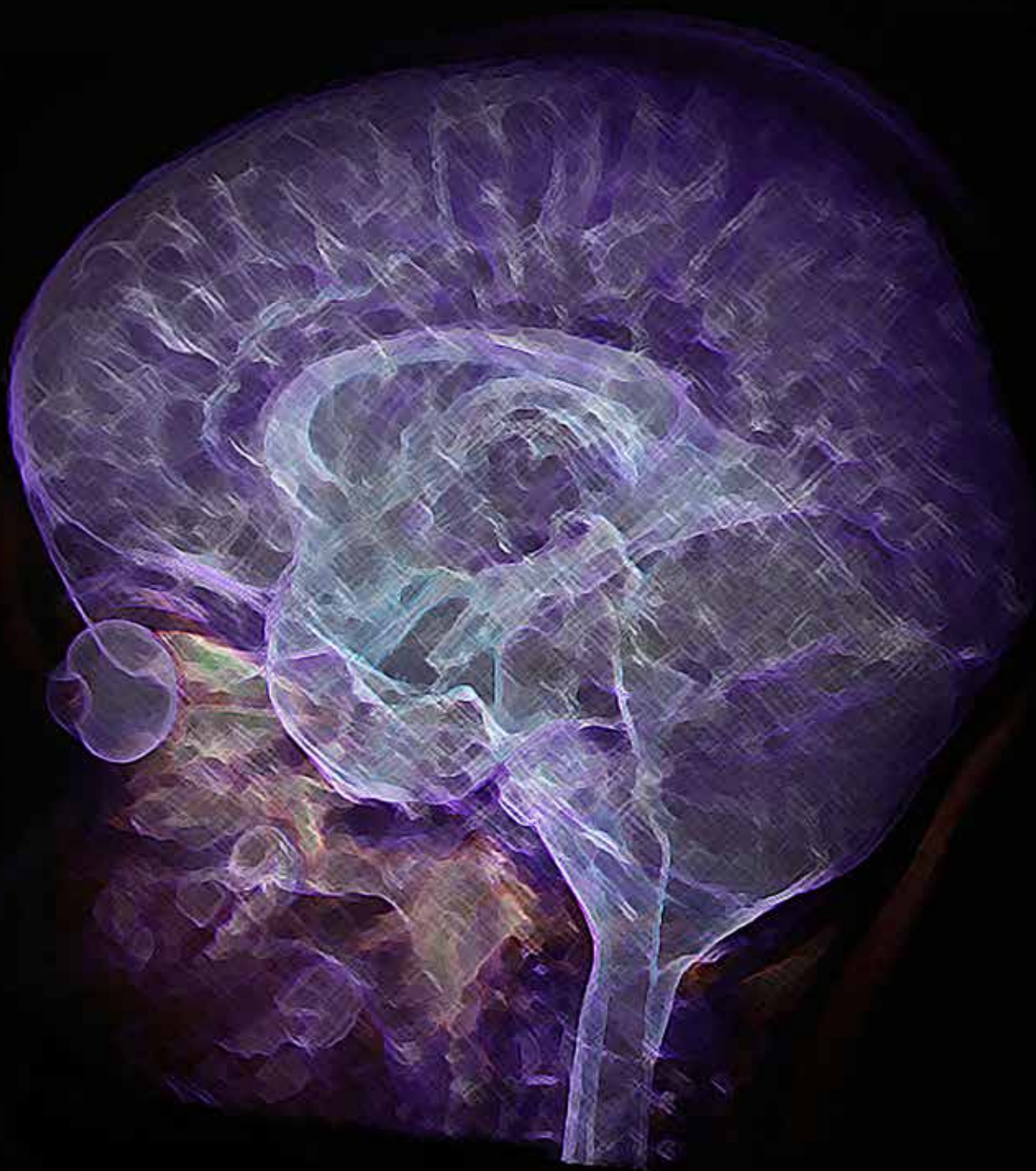


WELCOME TO THE EXCITING WORLD OF CMIV

ANNUAL SCIENTIFIC REPORT 2016



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2016 has been filled with exciting new projects and important visits. The expanded facilities has allowed more dedicated time for research especially with the addition of the new 3T MRI.		During 2016 six of the CMIV PhD students have finished their studies and defended their dissertations. The PhD students and the research school are an important part of CMIV and we are proud to present their dissertations here.	
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CMIV conducts focused frontline research within multidisciplinary projects providing solutions to tomorrow's clinical issues.		Through unique collaborations with the industry it is possible for CMIV to always have the latest and most advanced equipment.	
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The 2016 flagship projects were selected by the CMIV scientific council. The projects together represent the broad and multi-disciplinary research at CMIV. The flagship projects were chosen through a nomination procedure and the resulting projects complement each other in modalities, project stage and medical area.		CMIV is governed by its Board of Directors, with representatives from academia, health care and industry.	
RESEARCH PROJECTS	26	PUBLICATIONS	142
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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.		The list presents a good representation of articles and conference proceedings published by the CMIV researchers in the past year.	
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Ever since the start in 2002 the CMIV foundation has been the collaboration between university, health care and industry with focus on bringing technology and medicine together to create patient values.		Since CMIV is part both of the university and the county council the finances are also split in two parts.	



PREFACE

Since the move in 2015 it has been a work in progress to get everything in place to create an even better multidisciplinary research environment. During the autumn of 2016 we could finally install our latest MR scanner. It offers a unique 3T MRI platform to help CMIV to tackle the most demanding MRI research challenges today and tomorrow. From the start it has worked as planned and produced predominantly neurological research that has been published in high ranked scientific journals and at the same time contributed to great clinical value for patients.

Since we moved in to our new facility there has been great achievement in several of CMIV's research fields such as fat and cardiac research. For the first time cardiac flow data have been

acquired from conventional cardiac computed tomography examinations. This research has great clinical potential. One of our focus areas, digital pathology is embarking on a similar digitization journey as radiology experienced. The use of digital techniques will probably have a greater positive impact on pathology than it had on radiology.

Research in the borderland between radiology and pathology, "Integrated diagnostics", has a great potential. I hope that CMIV in 2017 can move further in this direction and create a national platform for large-scale analytical imaging based in Linköping with Linköping University/ CMIV, Sectra and Region Östergötland as core partners.

To emphasize the importance of integrated diagnostics we are presenting this as the theme of the annual Swedish

radiology congress "Röntgenveckan 2017" that is hosted by CMIV and the Radiology Department in Linköping. The planning has intensified and we are looking forward to the conference in September 2017. The program is looking great!

To summarise 2016 offered exciting results and many new projects started. The future is bright thanks to collaboration with the outstanding individuals at CMIV as well as the unique twinning of academic disciplines!



Anders Persson
Director of CMIV

HIGHLIGHTS 2016

At CMIV, 2016 has been filled with exciting new projects and important visits. The expanded facilities has allowed more dedicated time for research especially with the addition of the new 3T MRI. Here you will find the highlights of the year.

THE CMIV CHAIRMAN TAKES THE LEAD IN ESR

The chairman of the CMIV board Professor Katrine Åhlström Riklund took over as chairman of the ESR board of directors for 2016.

Katrine first lead the organization committee for the European Congress of Radiology 2016 in Vienna. The congress is the annual meeting of the ESR and has over 25,000 participants from all over the world. During the meeting she also took over the chairman post of

the ESR board from the Italian Lorenzo Bonomo. She is the first woman and the first Swede to man the honorable post.

The European Society of Radiology (ESR) was founded in February 2005 by merging the European Congress of Radiology (ECR) and the European Association of Radiology (EAR), thus establishing a single house of radiology in Europe. The ESR is an apolitical, non-profit organization, dedicated to

promoting and coordinating the scientific, philanthropic, intellectual and professional activities of Radiology in all European countries.



RÖNTGENVECKAN 2017 I LINKÖPING

Next year the annual national radiology congress Röntgenveckan will be held in Linköping. The organizers are the Radiology clinic at Linköping University Hospital together with CMIV. The con-

gress is expected to attract 1,500 visitors from the field of radiology. Behind the annual meeting are the Swedish Society of Radiology and the Swedish Society for Radiology Nurses. The theme of the

week will be Integrated Diagnostics. The responsibility for the congress was handed over to the new organizing committee at the grand dinner during Röntgenveckan 2016.



THE MINISTER FOR HIGHER EDUCATION AND RESEARCH, HELENE HELLMARK KNUTSSON VISITS CMIV

During spring the minister for higher education and research, Helene Hellmark Knutsson visited CMIV together with the LiU Vice Chancellor Helen Danne-tun. The visit was part of the minister's day at LiU. Director Anders Persson presented CMIV and Elin Kindberg

from Sectra talked about digital pathology and the VINNOVA project DigiPat3. The minister was impressed by the cross-disciplinary environment and suggested that the Minister for Health Care, Public Health and Sport should visit as well.

AMRA WILL ANALYZE 100,000 MRI SCANS FOR FAT AND MUSCLE CONTENTS

The UK Biobank, a nonprofit biological data repository in Stockport, has announced plans to scan the organs of 100,000 people over the next 6 to 8 years. The snapshots, taken with magnetic resonance imaging (MRI) and other standard techniques, will be linked to diverse data on health and lifestyle, allowing researchers to improve understanding and diagnoses of diseases such as cancer, dementia, arthritis and osteoporosis, and coronary heart disease.

The CMIV spin-off AMRA is involved

in the study and will analyze the fat and muscle volumes in the MRI images using the software developed at CMIV and AMRA.

The UK Biobank was set up in 2006 by the Medical Research Council (MRC) and the Wellcome Trust. The goal was to create a resource for health researchers by gathering health-relevant data—such as diet, physical activity, lifestyle, and cognitive function—as well as samples of blood and DNA from half a million people in the United Kingdom. To allow analysis of



health outcomes, these data are linked to the individuals' health records from hospitals, death registers, and, now, general physicians.

A pilot project to add biomedical images was recently completed with scans of 8,000 people. Data will be accessible to health scientists who register with Biobank. Existing data are currently being studied by about 2,700 researchers from the United Kingdom and other countries, in both academia and industry.

HEAVY LIFT-OFF FOR NEUROLOGY RESEARCH

A new MRI camera was installed at CMIV. The center now has three MRI cameras, which will allow more research time. This is a welcome addition since the pressure on the two present cameras has been high during the past year.

The new camera is a state of the art Siemens MAGNETOM Prisma 3T equipped to specialize in neurological examinations and spectroscopy.

The MRI weighs 12.5 tons and moving it into the facility took some effort. The move was done during the weekend to avoid disturbing the wards on the floors below as the ceiling had to be reinforced.



SOFTWARES FOR fMRI YIELD ERRONEOUS RESULTS

In an article published in the highly-ranked journal PNAS the CMIV researchers Anders Eklund and Hans Knutsson together with Thomas Nichols of the University of Warwick suggests that common statistical methods used to analyze fMRI data cannot be trusted. The study shows that the traditional statistical methods give rise to a high level of false positive results.

The article “Cluster failure: why fMRI inferences for spatial extent have inflated false positive rates” has been widely discussed in media, New York Times among others, and ended up number one on the Linköping University top list for articles discussed in social media, far ahead of the number two article.

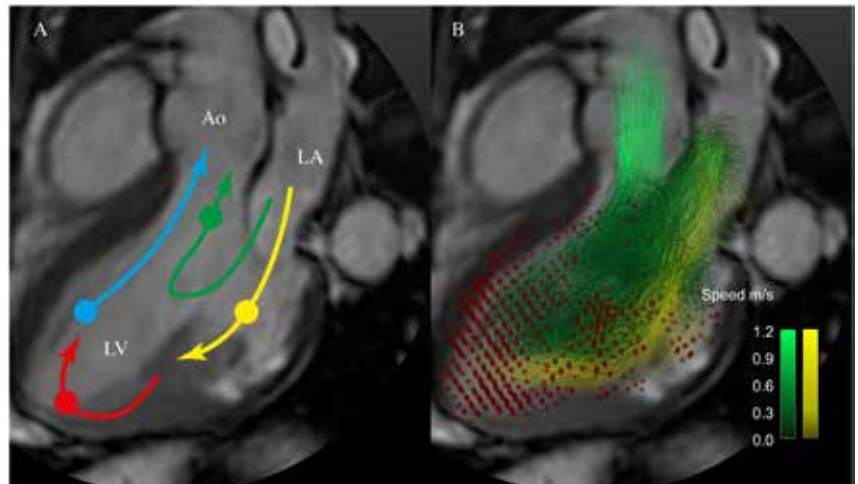




AUNT MINNIE HIGHLIGHTS CMIV PROJECT

In the article "4D flow MRI shows smallest hint of LV dysfunction" Aunt Minnie Europe highlights the CMIV project "Altered Diastolic Flow Patterns and Kinetic Energy in Subtle Left Ventricular Remodeling and Dysfunction Detected by 4D Flow MRI" published in PLOS One in mid August.

The research by Carl-Johan Carlhäll and colleagues shows that four-dimensional flow MRI can depict even subtle changes in left ventricular (LV) function, bringing new insight to the diagnosis of patients with mild left ventricular dysfunction and remodeling.



THE FERNSTRÖM PRIZE TO INDIA MORRISON

This year the Fernström prize was awarded the CMIV researcher India Morrison. She received the prize for her "successful cross-disciplinary research on the role of touch sensibility for well being and pain."

India Morrison's research involves human neuroimaging techniques, particularly functional magnetic resonance imaging (fMRI), including mapping of white matter connections in the brain using diffusion tensor imaging (DTI) and functional connectivity using resting state imaging. It also seeks to characterize gene-brain associations between neural variables and single



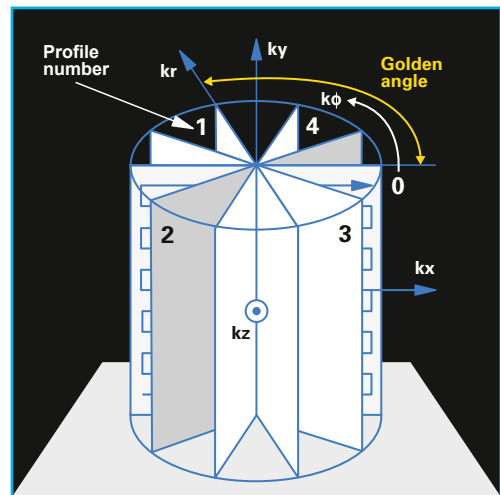
nucleotide polymorphisms (SNPs), and to relate behavioral and neural variables to measures indexing sympathetic nervous system responses and autonomic modulation.

