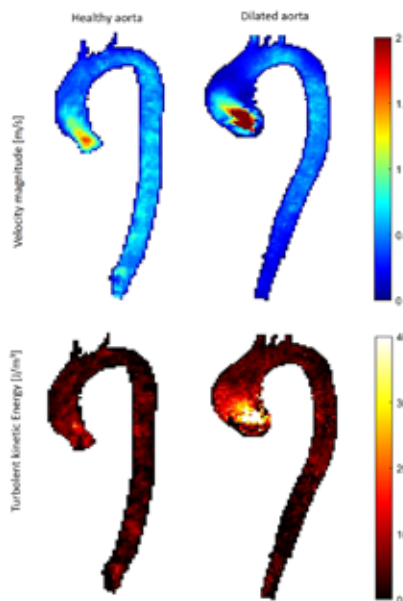


Figure 2. Example of preliminary results. Blood velocity magnitude (up) and turbulent kinetic energy (bottom) at peak systole are shown for one control (left) and one case (right).

## PROJECT INFORMATION

### Supervisors

Petter Dyverfeldt, Lena Jonasson, Tino Ebbers

### Project

Ascending Aortic Dilation - AscA project

### Short CV

Master's degree in biomedical engineering, Biomechanics and Biomaterials, Politecnico di Milano University, Milan, Italy  
Erasmus, Universiteit Twente, Enschede, Netherlands

in aortic wall properties or blood flow. We want to achieve this aim by means of advanced Cardiovascular Magnetic Resonance (CMR) imaging.

**Study Population:** The project's study cohort is a subsample from the Swedish CardioPulmonary BioImage Study (SCAPIS) cohort in Linköping, including 5,000 individuals. Subjects in SCAPIS with AA diameter  $\geq 40$  mm at CT or echocardiography have been included in the study as cases ( $n = 70$ ). An age and sex matched control group with non-dilated AA ( $n = 147$ ) has been recruited from the same population.

**Cardiovascular Magnetic Resonance Imaging:** The selected cohort will undergo a defined CMR imaging protocol, including time-resolved three-dimensional PC-MRI with three-directional velocity encoding (4D flow MRI), an advanced CMR technique that allows for off-line quantification of blood flow. Images will be properly processed in order to compute relevant quantitative parameters, reported in Figure 1.

**Significance:** By improving our understanding of AA dilation and exploring new measures to discriminate between cases and controls, this project may lead to new ways to improve risk stratification for subjects with AA dilation.

**Preliminary Results:** In Figure 2 an example of preliminary results is represented. Maximum intensity projection images of blood velocity magnitude (up) and turbulent kinetic energy (bottom) are shown for one control (left) and one case (right). We can clearly visualize the altered flow in the dilated patient, which seems to be associated to higher turbulence. ◀

## A Cardiovascular Model for Blood Pressure Regulation

High blood pressure, or hypertension, is one of the most common health issues today with 22% adults affected worldwide, and is twice as common in patients with type 2 diabetes (T2D). Hypertension is defined in Europe as a systolic and/or diastolic blood pressure persistently above 140/90 mmHg. Blood pressure and blood flow is tightly interconnected, and a high blood pressure requires the heart to work harder to pump blood through the body. Uncontrolled hypertension is a risk factor for cardiovascular diseases such as coronary artery disease, heart failure, and renal failure.

The basic underlying mechanisms of hypertension such as a dysregulated hormone system, alterations in nervous system activity and disturbed salt balance are known. However, the connection to other cardiovascular diseases is complex. Additionally, the treatment of hypertension usually involves lifestyle changes and trial- and error by testing several anti-hypertensive drugs. There is a need of deeper understanding of the changes in flow- and pressure regulation during hypertension and especially in T2D patients.

Therefore, the goal of this project is to further understand the mechanisms behind regulation of blood pressure and what happens when the blood pressure gets too high. The first step is to investigate blood flow dynamics in hypertensive and non-hypertensive individuals, and T2D patients and controls. Blood flow can be measured non-invasively using four-dimensional magnetic resonance imaging (4D Flow MRI) which allows for 3D visualization of blood flow over time. By combining this flow data with a car-

diovascular mathematical model, more information can be extracted that otherwise is hard to measure non-invasively. For instance, parameters of the contraction and relaxation of the left ventricle and propagation of the pressure wave can be extracted.

A cardiovascular model that can describe the flow and pressure dynamics of healthy individuals is previously developed in the group. The model is now further developed to create personalized blood flow models for T2D patients and controls. This gives assessment of new model-derived biomarkers, which are compared between hypertensive and non-hypertensive individuals, as well as between T2D patients and controls. The study has the potential to bring new insights to the mechanisms of flow and pressure regulation behind hypertension with and without T2D, and to provide a new clinical tool for diagnostics. ◀

### PROJECT INFORMATION

#### Supervisors

Gunnar Cedersund, Tino Ebbers, Carl-Johan Carlhäll

#### Project

The cardiovascular functional avatar in action (Avatar)

#### Short CV

Bachelor's degree in Engineering Biology, Linköping University, 2015–2018  
Research preparatory course I and IIb, 2018–2019





v ischemisk hjärtsjukdom

Wasa Uden  
Cardiac Medicine  
Dissertation

# Dissertations

During 2020 four of the CMIV PhD students finished their studies and defended their theses. The PhD students and the research school are an important part of CMIV and we are proud to present their theses here.