CMIV IMAGING CHAIN

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



Information is gathered using novel imaging equipment



Raw data is processed using complex calculations and algorithms

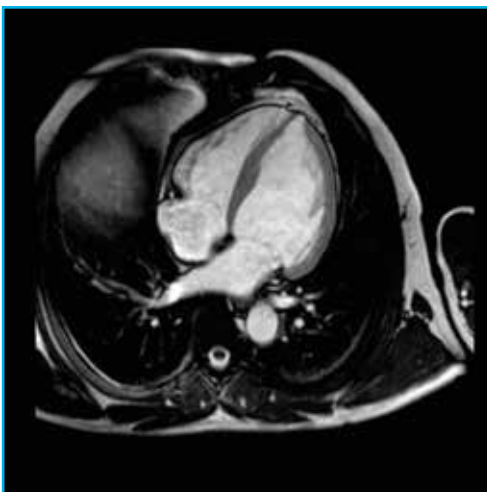
Today, CMIV conducts focused front-line research within multi-disciplinary projects providing solutions to tomorrow's clinical issues. The mission is to develop future methods and tools for image analysis and visualization for applications within health care and medical research.

CMIV has a unique constellation in which research in the university provides the opportunity for clinical benefit in the region while the industry benefits nationally and internationally. The activities aim to combine different

demands were the university seeks publications in high quality journals and the region wishes that the research and development comes to patient benefit. CMIV's organization centrally located within the university hospital creates conditions that combine these requirements. Results from basic research in universities can be utilized in clinical research which can then result in scientific publications, and patient care.

The research projects at CMIV are all part of the imaging chain. Projects move dynamically through the chain

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



Important findings are visualized in a comprehensive way



Images and findings are used in patient care

A hand is shown interacting with a circular, glowing interface. The interface features several white icons on a dark background, including a gear, a microscope, a person, and a brain. The hand is positioned at the bottom right, with the index finger touching one of the icons. The background is dark and textured, suggesting a futuristic or medical setting.

FLAGSHIP PROJECTS

The 2016 flagship projects were selected by the CMIV scientific council. The projects together represent the broad and multi-disciplinary research at CMIV. The flagship projects were chosen through a nomination procedure and the resulting projects complement each other in modalities, project stage and medical area.



SEEING ORGAN FUNCTION

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

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

To diagnose degenerative brain

diseases the centers that control brain functions and the connections between them needs to be localized. New MRI techniques can provide this information and provide the basis for image-based measurement of disease severity in e.g. Alzheimer's disease.

– We have chosen to focus on the heart and brain as they are both vital organs, although essentially different from each other, says Professor Ingrid

Hotz, one of the partners of seeing organ function.

– Now in the second year of the project we can see that it pays off that CMIV has substantial knowledge in both fields with proven track record of world-class research, says Anders Ynnerman who is the principal investigator of the project.

In both areas different types of functional imaging are progressively



PROJECT INFORMATION

PROJECT NAME

Seeing Organ Function

PROJECT LEADER

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

MAIN PROJECT PARTICIPANTS

Anders Ynnerman, Magnus Barga, Tino Ebbens, Maria Engström, Markus Heilig (MD), Ingrid Hotz, Matts Karlsson, Hans Knutsson, Peter Lundberg, Anders Persson (MD), Karin Wårdell

GRANTS

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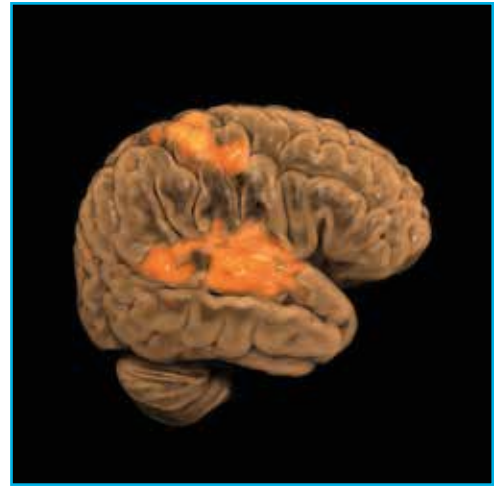
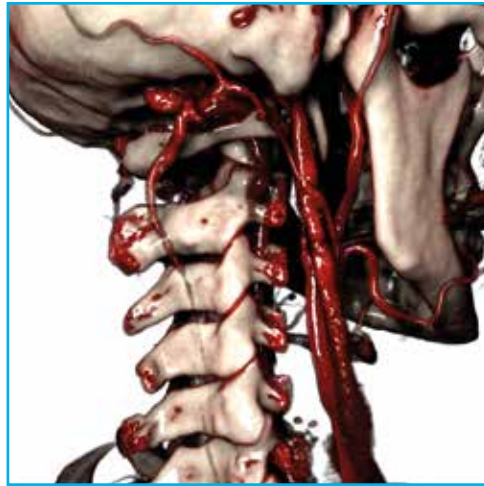
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Jonas Lantz, Lillian Henriksson, Anders Persson, Matts Karlsson, and Tino Ebbens. "Patient-Specific Simulation of Cardiac Blood Flow From High-Resolution Computed Tomography." *Journal of Biomechanical Engineering*, 138, no. 12 (2016): 121004.

Karin Lundengård, Gunnar Cedersund, Sebastian Sten, Felix Leong, Alexander Smedberg, Fredrik Elinder, and Maria Engström. "Mechanistic mathematical modeling tests hypotheses of the neurovascular coupling in fMRI." *PLoS Comput Biol* 12, no. 6 (2016): e1004971.

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





“It is exciting to see what is possible, bringing together researches with different background all working on one common vision”

- Ingrid Hotz

complementing the traditional imaging, and there is strong medical motivation for accelerating this progress. The Seeing organ function project takes on the urgent task of developing new methods to capture, process and present this rich functional information.

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

– For each sub-project we start with a medical problem and work interdisciplinary, linking medical research and clinical use with novel technical approaches to find new solutions, Ingrid

continues.

– The project is now entering its second phase and it is a pleasure to see how things are growing more and more together. First novel results integrating imaging, simulation and visualization become visible and we already can report some success stories.

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

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

The sub-project “Further system In-

tegration” will combine the results from the technical sub-projects into integrated tools for studying cardiac and brain function. This includes image-based models of the individual patient’s heart function and integration of data about brain activity, relations between the various centers and the concentration of neurotransmitters.

– Seeing organ function is a visionary project with ambitious goals. It is the first big project that engages CMIV as a whole, says Anders. The project is important for the development of image-based health care and takes on very important technical challenges.

– Having the possibility to be a part of such a visionary project, with this high impact in the area of medical IT is a privilege, Ingrid continues.

– It is exciting to see what is possible, bringing together researches with different background all working on one common vision.



LIVER FUNCTION EVALUATION

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

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

first week after the surgery is a critical time since the small sized liver has to manage the job of a full liver.

Today, determination of how much of the liver to remove is difficult as only a rough estimate of the liver function can be made. Occasionally, patients may suffer from liver failure following radical surgery. On the other hand, some patients are wrongly judged unfit for surgery when the rough estimate

suggests that they will not survive the procedure. With a better estimate of size and function in the liver residue more patients could be surgical candidates.

– The research project started when the hepatologist Stergios Kechagias asked me if I could help him to measure fat accumulation in the liver. After that the project has just continued to grow and evolve, says Professor Peter



PROJECT INFORMATION

PROJECT NAME

Liver Function Evaluation

PROJECT LEADER

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

MAIN PROJECT PARTICIPANTS

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

GRANTS

Swedish Research Council (VR/NT)
2009-2011/2012

Swedish Research Council (VR/MH)
2013-2015/2016

VINNOVA 2013-2017

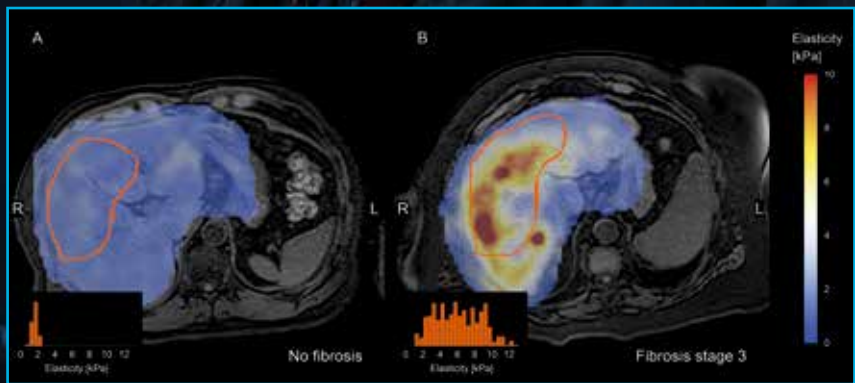
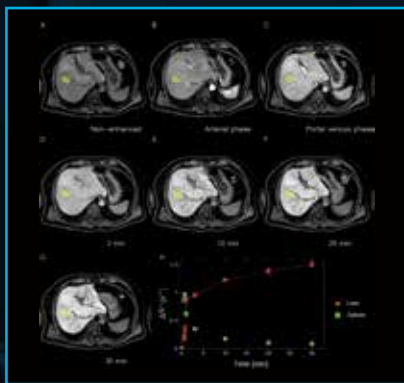
Swedish Research Council (VR/NT)
2015-2018/2019

KEY PUBLICATIONS

Norén B, Forsgren MF, Dahlqvist Leinhard O, Dahlström N, Kihlberg J, Romu T, Kechagias S, Almer S, Smedby Ö, Lundberg P [2013] Separation of Advanced from Mild Hepatic Fibrosis by Quantification of the Hepatobiliary Uptake of Gd-E0B-DTPA *Eur Radiol* 2013 Jan;23(1):174-81. doi: 10.1007/s00330-012-2583-2. Epub 2012 Jul 27.

Dahlqvist Leinhard O, Dahlström N, Kihlberg J, Sandström P, Brismar TB, Smedby Ö, and Lundberg P [2012] Quantifying differences in hepatic uptake of the liver specific contrast agents Gd-E0B-DTPA and Gd-B0PTA: a pilot study. *Eur Radiol*. 2012 Mar;22(3):642-53. Epub 2011 Oct 9.

Forsgren MF, Dahlqvist Leinhard O, Cedersund G, Lundberg P [2014] Physiologically Realistic and Validated Mathematical Liver Model Reveals Hepatobiliary Transfer Rates for Gd-E0B-DTPA Using Human DCE-MRI Data *PLoS ONE*, 2014 Apr 18;9(4):e95700. doi: 10.1371/journal.pone.0095700. eCollection 2014.



"I'm passionate about my research being closely related to healthcare. I always want to do things that are of direct value for the patient."

- Peter Lundberg

Lundberg, project manager of "Liver function evaluation".

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. Peter's research group has developed multimodal methods for analyzing the liver.

- Our MR protocol for analyzing the liver status is now ready to be tested in

the workflow at other hospitals. Peter continues. This is an important step in showing that our method is ready for routine use. Health economists will then analyze if the method has an economical value, or may increase the quality of care.

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 from diseased tissue regions.

- Together with the CMIV spinoff AMRA AB we are developing a tool where data from different types of liver measurements may be gathered. The

data will support the physician in determine how to treat the patient, Peter explains.

Apart from MR data the tool will also be able to collect other types of information. In line with this the project is investigating the possibility to use digital pathology in analyzing the biopsies and instead of a visual examination use image analysis to obtain a value of for example fat infiltration.

Peter says that the project is dependent on the collaboration between university, healthcare and industry.

- CMIV means everything for the project. Without the center it would be impossible to realize our ideas since we need the competence from all three cornerstones as well as advanced tools in an environment suitable for patients.

-I'm passionate about my research being closely related to healthcare. I always want to do things that are of direct value for the patient, Peter concludes.

A patient is lying inside a Philips MRI scanner. The patient is wearing a green hospital gown and is positioned on the scanner's bed. The scanner's gantry is visible above the patient, with the Philips logo on it. The lighting is dim, typical of an MRI room.

SAND:MAN

Sleep is a naturally recurring state, which still is a mystery since its function and purpose is not fully understood. In this project we explore the neural networks of the human brain that are involved in the regulation of sleep and wakefulness. For this quest, patients with sleep disorders provide keys to the understanding of why we sleep and why we wake up.

Sleep disorders range from severe sleep difficulties, insomnia, to problems with too much sleep, hypersomnia. These disorders are often associated with a variety of other symptoms, such as cognitive dysfunction, making sleep disorders difficult to diagnose and treat.

– In this project, we have previously investigated patients with periodic idiopathic hypersomnia, or the Kleine-

Levin syndrome, using magnetic resonance imaging (MRI) and cognitive tests. Our ongoing study is about brain function and body composition in adolescents with narcolepsy, says Professor Maria Engström project manager of the SAND:MAN project.

Narcolepsy is characterized by daytime sleep attacks, poor nighttime sleep, and sudden loss of muscle tonus (cataplexy) caused by the loss of certain

neurons in the hypothalamus. These neurons produce a neurotransmitter, orexin, that takes part in the regulation of sleep and wakefulness, and also body metabolism. The relation between brain function and the various clinical symptoms in narcolepsy is still unclear.

– We use functional MRI (fMRI) and simultaneous electroencephalography (EEG) to explore the relation between brain function and clinical symptoms in



PROJECT INFORMATION

PROJECT NAME

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

PROJECT LEADER

Maria Engström, IMH/Radiological Sciences

MAIN PROJECT PARTICIPANTS

Natasha Morales-Drissi, Suzanne Witt, Anne-Marie Landtblom, Tove Hallböök, Atilla Szakacs, Thomas Karlsson, Henrietta Ståhlbrandt, Peter Lundberg, Anders Tisell, Sofie Tapper, Karin Lundengård, Sebastian Sten.

GRANTS

FORSS 2012-2018

KEY PUBLICATIONS

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

Suzanne T Witt, Natasha Morales Drissi, Sofie Tapper, Anna Wretman, Attila Szakács, Tove Hallböök, Anne-Marie Landtblom, Thomas Karlsson, Peter Lundberg, Maria Engström. Evidence for cognitive resource imbalance in adolescents with narcolepsy. In revision *Brain Imaging and Behavior*, 2017.

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

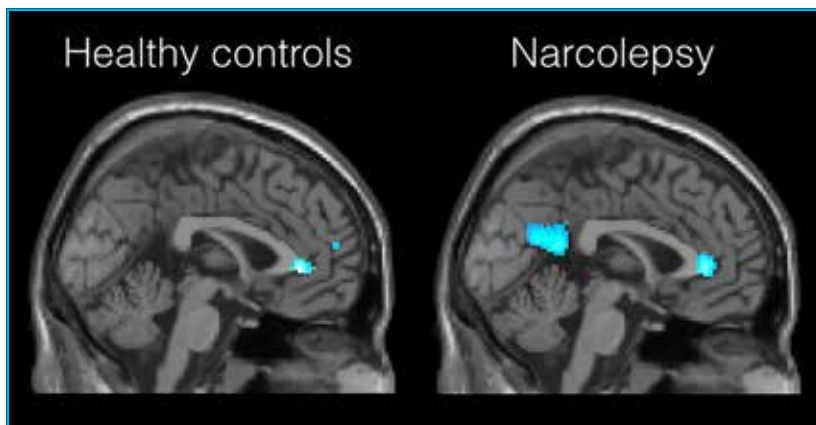


Figure 1: Narcolepsy patients had decreased deactivation in the default mode network compared to healthy controls.

narcolepsy, Maria continues.