*Markus Karlsson*

Linköping University, Department of Medicine, Health and Caring Sciences

# Non-Invasive Characterization of Liver Disease: By Multimodal Quantitative Magnetic Resonance

**T**here is a large and unmet need for diagnostic tool that can be used to characterize chronic liver diseases (CLD). In the earlier stages of CLD, much of the diagnostics involves performing biopsies, which are evaluated by a histopathologist for the presence of e.g., fat, iron, inflammation, and fibrosis. Performing biopsies, however, have two downsides: I) biopsies are invasive and carries a small but non-negligible risk for serious complications, II) biopsies only represents a tiny portion of the liver and are thus prone to sampling error.

Moreover, in the later stages of CLD, when the disease has progressed far

enough, the ability of the liver to perform its basic function will be compromised. In this stage, there is a need for better methods for accurately measuring liver function. Additionally, measures of liver function can also be used when developing new drugs, as biomarkers for drug-induced liver injury (DILI), which is a serious drug-safety issue.

Magnetic resonance imaging (MRI) is a non-invasive medical imaging modality, which have shown much promise with regards to characterizing liver disease in all of the above mentioned aspects. The aim of this PhD project was to develop and validate MR-based methods that can

be used to non-invasively characterize liver disease.

In paper I the MR-method for measuring liver iron content was investigated by  $R^*$  mapping. In paper II, T1 mapping was used instead, whereas in paper III and IV the focus was to study liver function by dynamic contrast-enhanced MRI (DCE-MRI). Finally, in paper V a method for translating DCE-MRI liver function parameters from rats to humans was developed, which could be useful in developing new drugs. In summary, this thesis has shown that multimodal quantitative MR has a bright future for characterizing liver disease from a range of different aspects. ◀

*Sebastian Sten*

Linköping University, Department of Medicine, Health and Caring Sciences

# Mathematical Modeling of Neurovascular Coupling

**T**he brain is critically dependent on the continuous supply of oxygen and glucose, which is carried and delivered by blood. When a brain region is activated, metabolism of these substrates increases rapidly, but is quickly offset by a substantially higher increase in blood flow to that region, resulting in a brief oversupply of these substrates. This phenomenon is referred to as functional hyperemia and forms the foundation of functional neuroimaging techniques, such as functional Magnetic Resonance Imaging (fMRI), which captures a Blood Oxygen Level-Dependent (BOLD) signal. fMRI exploits these BOLD signals to infer brain activity, an approach that has revolutionized the research of brain function over the last 30 years. Due to the indi-

rect nature of this measure, a deeper understanding of the connection between brain activity and hemodynamic changes – a neurovascular coupling (NVC) – is essential in order to fully interpret such functional imaging data. NVC connects the synaptic activity of neurons with local changes in cerebral blood flow, cerebral blood volume, and cerebral metabolism of oxygen, through a complex signaling network, consisting of multiple different brain cells which release a myriad of distinct vasoactive messengers with specific vascular targets.

To aid with this complexity, mathematical modeling can provide vital help using methods and tools from the field of Systems Biology. Previous models of the NVC exist, conventionally describing

quasi-phenomenological steps translating neuronal activity into hemodynamic changes. However, no mechanistic mathematical model describing the known intracellular mechanisms or hypotheses underlying the NVC, and which can account for a wide variety of NVC related measurements, currently exists. Therefore, in this thesis, we apply a Systems Biology approach to develop such intracellular mechanisms-based models using in vivo experimental data consisting of different NVC related measures in rodents, primates, and humans.

This new model-based understanding opens the door for a more integrative approach to the analysis of neuroimaging data, with potential applications in both basic science and in the clinic. ◀

*Anette Karlsson*

Linköping University, Department of Biomedical Engineering

# Quantitative Muscle Analysis Using Magnetic Resonance Imaging

**R**ecent research shows that a decrease in muscle volume and an increase in fat infiltration is related to several diseases and syndromes such as chronic pain, diabetes, inflammation and ageing. However, the onset and progression of disease and the effect of potential intervention effects are not fully understood, partly due to insufficient measurement tools. For early diagnosis and correct treatment plans we need an accurate and precise measurement tool for detecting changes in muscle composition. Magnetic resonance imaging is an excellent tool since we can get three dimensional images showing both organs and fatty tissue. However, challenges re-

main, and this thesis is about solving some of them.

One challenge is to make the result quantitative since the signal will not be equal between the MR scans. Therefore, a technique that calibrates every image element based on its fat content is used. It is shown in the thesis that the method was insensitive to changes in both field strength and image resolution. Another challenge is to make the muscle composition analysis effective. Since it is extremely time consuming to delineate muscles in MR images, another aim of this thesis was to develop an automatic muscle delineating method. The developed method is used in the, to date,

largest imaging study of the world where MR scans from 100,000 individuals are acquired. The method was also used in a clinical study. Individuals with higher selfreported disability after a whip-lash-trauma on their neck had a higher fat infiltration compared to individuals with milder symptoms and to healthy controls.