The method is based on the fact that the blood flow is increased in activated areas of the brain to supply energy and oxygen. It is the blood oxygenation differences between active state and rest that is measured with fMRI.

Originally Maria optimized the method for surgery planning but when she met Professor Anne-Marie Landtblom who is interested in the Klein-Levin syndrome they started to collaborate.

-In the beginning it was difficult to know how to interpret the results. Is it good with high brain activity or should it be low? Maria explains.

Maria Engström is a former nurse who went back to school to study theoretical physics. Now she combines her knowledge in medicine and physics to investigate how the brain works.

- I have a genuine interest in finding out how things work. It is what pushes me forward in my research.

To further understand what the method measures and how the brain

works the research group uses mathematical modeling and system biology. What is biologically causing the increased blood flow? Maria is building theoretical models of the process and tests it against the data collected from patients.

To understand the sleep disorders are of equal importance as to understand how normal sleep works for the research group. Ultimately it's about understanding the brain.

-When trying to understand the normal function it can be very helpful to start with investigating something that is wrong. It's part of a detective work, Maria continues.

In our first study, we observed that adolescents with narcolepsy have altered resting state brain dynamics. Compared to healthy controls, they were less likely to stay in a specific brain microstate, related to the default mode network, which is active when the brain is at rest. We concluded that narcolepsy might be accompanied with a disrupt-

tion in the default mode network that is disease specific. This conclusion was supported by our second study where we investigated working memory function. Many patients with narcolepsy complain about subjective working memory problems, but research has not found objective evidence. In our study, we neither found signs of working memory performance deficits nor specific brain dysfunction related to working memory. However, we did find an imbalance of cognitive resources manifested by decreased activation of the default mode network pointing to a dysregulation within the sustained attention system, which could be the origin behind self-reported cognitive difficulties in narcolepsy.

Future research involve mathematical modelling to further investigate brain mechanisms in the default mode network and the hypothalamus in narcolepsy.



"I have a genuine interest in finding out how things work. It is what pushes me forward in my research"

- Maria Engström



RESEARCH PROJECTS

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



PROJECT NAME

Clinical Implementation of Synthetic MRI

PROJECT LEADER

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

MAIN PROJECT PARTICIPANTS

Anne-Marie Landtblom, Peter Lundberg, Maria Engström, Tino Ebbers, Ebo de Muinck, Ida Blystad, Jan Engvall, Stefan Tell, Peter Johansson, Sten Bergström, Lisa Warnroth, Anders Swenningsson, Richard Birgander, Elna-Marie Larsson, Tobias Granberg

KEY PUBLICATIONS

Modelling the presence of myelin and oedema in the brain based on multi-parametric quantitative MRI. M Warntjes, M Engström, A Tisell, P Lundberg. *Frontiers in Neurology* 2016, doi 10.3389

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CLINICAL IMPLEMENTATION OF SYNTHETIC MRI

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

A close collaboration between researchers at CMIV and the University hospitals in Linköping, Umeå, Örebro, Uppsala and Göteborg ensured the

clinical relevance of the technique. A number of technical and clinical studies were performed to validate the various aspects of synthetic MRI on scan time reduction and automatic brain segmentation. A spin-off company, SyntheticMR AB, was created to ensure an installable, safe product including the necessary regulatory requirements. After this initial prototype phase more hospitals became involved, among which a number in the EU and US, to introduce synthetic MRI as a standard procedure into the clinical workflow. For example, the Sahlgrenska University Hospital, the entire County Council of Västerbotten and Linköping use it

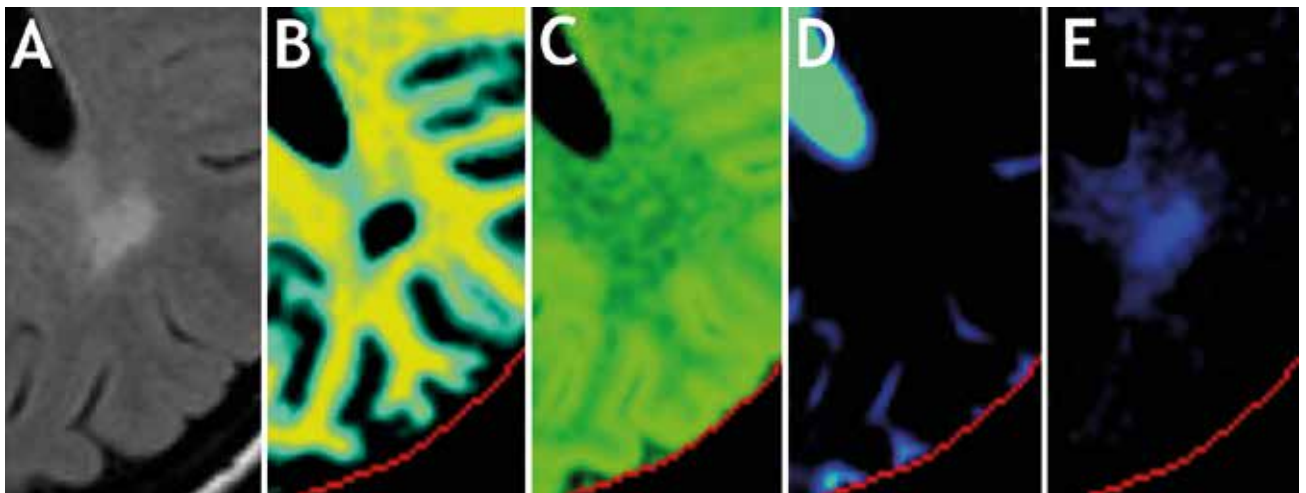


Figure 1. Example of synthetic MRI on an MS patient, showing new kinds of brain segmentation. Only a zoomed part of an axial slice is shown. Based on a single acquisition, different conventional images can be recreated such as a T1W, T2W or FLAIR (A). Using the same data, tissue can be assessed, in this case on the presence of myelin (B), cells (C), cerebrospinal fluid (D) and edema (E). Automatic tissue segmentation enables more objective patient monitoring since these values can be monitored over time and compared to a healthy reference.

as standard protocol for MS patients. Queen Silvia Hospital in Gothenburg and Cincinnati Children's Hospital apply the approach for their pediatric scanning.

The major MR vendors GE Healthcare, Philips Healthcare and Siemens Healthineers now offer synthetic MRI as part of their product, based on the CMIV spin-off. More and more hospitals are starting to get familiar with the technique. An increasing number of evaluation projects are ongoing to validate the time reduction on the MR scanner and to assess the robustness of technique on diseases such as Multiple

Sclerosis, hydrocephalus, cancer and dementia in clinical practice.

Exciting new research ideas are worked on such as brain myelination assessment. Synthetic MRI is also tested on other anatomies e.g bone metastases and cartilage assessments. Further examples are the characterization of prostate tumors and of plaques in the large vessels. A new quantification sequence is developed which is so fast that the entire heart chambers can be measured within one single breath-hold. The latter one is now scaled up for higher resolution.

In the history of MRI general images

were acquired which were subjectively interpreted by radiologists. With the advent of synthetic MRI we believe that this is going to change dramatically: Scan times will be shorter and the decision support will be more based on numbers and statistics. Automated analysis can make the work of the radiologist both faster and more objective. The technique is available on the major scanner brands, which will decrease the variation between different hospitals. Synthetic MRI is a clear example of excellent cooperation between university, hospital and commercial companies, made possible by CMIV.

PROJECT NAME

Assessment of cardiovascular blood flow using 4D flow MRI

PROJECT LEADER

Tino Ebbers, Department of Medical and Health Sciences, Division of Cardiovascular Medicine & Department of Science and Technology, Division of Media and Information Technology

MAIN PROJECT PARTICIPANTS

Senior research leaders: Tino Ebbers, Carl-Johan Carlhäll, Jan Engvall, Petter Dyverfeldt

Post Doc: Jonas Lantz, Merih Cibis, Hojin Ha

PhD students: Belén Casas Garcia, Mariana Bustamante, Federica Viola, Magnus Ziegler, Jakub Zajac, Alexandru Fredriksson

GRANTS

Swedish Research Council 2011-2013
European Research Council 2013-2017

KEY PUBLICATIONS

Ha H, Lantz J, Haraldsson H, Casas B, Ziegler M, Karlsson M, Saloner D, Dyverfeldt P, Tino Ebbers T. Assessment of turbulent viscous stress using ICOSA 4D Flow MRI for prediction of hemodynamic blood damage. *Scientific Reports* 2016; 6:39773.

Svalbring E, Fredriksson A, Eriksson J, Dyverfeldt P, Ebbers T, Bolger AF, Engvall J, Carlhäll CJ. Altered Diastolic Flow Patterns and Kinetic Energy in Subtle Left Ventricular Remodeling and Dysfunction Detected by 4D Flow MRI. *PLOS ONE* 2016; 17:11(8):e0161391.

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

ASSESSMENT OF CARDIOVASCULAR BLOOD FLOW USING 4D FLOW MRI

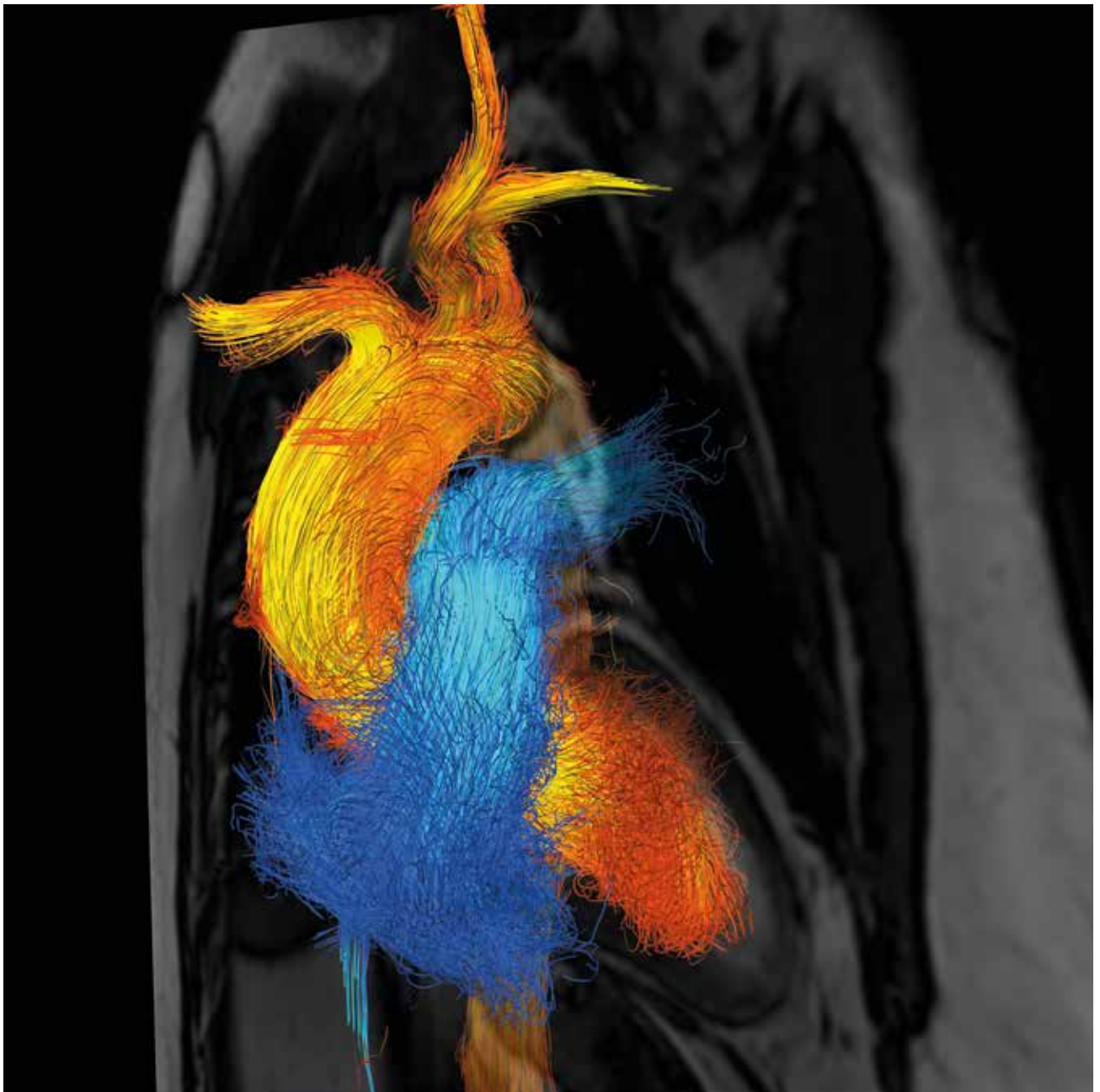
The primary purpose of the cardiovascular system is to drive, control and maintain blood flow to all parts of the body. The heart acts as the pump in this system, and has as task to move blood through the body. Using a complex and ingenious interplay between muscle contraction and valve function, it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

Sometimes small abnormalities occur at birth or by disease, cardiovascular diseases are often found in obesity, diabetes and an aging population. The

heart can compensate for these to some extent, but they can also lead to inefficient pump function and sometimes to a cascade of more severe abnormalities.

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

Imaging that is focused on answering the most relevant questions, with an



eye towards tangible improvements in diagnosis, therapy and outcomes can facilitate treatment of cardiac patients with higher quality and lower costs.

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

The project has developed a method for flow quantification using MRI which allows for simultaneous meas-

urement of time-resolved, three-dimensional (time + 3D = 4D) blood flow velocity and turbulence intensity. This method reveals blood flow patterns in the heart and the large vessels.

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

Studying cardiovascular blood flow dynamics in patients and healthy subjects will improve our understanding of

the roles of flow dynamics in health and disease, leading to improved cardiac diagnostics, novel assessments of pharmaceutical, interventional, and surgical therapies, and promoting exploration of new avenues for management of cardiac disorders.

PROJECT NAME

The Interrelationship Between Blood Flow and Vascular Disease

PROJECT LEADER

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

MAIN PROJECT PARTICIPANTS

Magnus Ziegler, Jonas Lantz, Marcus Lindenberger, Martin Welander, Carl-Johan Carlhäll, Tino Ebbers, Ebo de Muinck, Toste Länne

GRANTS

Swedish Research Council
Forskningsrådet i Sydöstra Sverige (FORSS)

KEY PUBLICATIONS

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

Pulse Wave Velocity with 4D Flow MRI: Systematic Differences and Age-Related Regional Vascular Stiffness. *Magn Reson Imaging* 2014; 32(10):1266-71.