In this thesis it is shown that the muscle composition analysis method is accurate, effective and has a clinical relevance. The method therefore has potential to be used in large and/or longitudinal clinical studies in order to increase the knowledge regarding muscle related diseases and syndromes of today. ◀

*Mårten Sandstedt*

Linköping University, Department of Medicine, Health and Caring Sciences

# Computed Tomography of the Coronary Arteries: Developmental and Prognostic Investigations

**C**omputed tomography (CT) is increasingly used for investigations of patients with suspected coronary artery disease (CAD).

This thesis evaluated the performance of a computed tomography-based fractional flow reserve (CT-FFR) software (study I), an AI-based, calcium scoring computed tomography (CSCT) software (study III), and a photon-counting detector (PCD)-CT (study IV). Also, the prognostic value of coronary computed tomography angiography (CCTA) was studied (study II).

The performances of both software programs were compared with standard references, being represented by

fractional flow reserve (FFR) measurements (study I), and coronary artery calcification (CAC) scores from a semi-automatic software (study III), respectively. The PCD-CT performance on CAC quantification was compared with corresponding results from an energy integrating detector (EID)-CT, using micro-CT as the standard reference (study IV). The prognostic study merged registries to identify major adverse cardiac events (MACE), having a follow-up time of up to 7.5 years (study II).

The CT-FFR and CSCT software correlation and agreement to corresponding standard references were good and excellent, respectively. Also, both software

programs had time-saving potential (study I and III). The CAC quantification was more accurate using PCD-CT than EID-CT (study IV). The prognosis was excellent in patients with normal coronary arteries, but progressively impaired in patients with increasing grade of CAD (study II).

The thesis conveys developmental advances for CAD investigations and adds prognostic follow-up data. The results may benefit patients by an increased accuracy in the CT evaluation of CAD and can contribute to a more efficient workflow and better clinical follow-up strategies. ◀



# Equipment

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

## CT

**CT1** – Photon counting research CT scanner, prototype based on Siemens Healthineers SOMATOM x.cite.

**CT2** – The Siemens Healthineers 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

**MR1** – The Siemens 3.0T Prisma has a 60 cm bore and gradients with 80mT/m and 200 T/m/s simultaneously, which facilitate fMRI and DTI studies in a 64 receive channels head coil. The coil concept also offers high coil density using parallel transmit technology called TimTx

TrueShape for cardiac, abdominal and musculoskeletal examinations.

**MR2** – The Philips Ingenia 3.0T has a 70 cm bore. It is equipped with Xtend gradient system (up to 45mT/m and 200 T/m/s) and two parallel RF transmission channels (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.





**MR3** – The Philips Achieva 1.5T has a 60 cm bore and is equipped with Nova Dual gradients (up to 66 mT/m and 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 185 dB.

Advanced fMRI research is possible using video glasses with built-in eyesight correction as well as eye-tracking, and it is also possible to combine these measurements with simultaneous multichannel MR-EEG. Other specialty equipment includes several MR-elastography (MRE) systems for both 1.5 T and 3 T, based on both electrodynamic and gravitational transducers. Our MRE-capability is best in class and can be used to quantify changes of the biomechanical properties of pathologies, as is caused by fibrosis and inflammation. We have also access to a unique installation of multi-nuclear MR spectroscopy, allowing us to investigate both static and dynamic energy metabolism in tissues. The latter is highly facilitated by our MR-compatible MR-ergometers for quantitative cardiac and muscle research.

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

#### **DIGITAL PATHOLOGY AND ANNOTATION**

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

#### **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. 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 Å~ 2,160). The Barco Laser 3D has a native 6-primary color-3D system. The system uses a Barco E2 Image processor, 4K Native 12 bits/color 3D input/output. The computer to screen connections are run by the Lightware mx-33R Digital Crosspoint matrix.