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THE INTERRELATIONSHIP BETWEEN BLOOD FLOW AND VASCULAR DISEASE

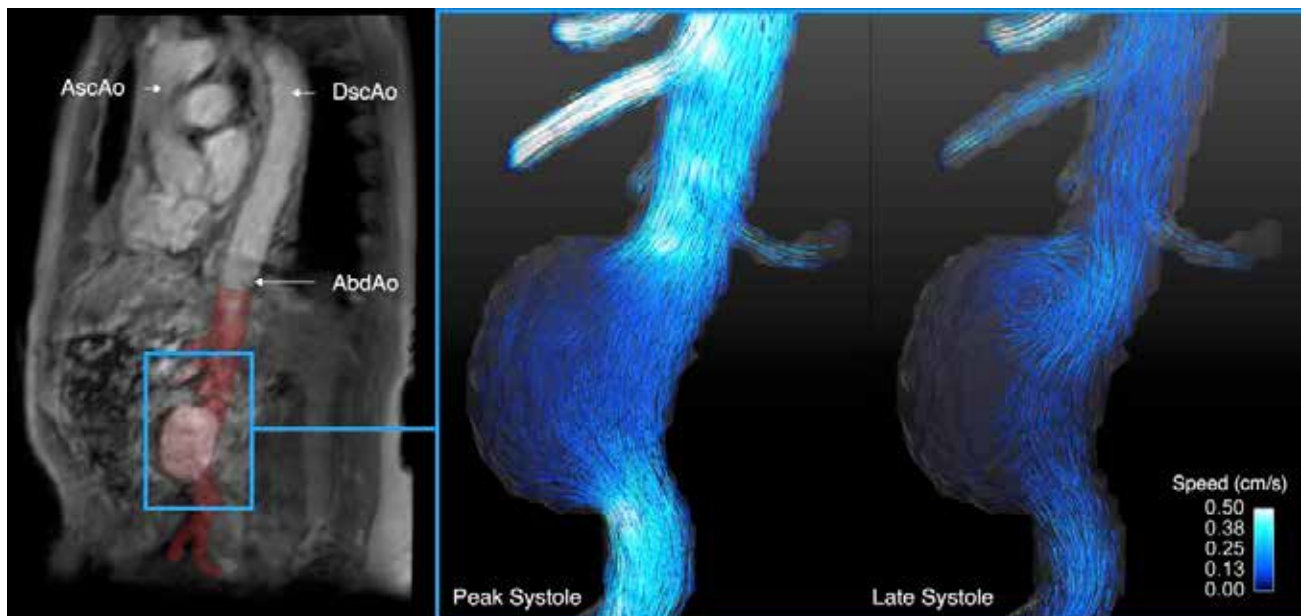
The main purpose of our arteries is to distribute blood to the organs of our body. Arteries can sometimes become constricted and this may affect the blood flow to downstream vasculature. Today, the risk that a constriction affects the blood flow is assessed based on the size of the constriction. It has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

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

Many arterial diseases are related to atherosclerosis. The atherosclerotic disease process starts when we are young

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

The more advanced stages of atherosclerotic disease are characterized by large deposits of fat in the arterial wall. These deposits, plaques, constrict the arterial lumen. The plaques may rupture, which can cause stroke or a heart attack. The blood flow in constricted arteries can become turbulent. Several studies indicate that turbulent forces increase the vulnerability of the



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

plaques and the risk of rupture. Today's techniques for assessing the effects of flow on the vessel wall focus on forces that exist also in normal blood flow in healthy arteries. However, methods that permit assessment of the impact of turbulent forces do not exist.

We develop methods for the determination of pressure wave velocity and the effects of turbulent flow on the vessel wall. In achieving our goals, we plan to

use an advanced magnetic resonance imaging (MRI) technique referred to as 4D flow MRI, which permits comprehensive assessment of time-varying three-dimensional (time + 3D = 4D) blood flows. This technique has the potential to unveil information about key aspects of blood flow. However, dedicated research efforts are needed to realize this potential.

Being able to measure aspects of

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

PROJECT NAME

DOPPLER-CIP

PROJECT LEADER

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

MAIN PROJECT PARTICIPANTS

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

GRANTS

EU grant, 2010-2014

KEY PUBLICATIONS

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

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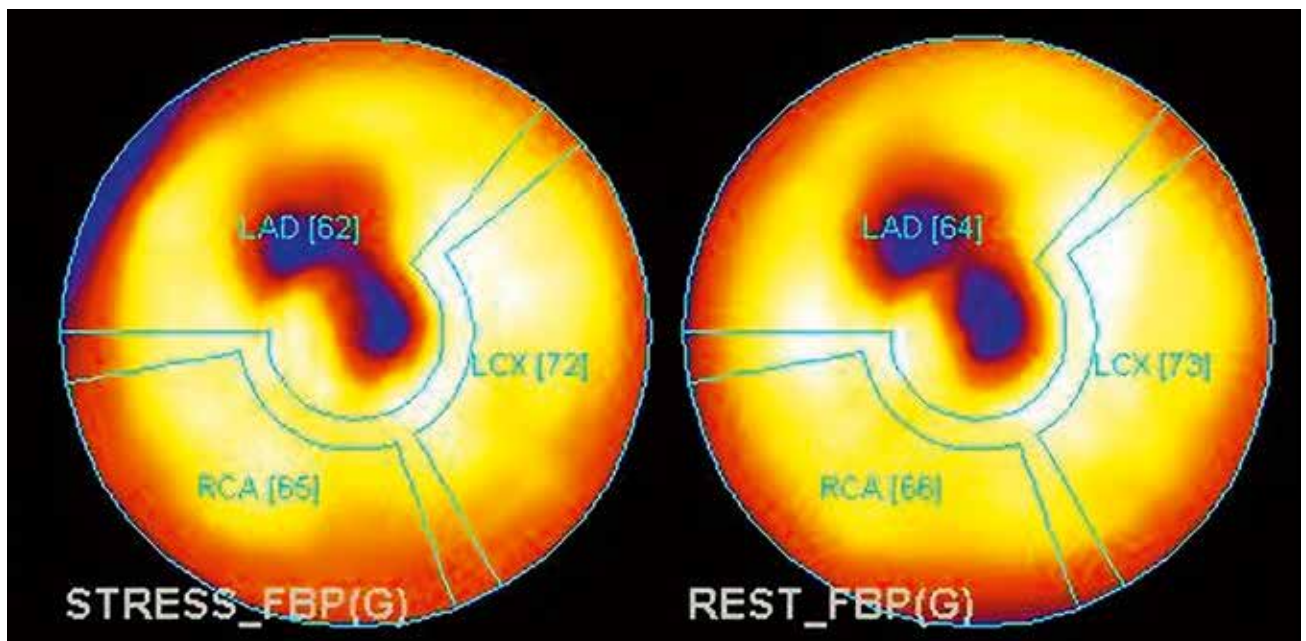
DOPPLER-CIP

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

Restoring blood flow to a region of chronic ischemia can stop the process of remodeling and allow partial or full

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

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



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

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

registered.

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

In Linköping, almost all 192 patients have undergone at least three stress imaging tests. We will have an excellent opportunity to compare the different modalities in our local material. The patients in this study have helped us

develop new MRI-based methods for the measurement of wall motion abnormalities and for 3D-visualization of intracardiac blood flow.

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

MEASURING CARDIAC PERFUSION USING DYNAMIC CT ADENOSIN TESTING

PROJECT NAME

Measuring cardiac perfusion using dynamic CT adenosin testing

PROJECT LEADER

Jan Engvall, Department of Medical and Health Sciences, Division of Cardiovascular Medicine and Anders Persson, Department of Medical and Health Sciences, Division of Radiological Science

MAIN PROJECT PARTICIPANTS

Jakob de Geer, Marcus Gjerde, Petter Quick

GRANTS

Magnus Bergvalls stiftelse

KEY PUBLICATIONS

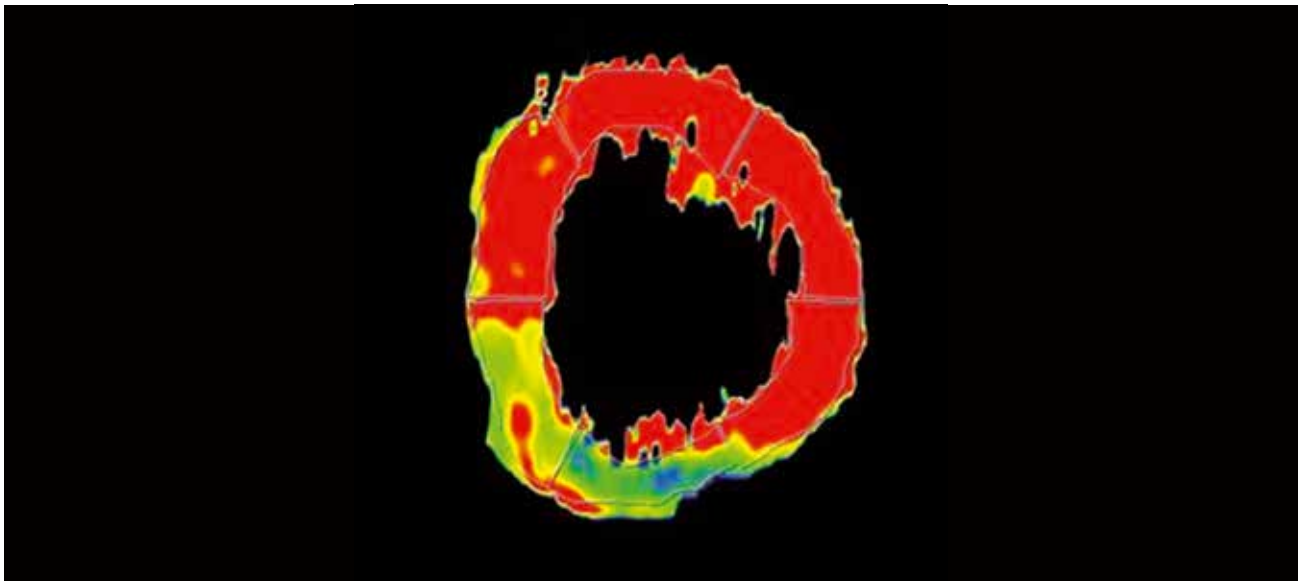
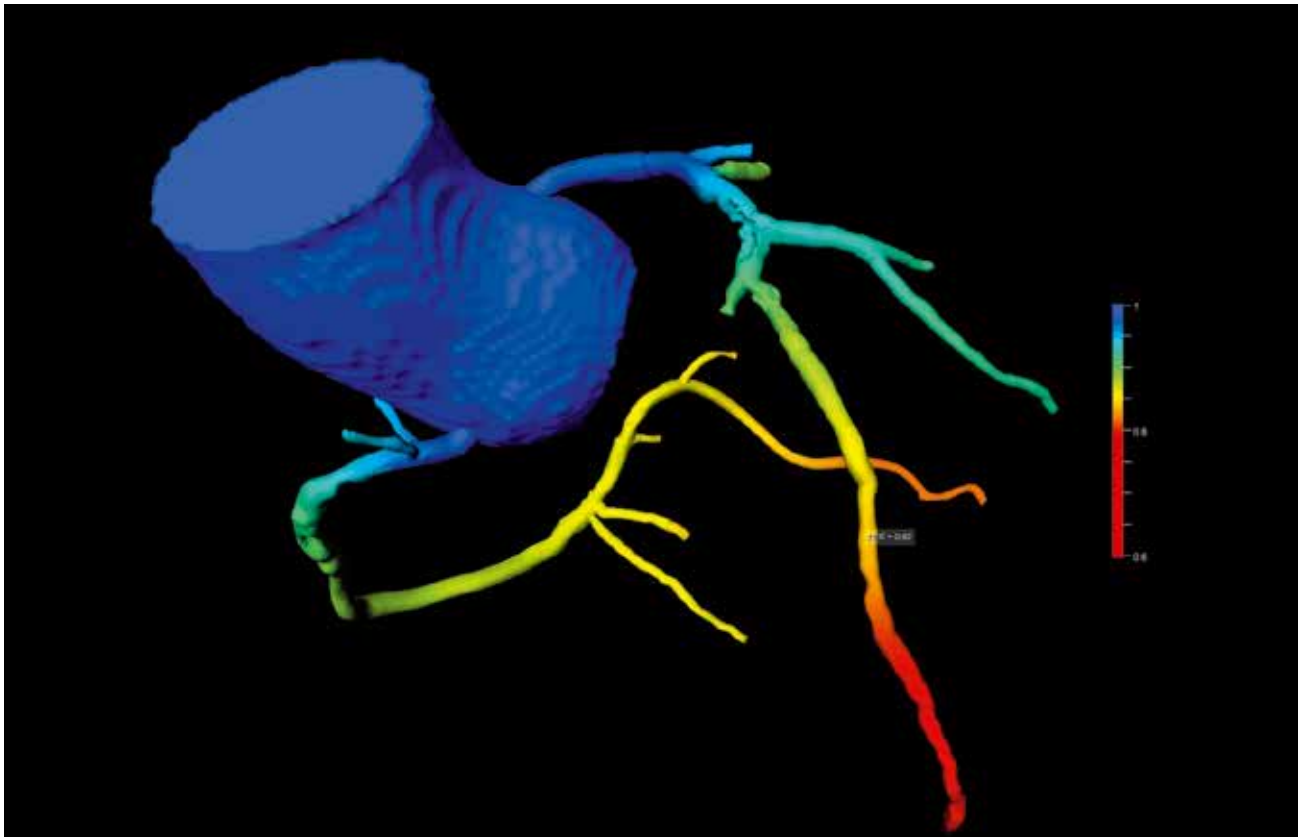
DeGeer J, Gjerde M, Olsson E, Brudin L, Persson A, Engvall J. Large variation in blood flow between left ventricular segments, as detected by Adenosine stress dynamic CT perfusion. *Clinical Physiology and Functional Imaging* 2014 May 19. doi:10.1111/cpf.12163

Atherosclerotic coronary artery disease is caused by changes to the wall known as plaque. The plaque consists of deposits of cholesterol, cells and calcium sometimes causing obstruction to the coronary flow. The diagnosis of coronary artery disease rests on the visualization of atherosclerotic plaque or limitations to flow. Invasive investigation should be reserved for patients with a high likelihood of significant disease. Various exercise tests are employed to uncover effects of obstruction that may be silent at rest.

Myocardial blood flow may be visualized in different ways, most often using a gamma camera to trace the myocardial uptake of injected markers. The relationship between myocardial blood flow and the tracer molecules has been shown to be fairly linear within the range of normal resting coronary flow while uptake rolls off with increasing flow.

An alternative approach to calculating myocardial blood flow could be to use effects of angiographic contrast media in cardiac computed tomography (CT). Recent improvement in CT technology with higher temporal resolution and more advanced software has motivated a renewed interest in this method.