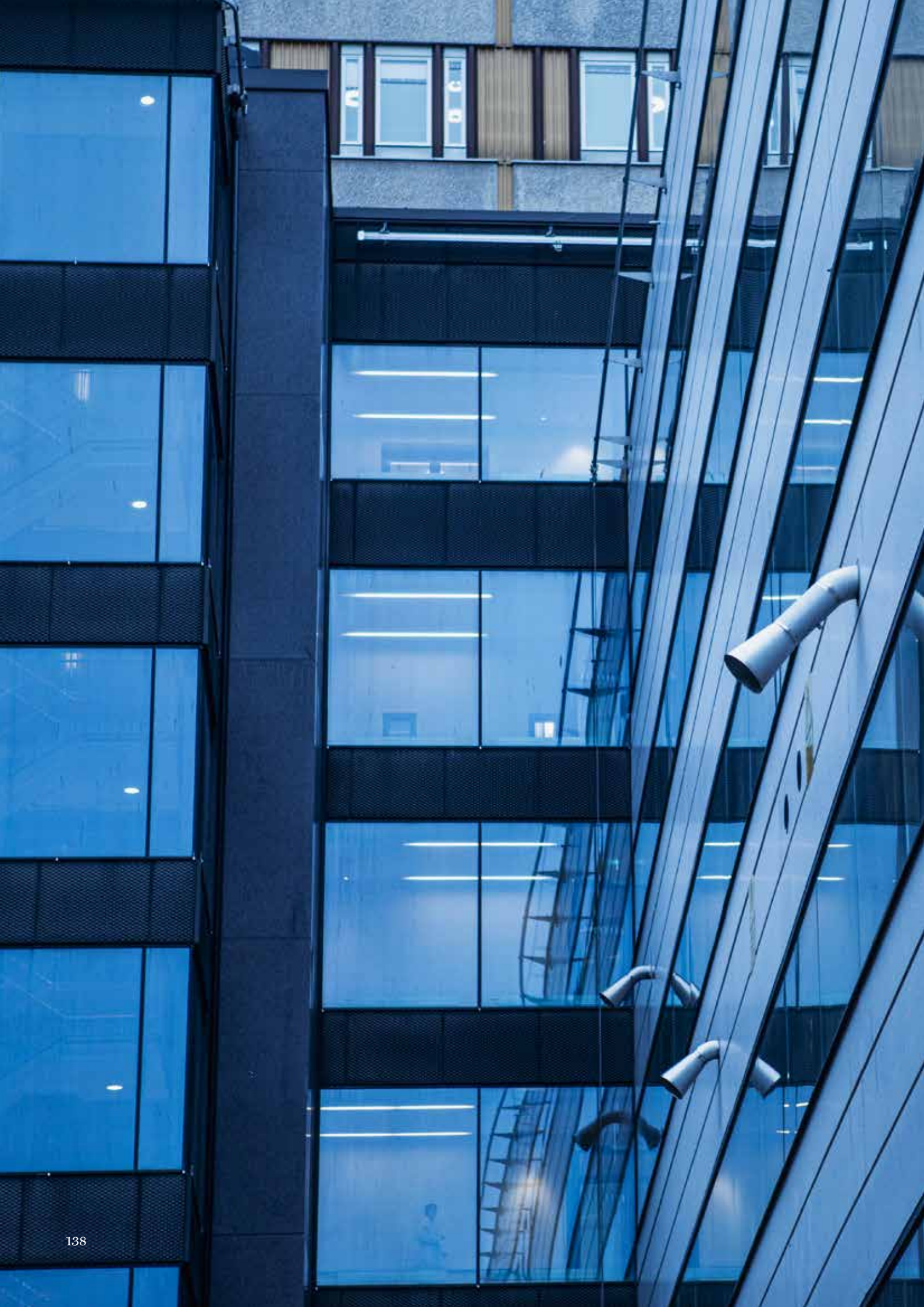
The Wirecast 7.3 Recorder system allows recording and online streaming. During 2018 Wranne was upgraded to an advanced Zoom room enabling remote meetings and education. In addition to the theatre there is also a 55" Sectra visualization table and a wall mounted 85" Sectra visualization monitor with ten 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.

#### **COMPUTING AND STORAGE**

CMIV has its own server facilities hosting servers for secure handling of sensitive data, research calculations, analysis and NAS backup. In 2019 an HP Tetralith supercomputer and a new data storage unit of 660 TB were installed.

CMIV is the host for the AIDA infrastructure, where the flagship is the DGX-2 system from Nvidia with 16 high-end GPU:s available for all AIDA partners across Sweden to use for AI training. The service has been validated secure enough for processing sensitive personal data. Thanks to the good collaboration with Region Östergötland, the DGX-2 system was installed in the hospital's server hall in November for increased technical and physical security. ◀