There are a number of critical prerequisites for using this approach: the scanning of the left ventricle must be fast to be able to detect the short-lived phase of increase in attenuation that comes with the wash-in of contrast, the X-ray detector has to be large enough to allow coverage of the entire heart and reconstruction and evaluation of the recording need to be fast and accurate. Ideally, the contrast medium itself should not induce any change in coronary flow. A number of smaller studies have been published but the method still



needs extensive validation before being incorporated into clinical practice. Thus, the purpose of this study was to evaluate the variation in blood flow in cardiac segment determined to be normal or abnormal according to the gamma camera result. In addition, we wanted to compare CT blood flow values obtained with manual delineation

of the cardiac wall with those obtained with automated software.

A positive but moderate correlation was found between CT and the gamma camera. Large variations in CT blood flow were detected which suggests that a single cut-off value for stress myocardial blood flow is inadequate to detect ischemic segments.

The study now continues along two different paths: one repeating the study with an improved CT-scanner with a larger detector, and the other along the path of using non-invasive calculation of fractional flow reserve, to improve the prediction of significance of coronary stenoses detected by CT.

PROJECT NAME

Scapis-Echo

PROJECT LEADER

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

MAIN PROJECT PARTICIPANTS

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

GRANTS

KAW, Swedish Heart and Lung Foundation

KEY PUBLICATIONS

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

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SCAPIS-ECHO

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

SCAPIS is aiming for improved diagnosis and treatment of cardiovascular and lung disease. In total 30,000 healthy individuals in the age

of 50-64 years will be examined in the study. Of these 5,000 will be examined in Linköping. The participants' lungs and cardiovascular system are examined with computed tomography and ultrasound. All the collected data will be saved in a knowledge bank, which will be a national resource used for research.

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

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

However, other studies have shown that myocardial function is another powerful predictor of prognosis. A third predictor has been suggested, namely the presence of mechanical disper-

sion. Mechanical dispersion has been thought to represent the mechanical effect of electrical dispersion, which in itself represents an electrical instability that could be derived from previous myocardial scarring.

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

Therefore, the purpose of Scapis-echo is to determine global longitudinal strain amplitude and peak systolic

dispersion in the Linköping Scapis population of 5,000 participants 50-64 years of age. The participants undergo an echocardiographic study as an additional part of their evaluation in Scapis, which also performs coronary CT and an extensive mapping of cardiopulmonary risk factors.

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

MAGNETIC RESONANCE AND CAROTID ULTRASOUND OBSERVATIONS

Worldwide, the most common cause of death is cardiovascular disease and the dominant cause of cardiovascular disease is atherosclerosis. Atherosclerosis is caused by accumulation of fat, primarily cholesterol in the wall of arteries. When the fat builds up in the arterial wall it causes thickening of the vessel wall and the thickened area bulges out into the vessel, causing narrowing of the artery.

The areas with fat accumulation are called atherosclerotic plaques. Sometimes these plaques rupture causing a blood clot to form. This causes a heart attack if it happens in the arteries of the heart or a stroke if it happens in the arteries feeding the brain.

We have developed an imaging method to identify plaques that are at high risk of rupture. We anticipate that this method will allow us to identify patients with rupture prone plaques and treat them before they suffer from a heart attack or stroke. The method uses magnetic resonance imaging (MRI) and can measure how much fat and blood there is inside atherosclerotic plaques (Figure 1). Plaques with a high fat content and a lot of blood are at higher risk of rupture since fat and blood increase inflammation inside a plaque and inflammation leads to rupture.

Atherosclerotic plaques lead to narrowing of arteries and when blood flows through such a narrowing there is a lot of turbulence immediately behind the narrowing. Turbulent blood flow acts

on the vessel wall and increases inflammation inside the plaque (Figure 2).

In this project we study patients who are scheduled for surgical removal of atherosclerotic plaque. Before surgery, the patients undergo MRI of their carotid arteries and we measure the amount of fat and blood inside the plaque as well as the amount of turbulence. After surgery we study the plaque in a microscope. For this purpose the plaque is cut into a series of very thin sections and the amount of fat and blood as well as the amount of inflammatory cells is measured on each section. Then a 3D reconstruction of the plaque is generated based on these sections. This 3D rendering is compared with the MRI images by overlaying images (Fig. 3).

We have now validated the MRI method for quantification of fat and blood in plaques using 3D histology volumes from five patients who underwent MRI before carotid endarterectomy surgery. We have established that the volume of fat and blood in the plaque as measured by 3D histology correlates strongly to the fat and blood fraction as measured by MRI throughout the plaque. Thus, we show that fat and blood measured from Dixon MRI reliably quantifies the extent of hemorrhage and fat in atherosclerotic plaques as validated by 3D histology.

PROJECT NAME

Magnetic Resonance and Carotid Ultrasound Observations (MR CARUSO)

PROJECT LEADER

Ebo de Muinck, M.D., Ph.D, Department of Medical and Health Sciences, Division of Cardiovascular Medicine

MAIN PROJECT PARTICIPANTS

Marcel Warntjes, Petter Dyverfeldt, Johan Kihlberg, Rodrigo Moreno, Daniel Forsberg, Toste Lanne, Anne-Marie Landtblom, Darren Treanor

GRANTS

Swedish Heart and Lung Foundation

KEY PUBLICATIONS

Moreno R, Koppal S, de Muinck ED. Robust estimation of distance between sets of points. *Pattern Recognition Letters* 2013;34:2192-2198.

Sandeep Koppal, Marcel Warntjes, Jeremy Swann, Petter Dyverfeldt, Johan Kihlberg, Rodrigo Moreno, Derek Magee, Nicholas Roberts, Darren Treanor, Ebo D de Muinck. Direct in vivo Quantification of Intraplaque Hemorrhage and Fat in Atherosclerosis by Magnetic Resonance Imaging. *American Heart Association Annual Scientific Sessions 2014, November 15 - 19, Chicago IL, USA.*

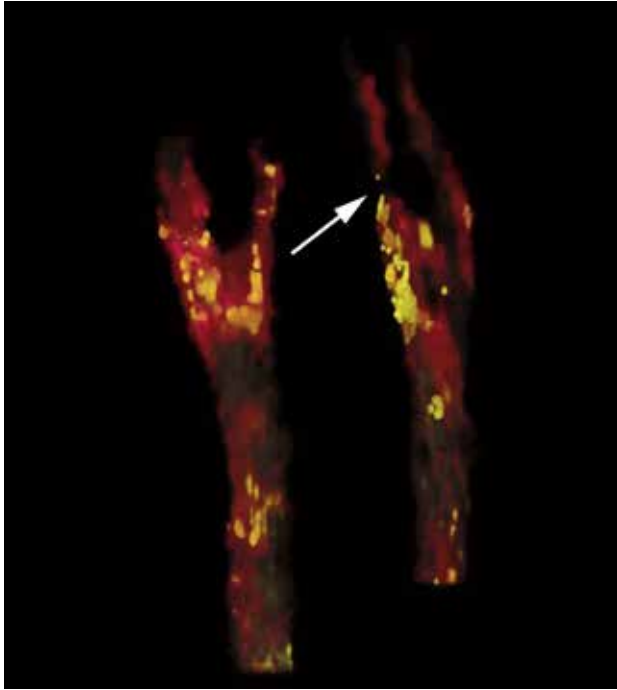


Figure 1. Magnetic resonance image of a patient with atherosclerotic plaque in both carotid arteries. The plaque has caused a severe narrowing in the right carotid artery (arrow). The amount of fat in the plaques is shown in yellow and the amount of blood is in red.

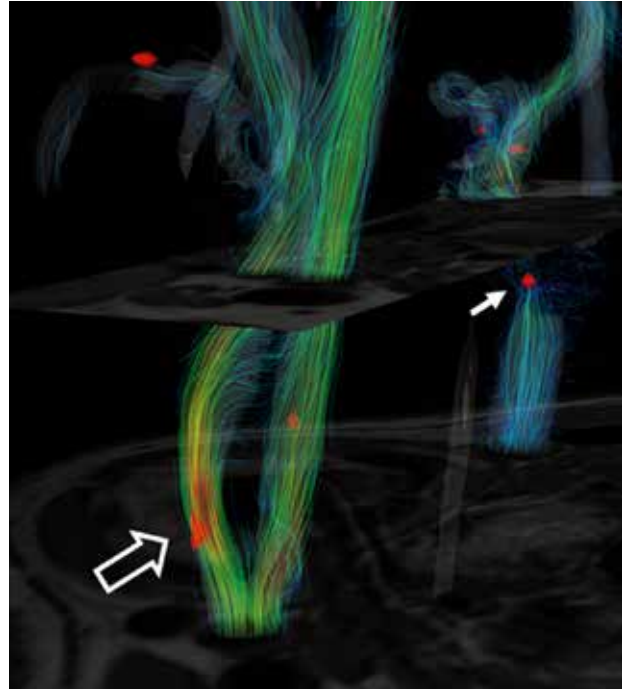


Figure 2. MRI turbulence data from a patient with carotid artery stenosis. The intensity of turbulence is graded according to a color scale, showing areas with a lot of turbulence in red and yellow downstream from a carotid artery stenosis (solid arrow) and at the outer wall of the contra-lateral internal carotid artery (open arrow).

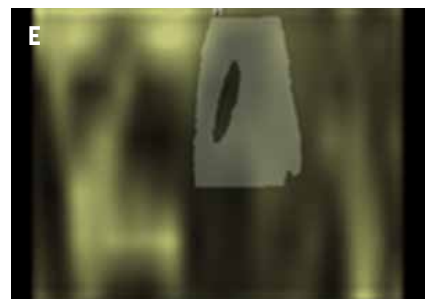
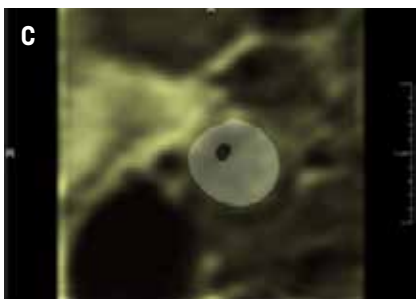
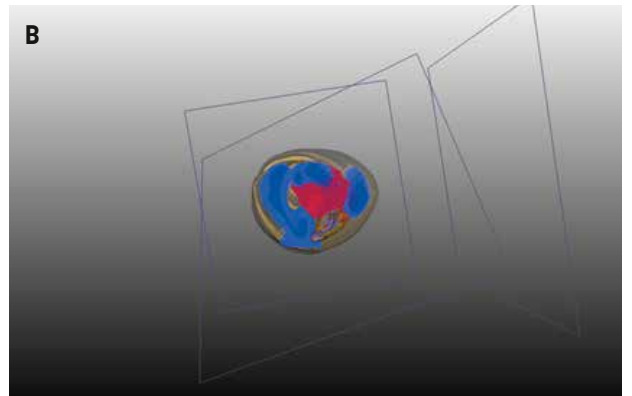
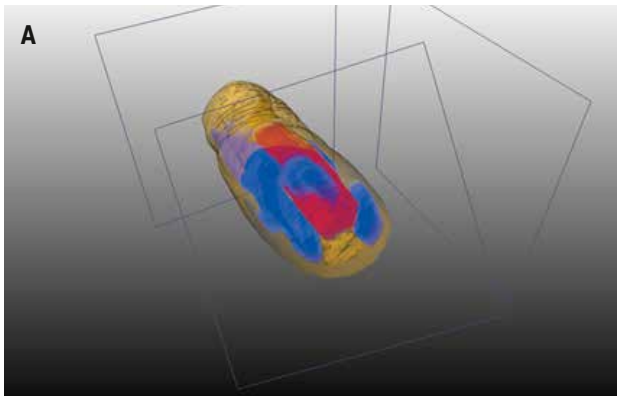


Figure 3. A-B 3D histology rendering of the atherosclerotic plaque showing the areas of internal hemorrhage (red) and lipid rich necrotic core (blue) within the lesion (yellow). C-E Spatial registration of 3D histology over 3D T1 weighted black blood sequence in an orthographic representation.

PROJECT NAME

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

PROJECT LEADER

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

MAIN PROJECT PARTICIPANTS

Eva Nylander, Jan Engvall, Tino Ebbers

GRANTS

Svenska Läkar­sällskapets Projektanslag 2014-2016

KEY PUBLICATIONS

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

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HISTOLOGICAL AND FUNCTIONAL CHANGES IN LEFT VENTRICULAR FUNCTION DUE TO AORTIC STENOSIS

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

Operation is indicated when the valve disease affect hemodynamics and left ventricular function (LVF). Present guidelines suggest surgery when patients are presented with symptoms and/or echocardiographic

parameters. These manifestations are fairly crude as both symptoms and left ventricular dilatation are appearing late in the natural history of the aortic valve disease. Furthermore, we showed previously that symptoms and LVF do not correlate.

In order to be able to keep up performance the LV compensates minor changes by hypertrophy. Further changes present even at histological level as diffuse fibrosis. It is known that regional fibrosis e.g. after myocardial infarction leads to impaired ventricular function. However, there is no informa-

tion available in the medical literature on exactly how diffuse fibrosis affects LVF and whether these are reversible. Thus, understanding how fibrotic changes of the heart muscle are connected to the impairment of LVF could give valuable information.

Previous studies have verified fibrotic regions following myocardial infarction on cardiac magnetic resonance imaging (cMRI). Thus cMRI was proved to be a useful diagnostic modality for myocardial viability and this knowledge has already been translated to clinical practice. While fibrosis is focal and

concentrated in myocardial infarction there is no in-vivo information on the distribution of the fibrotic tissue in the mass of the human heart muscle in aortic valve disease which makes validation of cMRI images by means of histology necessary.

In our ongoing study we validate cMRI (special sequences developed at CMIV) as a diagnostic tool for diffuse myocardial fibrosis and to evaluate the effect of fibrosis on myocardial function. We hypothesize that the amount and the location of the fibrotic tissue can be connected to impairment of LVF

in severe aortic valve disease. By using cMRI we intend to gain information on whether this impairment is reversible following surgery.