# Organization

CMIV is governed by the 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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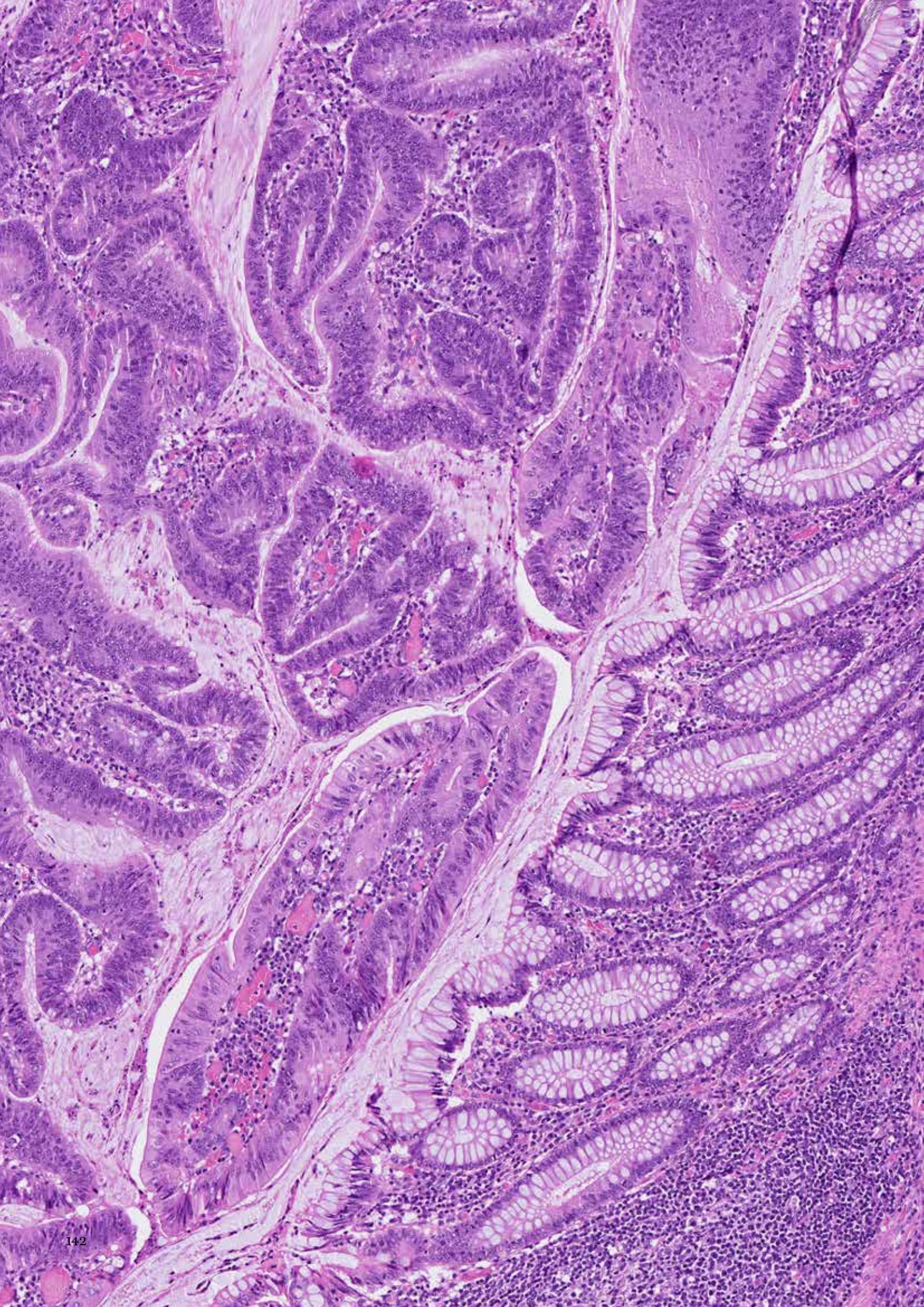
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# Publications

The CMIV research efforts lead to a steady stream of scientific publications. An overview of the 2020 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.

Pathology image.



# 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 KTH Royal Institute of Technology; data source: Clarivate Analytics Web of Science.

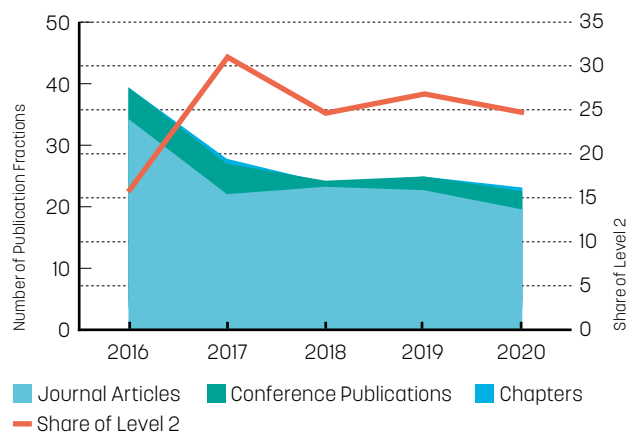
## Norwegian Model, 2016–2020

TABLE 1

Publications published in journals and with publishers in the Norwegian list	Number of Publications	Number of Publication Fractions	Share of Level 2, %
Journal Articles	282	122.8	28
Conference Publications	30	16.1	0
Chapters	2	1.7	0
Books	0	0.0	0

Share of level 2 publications, total: 24%

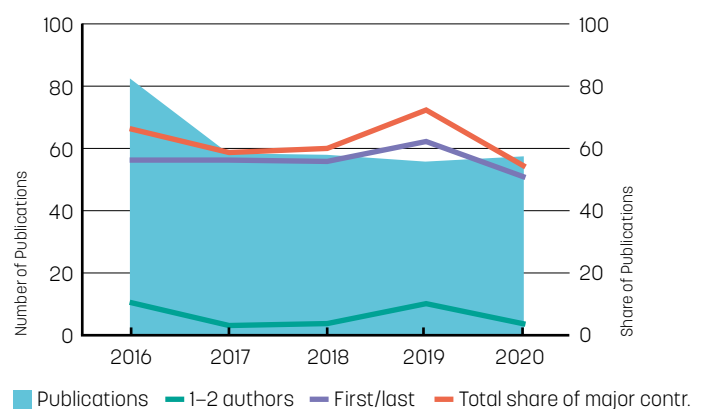
FIGURE 1A



Publication fraction refers to the part of the publication that can be linked to the unit. E.g., the fraction is 0.5 if two out of four authors belong to the unit.