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

PROJECT NAME

Quantitative Assessment of Trabecular Bone Structure

PROJECT LEADER

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

MAIN PROJECT PARTICIPANTS

Eva Klintström, Rodrigo Moreno (KTH), Torkel Brismar (KI)

GRANTS

Swedish Research Council (VR-NT) 2007-09
VINNOVA/EuroStars 2015-17

KEY PUBLICATIONS

Klintström E, Klintström B, Moreno R, Brismar TB, Pahr DH, Smedby Ö. Predicting Trabecular Bone Stiffness from Clinical Cone-Beam CT and HR-pQCT Data; an In Vitro Study Using Finite Element Analysis. *PLoS One*. 2016;11(8):e0161101. DOI:10.1371/journal.pone.0161101

Jörgens D, Smedby Ö, Moreno R. Steering second-order tensor voting by vote clustering. *Proceedings - International Symposium on Biomedical Imaging*, vol. 2016 - June (2016). DOI:10.1109/ISBI.2016.7493492

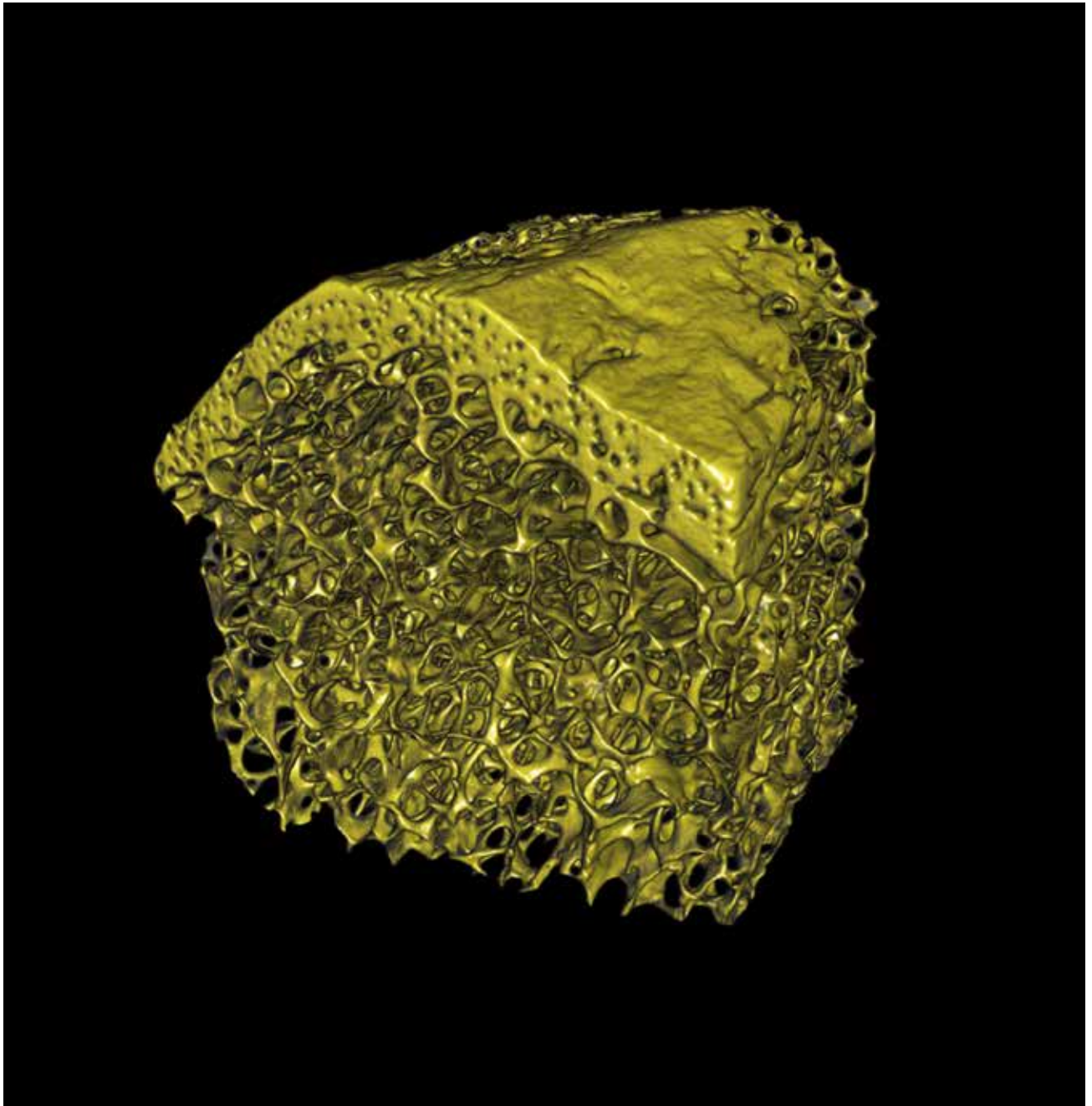
Moreno R, Smedby Ö. Vesselness estimation through higher-order orientation tensors. *Proceedings - International Symposium on Biomedical Imaging*, vol. 2016 - June (2016). DOI:10.1109/ISBI.2016.7493467

QUANTITATIVE ASSESSMENT OF TRABECULAR BONE STRUCTURE

Patients suffering from osteoporosis have an increased risk of fractures. When studying this in patients the amount of calcium in the bone is usually measured since this is reduced in osteoporosis. However, the condition is also characterized by a change in the internal structure of the bone, which may be more important for its strength than the reduced calcium content. The internal structures of the bone are called trabeculae, and they are

usually portrayed as either narrow rods or flat plates. Earlier, the 3D microstructure could only be studied in bone specimens removed from the body, where properties such as the spacing and thickness of the trabeculae and the number of branching points can be measured.

This project aims to study this structure in the living human by using methods available in a radiological department, in particular different types of



computed tomography (CT) methods. Since the trabeculae often are less than $0.2\ \mu\text{m}$ thick, the limited resolution of the radiological methods may be a problem. Therefore, we have focused on developing new image processing techniques for as accurate measurements as possible in the available images.

To study how the structure of the bone differs between different directions we use mathematical concepts called tensors. With these rather

abstract tools, we can estimate the strength of the bone, which is what really matters for the patient. We have shown that our predictions agree well with results from Finite element modeling (FEM), a computational method that requires much longer time even on very fast computers.

We have also studied how the type of tissue structure that is present in trabecular bone can be characterized and enhanced using tensor methods. In

addition to bone structure this may be useful also for e.g. identifying vessels in CT or MRI images.

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

QUANTITATIVE MUSCULOSKELETAL IMAGING FOR ASSESSMENT OF IDIOPATHIC SCOLIOSIS

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

Choice of treatment, monitoring of progression, follow-up after surgery are all activities that to a large extent are based upon a single measure called the Cobb angle. The Cobb angle measures the angle of the spine as seen on frontal radiographs. However, although widely used in clinical practice, the Cobb angle is incapable to fully describe a spinal deformity. This has motivated researchers and clinicians to pursue the development of new techniques to better describe and assess spinal deformities, which in turn will allow a better understanding of scoliosis on an individual level and, thus, be able to device personalized treatment plans.

To achieve this, we have focused our research on the combination of metrics describing the local deformation of each vertebra with metrics describing the overall deformation of the spine. For imaging, we are utilizing 3D imaging, as provided by computed tomography (CT), which provides excellent opportunities to measure and assess spinal deformities. Current state-of-the-art CT

scanners with new low-dose examinations make the use of CT clinically feasible from a dose perspective.

Thus far, our work has focused on:

- Determining the relationship between the Cobb angle as observed from radiographs with the patient in standing and in supine position. This is relevant, since current clinical practice is based upon on the Cobb angle from radiographs with the patient in standing position and not in supine position as is the case for CT examinations.
- Developing computerized methods based upon advanced image analysis, which can be employed for measuring various metrics related to quantifying the 3D deformity in scoliosis. Automatic and robust methods are needed in order to limit the effects of intra- and inter-observer variability associated with manual methods.

Future work will focus on:

- Determining the relationship between the Cobb angle and the axial vertebral rotation. This is relevant, since the axial vertebral rotation is of many clinicians considered as a differentiating factor between different types of scoliosis.
- Investigating how the axial vertebral rotation is affected by different surgical techniques for correcting spinal deformities. In this study, we will collaborate with University Medical Center Utrecht in the Netherlands.

PROJECT NAME

Quantitative Musculoskeletal Imaging for Assessment of Idiopathic Scoliosis

PROJECT LEADER

Hans Tropp, Department of Clinical and Experimental Medicine, Division of Orthopaedics

MAIN PROJECT PARTICIPANTS

Ludvig Vavruch and Daniel Forsberg

GRANTS

VR 2008-2013
VINNOVA 2012-2014

KEY PUBLICATIONS

L. Vavruch, and H. Tropp. A Comparison of Cobb Angle: Standing Versus Supine Images of Late-onset Idiopathic Scoliosis. *Polish Journal of Radiology*, 2016 (accepted for publication)

D. Forsberg, C. Lundström, M. Andersson, and H. Knutsson. "Model-based registration for assessment of spinal deformities in idiopathic scoliosis", *Physics in Medicine and Biology*, vol. 59, iss. 2, pp. 311-326, 2014

D. Forsberg, C. Lundström, M. Andersson, L. Vavruch, H. Tropp, and H. Knutsson. "Fully automatic measurements of axial vertebral rotation for assessment of spinal deformity in idiopathic scoliosis", *Physics in Medicine and Biology*, vol. 58, iss. 6, pp. 1775-1787, 2013



A patient suffering from idiopathic scoliosis. Note that apart from the global sideways deformation of the spine, there are local deformations present. For example, vertebrae L1, T12 and T11 (i.e. vertebrae five, six and seven counted from the bottom) are deformed to have a so called wedge-like appearance.

4D ORTHOPEDIC KINEMATICS

Dislocation of the kneecap is one of several knee problems that can cause significant negative impact on the life of an individual. The initial treatment is to engage the patient in physical therapy and/or provide a knee brace. However, if this treatment is unsuccessful or if the condition is very severe (the kneecap has been dislocated on multiple occasions), then surgery is needed. This typically includes a reconstruction of the medial patellofemoral ligament (a ligament on the inside of the knee, stabilizing the kneecap). The purpose of the surgery is to stabilize and thereby restore the “normal” motion pattern/range of the kneecap. Surgery is considered successful if the kneecap feels stable and if the patient no longer experiences dislocations. Today there exist no standardized methods for precise quantification of the kneecap’s motion during continuous flexion and extension of the knee. The lack of quantitative metrics makes it very difficult to evaluate the large number of different surgical techniques that exists for treating patients suffering from dislocation of the kneecap. This is what we intend to remedy.

Over the last few years, computed tomography (CT) imaging has undergone a remarkable development. Today, state-of-the-art scanners can image the knee with a spatial resolution of $0.4 \times 0.4 \times 0.4 \text{ mm}^3$ and a temporal resolution of less than a second. Further,

improved detector technologies and new image reconstructions algorithms ensure that dose is kept as low as reasonably achievable. This presents CT as a relevant technique for imaging the knee to allow a quantitative assessment of the continuous motion of the kneecap during flexion and extension of the knee.

Thus far, our work has focused on:

- Define metrics for quantifying the kneecap’s motion pattern along with developing a method for measuring these metrics. By employing image analysis we intend the developed method to require as little user interaction as possible.

Future work will focus on:

- Studying the motion pattern of kneecaps from patients prone to dislocation of the kneecap and compare with control patients to determine what a healthy respectively pathological motion pattern/range of the kneecap is.
- Investigate how surgery affects the motion pattern of the kneecap for patients who have undergone surgery using the gracilis tendon (a tendon on the inside of the knee) to reconstruct the medial patellofemoral ligament.
- Evaluate the use of the developed method for assessing other knee problems, e.g. patients with injured anterior cruciate ligaments.

PROJECT NAME

4D Orthopedic Kinematics

PROJECT LEADER

Daniel Forsberg, Sectra AB

MAIN PROJECT PARTICIPANTS

Maria Lindblom, Anders Persson and Håkan Gauffin

KEY PUBLICATIONS

D. Forsberg, M. Lindblom, P. Quick and H. Gauffin. Quantitative analysis of the patellofemoral motion pattern using semi-automatic processing of 4D CT data, International Journal of Computer Assisted Radiology and Surgery, vol. 11, iss. 9, pp. 1731-1741, 2016

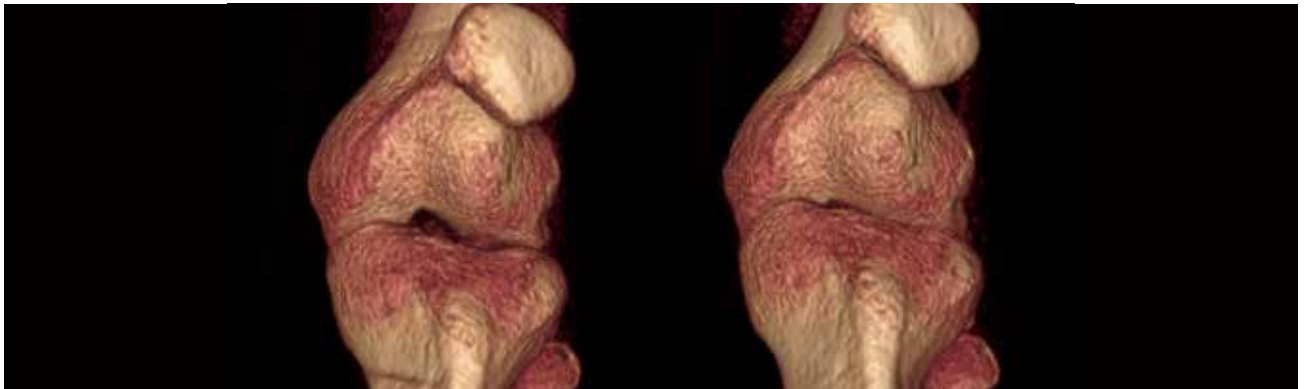


Figure 1. Preoperative imaging using CT for a patient with right knee prone to dislocation of the kneecap. Note how the kneecap moves to the side as the patient reaches full extension of the knee.