In the Norwegian model, the approved publishing channels are divided into two levels – level 1 (scientific channels) and level 2 (scientific channels that are leaders in their subject area). Level 2 publication channels may publish a maximum of 20% of the publications in each field of science. Level 2 means the proportion of fractionalized publications published in journals and with publishers at level 2. At a higher aggregate level, one can expect the proportion to be 20%.

FIGURE 1B. Major Contribution



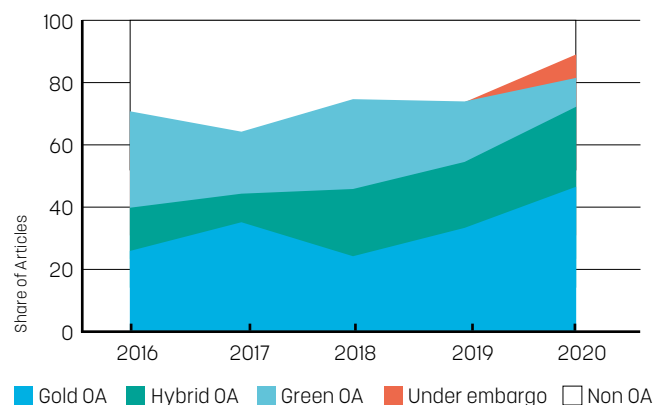
## Open Access, 2016–2020

TABLE 2

Share of publications published Open Access (incl. OA after an embargo period):

Journal Articles, %	75
Conference Publications, %	33
Chapters, %	50

FIGURE 2





Open access (OA) publication has been identified using data from Unpaywall (www.unpaywall.org). For articles, different types of OA publication are shown in the graph and data from Unpaywall is complemented by an in-house algorithm. Gold open access is defined as the article being published in an open access journal. Hybrid open access is defined as the article being published open access in a subscription journal. Green open access is defined as the accepted version of the article being published in fulltext in a repository.

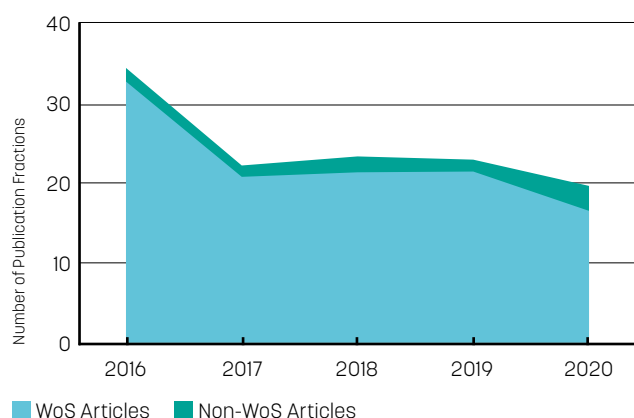
### Coverage in Web of Science, 2016–2020

TABLE 3

	Number of Publications	Number of Publication Fractions
Articles and conference publications*	284	127.9
<b>Coverage</b>		<b>%</b>
Journal articles		93
Conference publications		77

\*Articles, reviews, letters, proceedings papers i WoS.

FIGURE 3



The analysis is based on the Clarivate Analytics Web of Science database. In order for a citation analysis to be relevant and provide reliable values, a sufficiently large basis is required. We therefore report the number of publications / fractions in the database and provide a picture of the coverage rate for the journal articles in the database. All citation indicators are reported fractionalized, i.e., a weighting is made based on the number of authors that can be linked to the unit. Self-citations are excluded.

### Citation Analysis, 2016–2020

TABLE 4

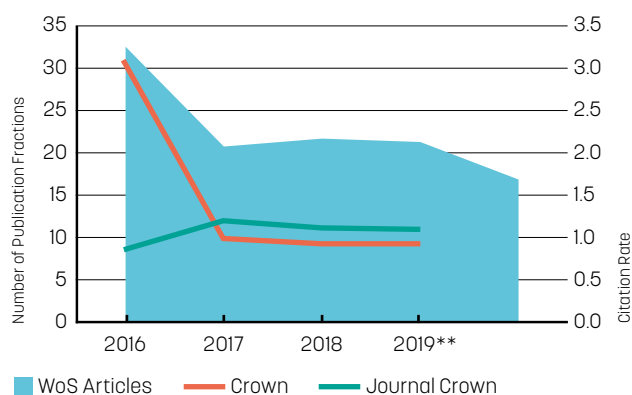
	Number of Publications	Number of Publication Fractions
Articles*	284	127.9

\*Articles, reviews, letters in WoS.

#### Results, field-normalized

Field-normalized citation rate (crown)	1.7
Share of highly cited articles (top 10%), %	13
Share of uncited articles, %	13
Field-normalized journal citation rate (journal crown)	1.04
Ranking of Journal Impact Factor (JIF), mean	0.68

FIGURE 4



\*\*The results from last year's articles should be interpreted with caution. Since the citation numbers for new articles are generally low, individual values can have a high impact on average values.

With less than 10 publication fractions, no values are shown on the citation indicators because the data is so small that individual values can have a high impact on the average values.

- Field normalized citation rate (Crown): A measure of the impact of the articles included in the analysis. This gives a comparative value with an international average for the same field, year and article type, where the value 1 corresponds to a world average. The field-normalized citation rate is reported fractionally, i.e., a weighting is made based on the number of authors. Self-citations are excluded. The average field-normalized citation rate for universities and colleges in Sweden is 1.18 for the years 2015–2018, according to the 2020 distribution data from the Swedish Research Council.
- Proportion of highly cited articles (top 10%): the proportion of publications that are among the 10% most cited works in the sub-

ject area and time period, i.e., publications with a very high impact.

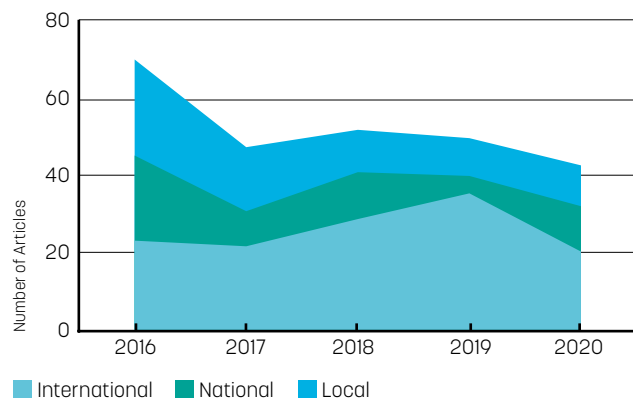
- Proportion of unquoted articles: indicates how the citations are distributed, i.e., if they are evenly distributed over the articles or if only a few of the articles are cited.
- Field normalized journal citation rate (Journal crown): A measure of the impact of the journals in which the unit has published. Provides a comparison value between the average value of citations for the journals in which the unit has chosen to publish and the average value of citations for all journals in the corresponding field. A value of 0.9 e.g., indicates that the journals in which the unit publishes are quoted 10% less than the average for the journals in the field as a whole.

### Co-Authorship – Geographical, 2016–2020

**TABLE 5**

Share of articles with international co-authorship, %	50
Share of articles with national co-authorship, %	22
Share of articles with local co-authorship, %	28

**FIGURE 5**



Proportion of publications in WoS where the unit has co-published with international, national and local authors (within and outside the academy). By local authors is meant authors from LiU and that category also includes sole authors. International collaboration is reported because studies have shown a higher citation rate for publications with international collaboration.

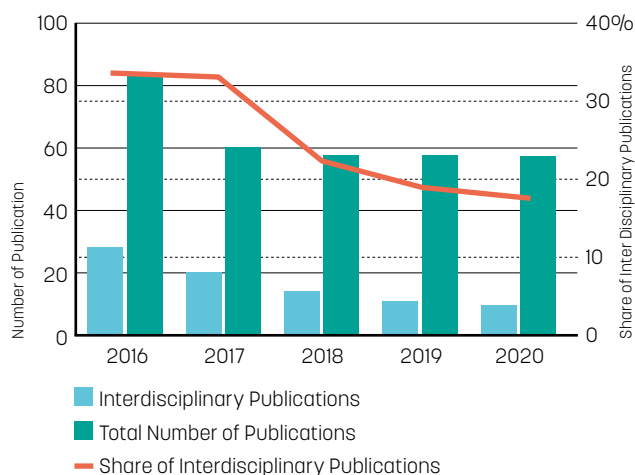
### Interdisciplinary Authorship (LiU faculties), 2016–2020

**TABLE 6**

**Publications with interdisciplinary authorship**

Number	82
Share, %	26

**FIGURE 6**





A lynx from Kolmården Wildlife Park investigated for cancer in the PCD-CT.

# Publications 2020

CMIV affiliated researchers are written in bold.

## PEER-REVIEWED ORIGINAL ARTICLES AND PROCEEDINGS

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Pinchaud N., Hedlund M., Landgren F., **Woisetschläger M.**, Forsberg D. (2020) Proactive Construction of an Annotated Imaging Database for Artificial Intelligence Training. Journal of digital imaging.

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## DISSERTATIONS

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Radiografer Mirjana Vukusic and Mats Jonsson are preparing Mona Cederholm for an fMRI exam.

# Annual Accounts

During 2020 CMIV had a turnover of more than SEK 55 million.  
The financial result for CMIV was SEK 95 thousand.

During the fiscal year of 2020 CMIV had several ongoing grant research projects. AIDA – Analytic Imaging Diagnostics Arena continued its work, being funded by VINNOVA. Seven projects funded by AIDA together with two clinical and one technical fellowship started during 2020.