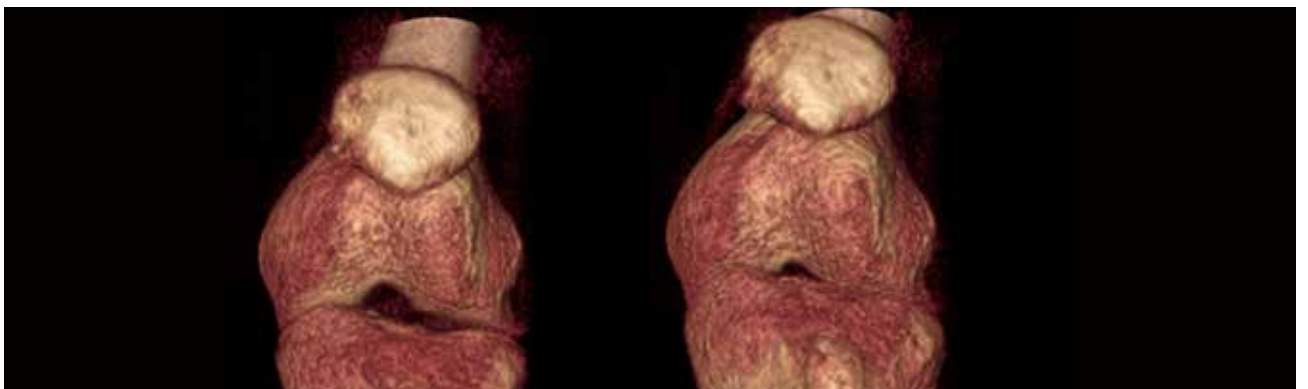
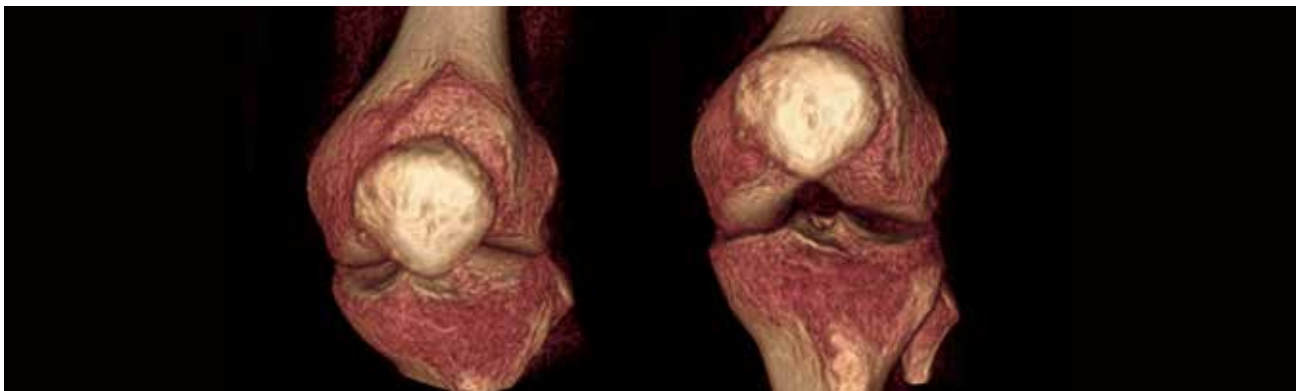


Figure 2. The same patient after reconstructive surgery. Now the kneecap stays much closer to the center of femur as the knee is extended.

PROJECT NAME

Health effects of resistance training on postmenopausal women

PROJECT LEADER

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MAIN PROJECT PARTICIPANTS

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GRANTS

Swedish Research Council

KEY PUBLICATIONS

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

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

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

HEALTH EFFECTS OF RESISTANCE TRAINING ON POSTMENOPAUSAL WOMEN

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

Vasomotor symptoms like hot flushes and sweating are reported by about 75% of all menopausal women. Until

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

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

and increased quality of life.

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

In the beginning and end of the study clinical outcomes as vasomotor symptoms, well-being, Body Mass Index, muscle strength and mass are measured. White and brown adipose tissue as well as browning of fat are measured with MRI. Also, production of myokines as irisin and adipokines, immunological markers and genetic variables

(length of telomeres) are analyzed.

By means of structured interviews we investigate how to best stimulate women to change life-style and why some women will not be successful.

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

In November 2016 we included and randomized the 65:th woman and probably by March 2017 all women

have gone through the 15 weeks of intervention or being in the control group. Thereafter blood analyses and all other analyses will be performed. Already a test-retest investigation has been performed with a number of MRI investigations performed twice.

Furthermore we are currently planning to prolong the study including all measurements after 24 months. We will then investigate a number of women who have been long-term compliant to regular exercise and compare with women who are again sedentary.

IMPACT OF VITAMIN D ON PHYSICAL TRAINING IN VITAMIN D DEFICIENT PATIENTS WITH COPD

PROJECT NAME

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

PROJECT LEADER

Lennart Persson, Department of Pulmonary Medicine, Region Östergötland

MAIN PROJECT PARTICIPANTS

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

GRANTS

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

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

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

the benefits of physical training.

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

If successful, the study will lead to a better understanding about the role

of vitamin D deficiency on the muscle waste observed among many COPD patients. Indeed, vitamin D may become a crucial vitamin to supplement before physical training is started.

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

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

Primary outcome is respiratory muscle strength measured as the maximal inspiratory pressure (MIP). Among

secondary outcomes studies on muscle strength and endurance of the dominant leg, metabolism of the quadriceps muscle of the dominant leg at rest and exercise (employing ³¹P-magnetic resonance (MR) spectrometry) and quantification of muscle, fat and bone tissues of the dominant leg (using MR) will be performed.

PROJECT NAME

Imaging of Brown Adipose Tissue

PROJECT LEADER

Magnus Borga, Department of Biomedical Engineering, Division of Medical Informatics

MAIN PROJECT PARTICIPANTS

Anders Persson, Olof Dahlqvist Leinhard, Thobias Romu, Nils Dahlström

GRANTS

KAW 2012-2017

KEY PUBLICATIONS

Martin E. Lidell, Matthias J. Betz, Olof Dahlqvist Leinhard, Mikael Heglind, Louise Elander, Marc Slawik, Thomas Mussack, Daniel Nilsson, Thobias Romu, Pirjo Nuutila, Kirsi A. Virtanen, Felix Beuschlein, Anders Persson, Magnus Borga, Sven Enerbäck, "Evidence for two types of brown adipose tissue in humans", *Nature Medicine*, 19(5): 631-634, 2013.

Thobias Romu, Louise Elander, Olof Dahlqvist Leinhard, Martin Lidell, Matthias Betz, Anders Persson, Sven Enerbäck, Magnus Borga, "Characterization of Brown Adipose Tissue by water-fat separated Magnetic Resonance Imaging", *Journal of Magnetic Resonance Imaging*, 42(6): 1639-1645, 2015.

Thobias Romu, Vavruch Camilla, Olof Dahlqvist Leinhard, Joakim Tallberg, Nils Dahlström, Anders Persson, Mikael Heglind, Martin Lidell, Sven Enerbäck, Magnus Borga, Fredrik Nyström, "A randomized trial of cold-exposure on energy expenditure and supraclavicular brown adipose tissue volume in humans", *Metabolism*, 65(6): 926-934, 2016.

IMAGING OF BROWN ADIPOSE TISSUE

The human body contains different types of adipose (fat) tissue that play different roles in the metabolism. While white adipose tissue (WAT) act as energy buffer, brown adipose tissue (BAT) converts stored energy (WAT) directly into heat that keeps us warm at least as infants and is also most likely of importance to us for longer than that.

Today's sedentary life style has generated a cluster of obesity related health problems commonly referred to as the metabolic syndrome. A positive energy balance will eventually lead to insulin resistance and ultimately type 2-diabetes, which in turn may cause e.g. heart attacks, stroke, kidney problems and also many types of cancers.

In recent years, Brown Adipose Tissue (BAT) has emerged as a highly interesting object of study in the search for future solutions to many of the major health care challenges related to the metabolic syndrome. Also, recent publications have shown relations between BAT and osteoporosis and sarcopenia (age related loss of muscle mass).

The lack of efficient tools for studying BAT in vivo, however, is a serious limitation hindering large clinical studies related to BAT. Until recently the only available method for in vivo imaging of BAT was positron emission tomography, which requires injection of

a radioactive substance in the subjects, clearly limiting its use in large prospective studies.

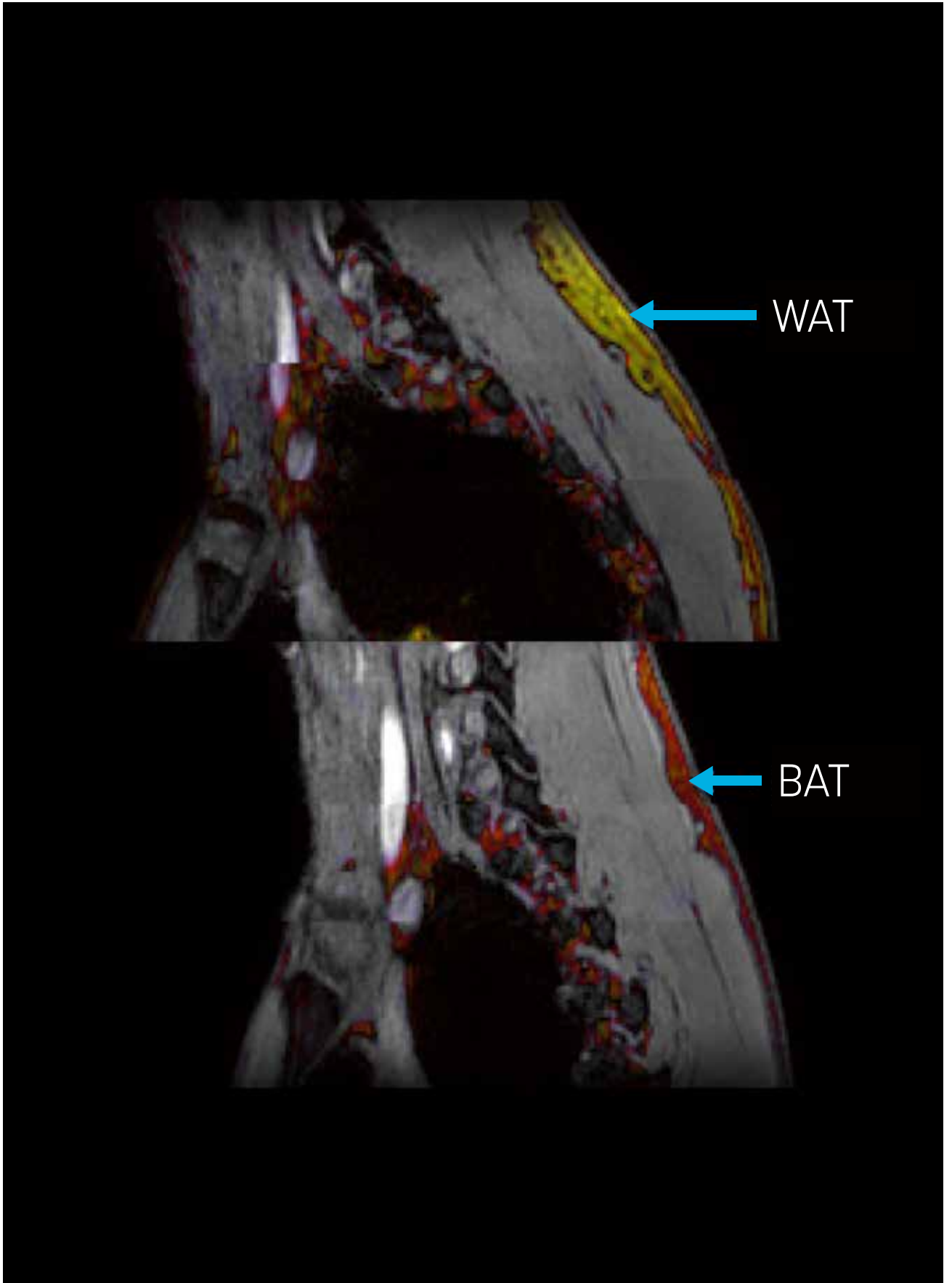
Manual assessment of the BAT images is extremely time-consuming, making larger studies impossible. Also, the reproducibility is limited in manual work. Computers on the other hand are very useful when it comes to reproducibility and speed.

The overall aim of this project is therefore to develop and evaluate accurate automatic methods for high-resolution in vivo imaging, classification and quantification of BAT using quantitative magnetic resonance imaging and dual energy computed tomography.

In parallel with the method development the project also studies the properties of brown fat and the possibilities to activate and even increase the amount of brown fat.

Results from the project show that it is possible to alter the constitution and amount of brown fat in rats by exposure to low temperatures. Studies are now performed on humans to see if it is possible to have the same effect.

The studies of brown fat involve professionals from multiple disciplines, patient recruitment and advanced equipment. Without a center as CMIV the project would be impossible to realize.



The image illustrates how BAT can be detected in the neck and shoulders using MRI that can quantify the amount of fat and water in the tissue. WAT contains almost 100% fat and is indicated in yellow. BAT contains approximately 50% water and is indicated in red.

SEMIAUTOMATIC LIVER VOLUME DETERMINATION AND SEGMENTATION

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

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

Magnetic resonance imaging (MRI) offers a noninvasive method to monitor liver function using liver specific contrast agents. However, in developing system biology models for describing the pharmacokinetics of hepatocyte-specific contrast medium, it is important to estimate the total liver volume and preferably also liver segment volumes. Although tools for liver segmentation using datasets from computed tomography have become easily available, useful applications aimed at MRI datasets are lacking.

Thus, a sub-project within the Liver Function Evaluation project was formed to evaluate software that was compatible with the late hepatobiliary

phase 3D datasets from examinations of patients with diffuse liver disease.

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

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

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

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

PROJECT NAME

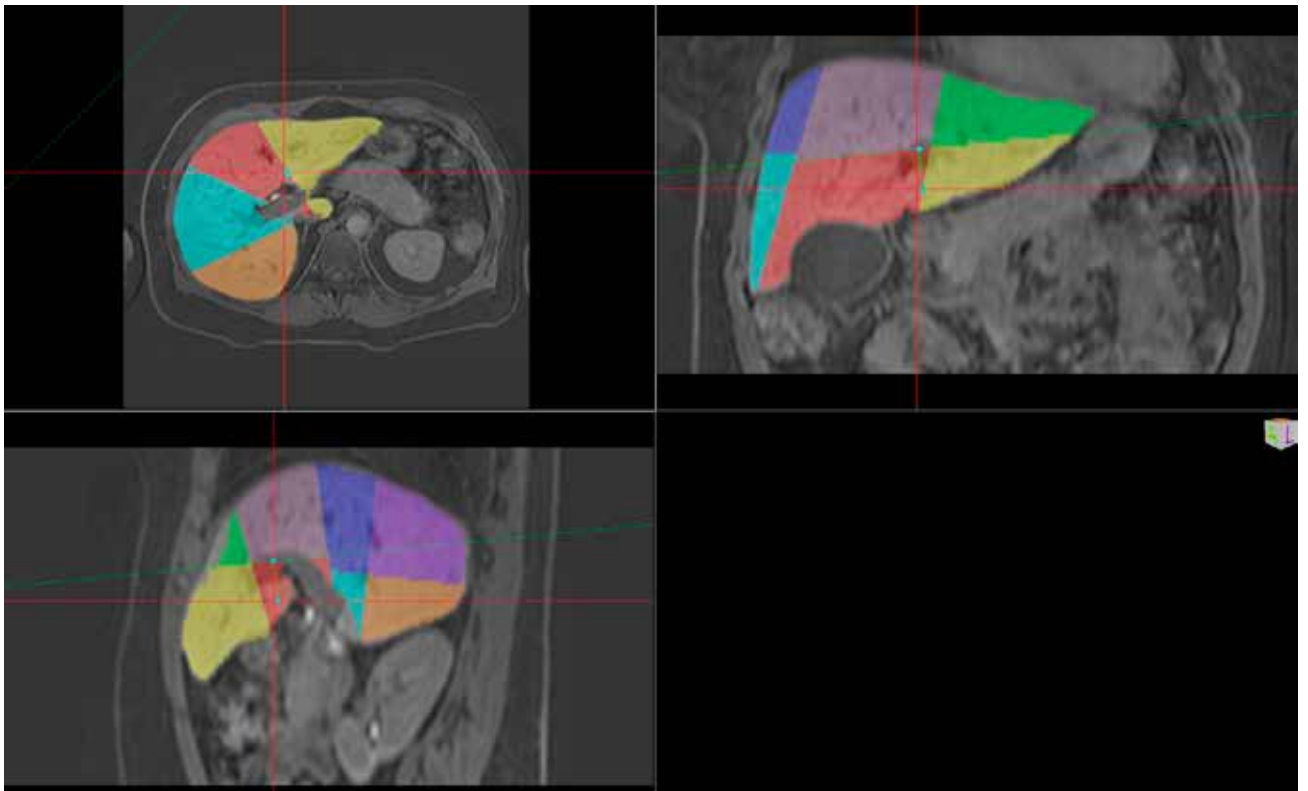
Semiautomatic Liver Volume Determination and Segmentation

PROJECT LEADER

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

MAIN PROJECT PARTICIPANTS

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



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)

WHOLE BODY MRI-BASED FAT AND MUSCLE MEASUREMENT

PROJECT NAME

Whole body MRI-based fat and muscle measurement

PROJECT LEADER

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

MAIN PROJECT PARTICIPANTS

Magnus Borga, Professor, Thobias Romu, PhD Student, Anette Karlsson, PhD Student, Thord Andersson, PhD Student, Patrik Tunon, MSc Student

GRANTS

FÖRSS Research council of Southeast Sweden 2012-2014

KEY PUBLICATIONS

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

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Dahlqvist Leinhard O, Johansson A, Rydell J, Smedby Ö, Nyström F, Lundberg P, Borga M. Quantitative Abdominal Fat Estimation Using MRI. 2008 19th International Conference on Pattern Recognition, ICPR 2008, art. no. 4761764.