The Visual Sweden-financed project MeDigiT continued with

prolonged financing during 2020. Research projects SCAPIS (Swedish Heart-Lung Foundation) and SCAPIS-AI platform (VINNOVA) continued their work during 2020. 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. ◀

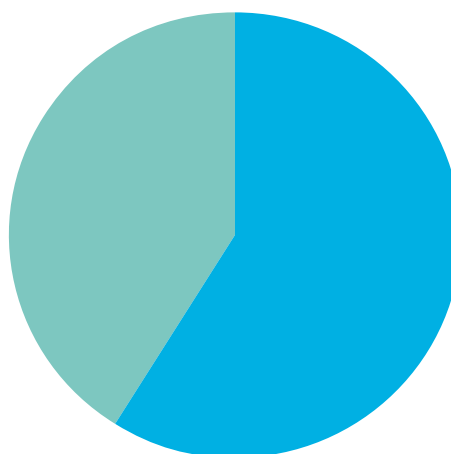
ECONOMIC SUMMARY	2016	2017	2018	2019	2020
<b>Total revenue</b>	40,655	48,165	52,059	56,266	55,007
EXPENSES					
Staff expenses	-16,978	-15,772	-16,711	-20,390	-22,480
Cost of premises	-9,135	-6,472	-6,657	-5,752	-6,647
Misc. Operating expenses	-12,158	-16,765	-18,704	-18,848	-17,928
Depreciation expenses	-6,781	-7,819	-8,129	-8,440	-7,848
Financial expenses	-132	-36	-151	-126	-11
<b>Total expenses</b>	-45,184	-46,864	-50,051	-53,556	-54,913
<b>Result of operations</b>	-4,519	1,300	2,008	2,710	95

NUMBERS IN THOUSANDS OF SEK

## Research Funding at CMIV 2010–2020

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.

- External Funds: kSEK 118,691
- Industrial Funds: kSEK 80,941

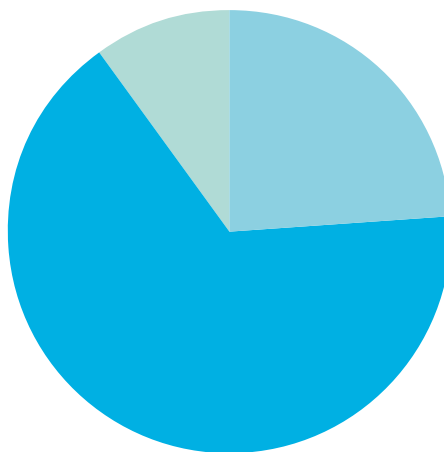


## CT Research and Clinic, %

All data deriving from clinical exams on the CMIV CT may also be used for research in accordance with ethical permits from the Swedish Ethical Review Authority.

### 2020

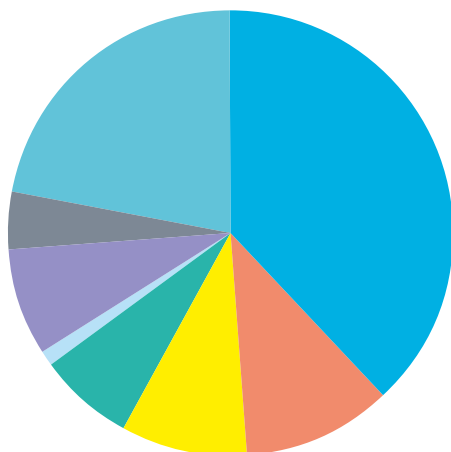
- Research, 24
- Clinic, 66
- Special exams only at CMIV CT, 10



## Distribution on Research on the MR Scanners, %

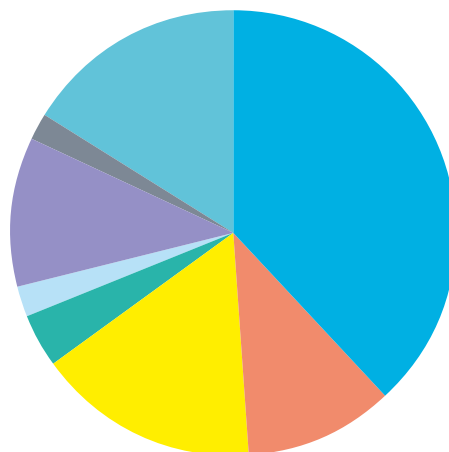
### 2020

- Musculoskeletal, 38
- Cardiovascular, 11
- Abdomen, full body, 9
- Spectro neuro, 7
- Development, 1
- fMRI, 8
- Neuro, 4
- CSAN, neuro, 22



### 2019

- Musculoskeletal, 38
- Cardiovascular, 11
- Abdomen, full body, 16
- Spectro neuro, 4
- Development, 2
- fMRI, 11
- Neuro, 2
- CSAN, neuro, 16





Radiographer Henrik Ekman and the Philips 3T MR Scanner.







The bridge between the new office building and CMIV.





The new building at the University Hospital with offices for CMIV researchers.