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

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

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

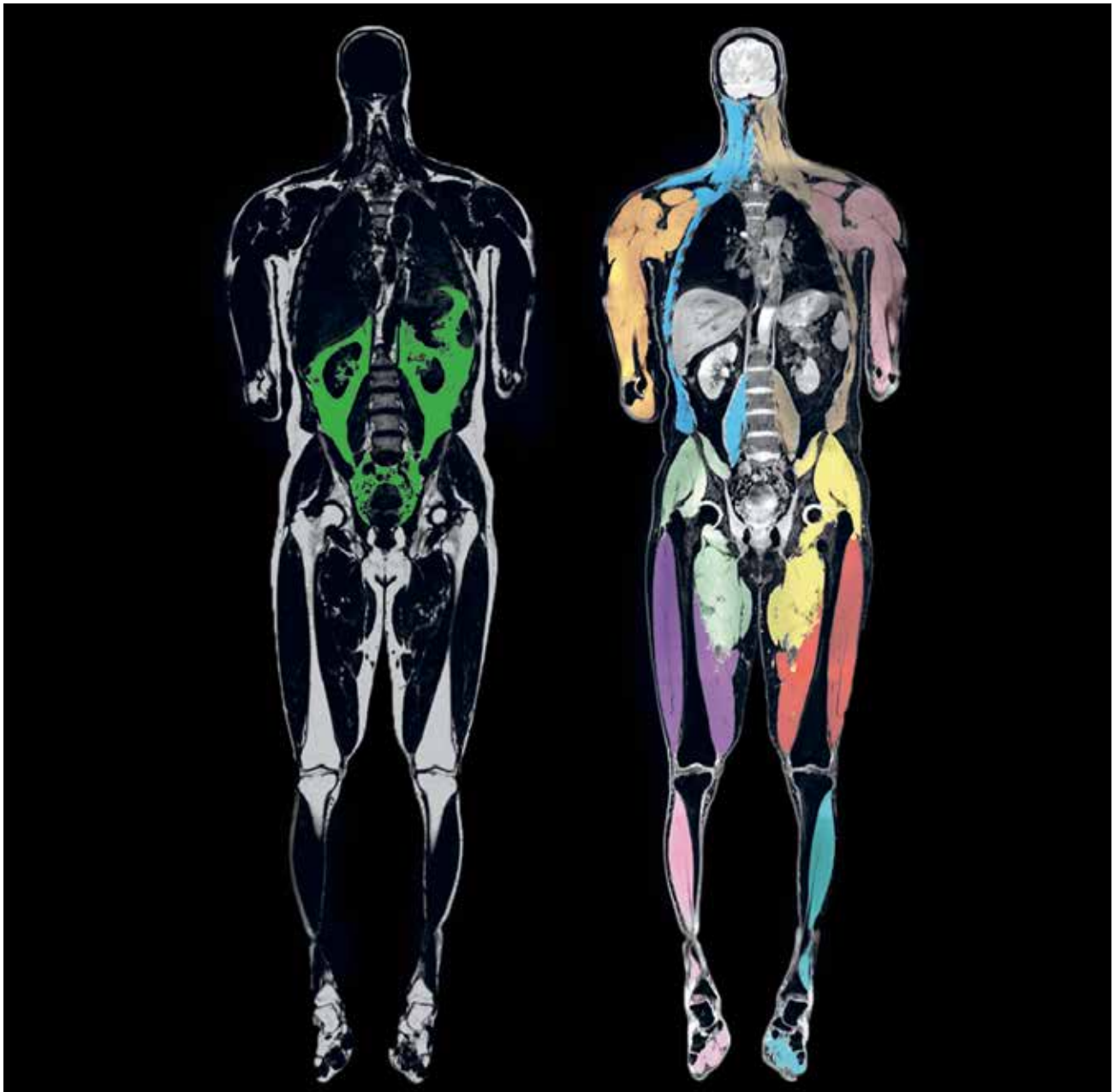
In this project we develop a technique for detailed analysis of fat and muscle tissue in the body based on whole body MRI examination (see figure). Recent

technical development of MRI scanners enables high-resolution images of the complete body without exposing the subject to ionizing radiation or other known health risks. The technique can be applied in large-scale research studies to provide a better understanding about different body composition phenotypes.

We apply the technique in a number of clinical studies. In one project we study fibromyalgia where we recently showed an increased fat content in the thigh muscles of fibromyalgia patients. Another project regards whiplash associated disorders, where fat infiltration in deep neck muscles may affect the outcome of patient rehabilitation. We also study the effect of anti-obesity therapies and the role of abdominal and liver fat in diffuse liver disease.

Furthermore, we use the technique to provide better understanding of Sarcopenia, the decline of muscle tissue with age, which is one of the most important causes of functional decline and loss of independence in older adults.

Another important application area of the technique is imaging of brown adipose tissue (BAT). Recently, we demonstrated the presence of BAT between the shoulder blades in human infants. BAT is an organ that allows non-shivering thermogenesis in mammals and is a potential target for anti-obesity therapies.



Automatically segmented whole body fat and water separated dataset from a 10 minutes MRI examination where abdominal fat (left) and different muscle groups (right) are shown in different colors.

PRESTO-CAN FOR THREE-DIMENSIONAL FUNCTIONAL MRI

PROJECT NAME

PRESTO-CAN for three-dimensional functional MRI

PROJECT LEADER

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

MAIN PROJECT PARTICIPANTS

Maria Magnusson, Olof Dahlqvist Leinhard, Helene van Ettinger-Veenstra

GRANTS

Swedish Research Council (VR), Cancerfonden, Knowledge foundation.

KEY PUBLICATIONS

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

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

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

As seen to the right in figure 1, there are more densely sampled data in the inner part of k-space. It has been shown that by removing parts of the inner over-sampled k-space at certain time points, the temporal resolution can be further increased. However, this gives

a more complicated sampling pattern and a non-trivial reconstruction. PRESTO-CAN has shown to provide excellent temporal resolution and satisfactory image quality.

The method was developed having functional MRI (fMRI) applications in mind. In fMRI, MRI-volumes are recorded during a time period when a person/patient performs a particular task. By analyzing the MRI time sequence, it is possible to detect brain activity. Accordingly, it is desirable with a high time resolution.

A major advantage of the PRESTO-CAN sequence is that it allows for whole brain coverage. We are currently finishing a comparative fMRI study between PRESTO-CAN and conventional techniques, like EPI. Figure 2 shows left and right fingers fMRI-activation computed from MRI-data based on PRESTO-CAN.

The rather simple geometry of PRESTO-CAN makes it easy to include standard procedures for speeding up the data acquisition further, such as parallel imaging which can be combined with unique 3D motion correction schemes. These possibilities will be investigated further.

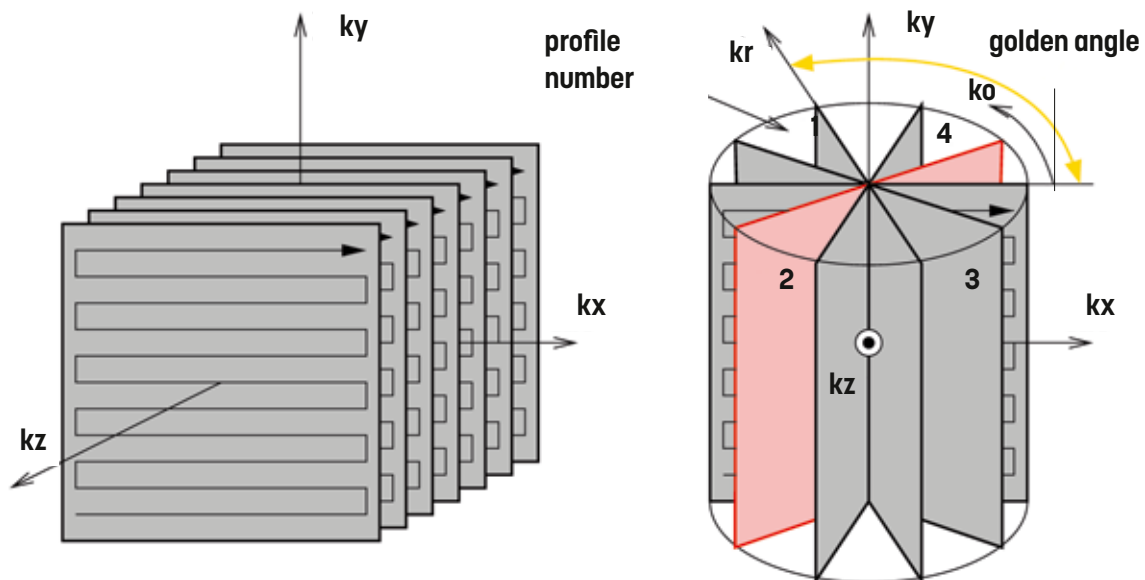


Figure 1. Left: 3D Cartesian sampling of k-space. Right: PRESTO-CAN sampling of k-space.

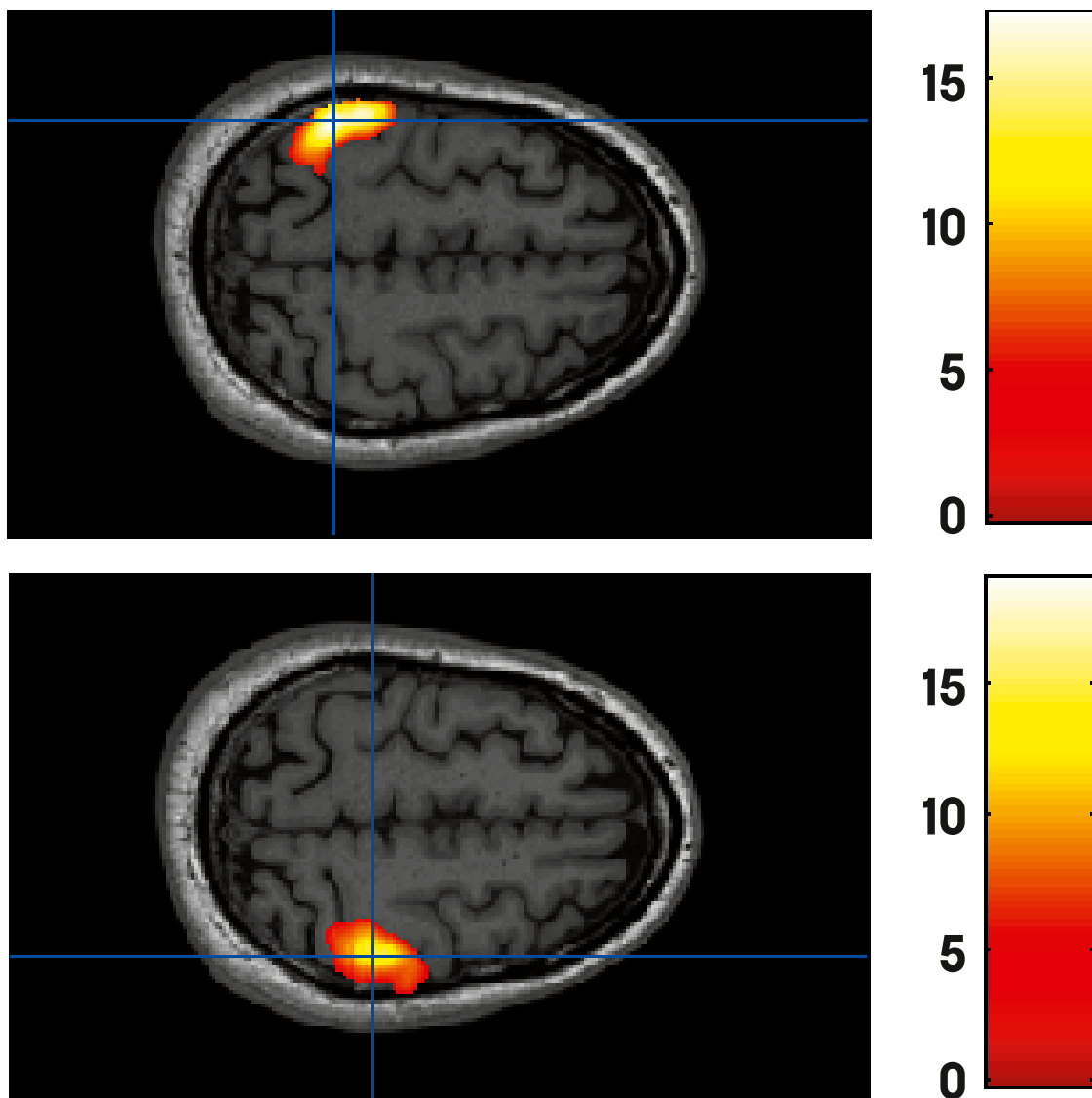


Figure 2 fMRI-activation computed from MRI-data based on PRESTO-CAN. Left: activation in left fingers motor cortex. Right: activation in right fingers motor cortex.

PROJECT NAME

The neurocorrelates of meditative practice

PROJECT LEADER

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

MAIN PROJECT PARTICIPANTS

Maria Engström

GRANTS

FORSS
Alzheimerfonden

KEY PUBLICATIONS

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

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

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

THE NEUROCORRELATES OF MEDITATIVE PRACTICE

When an individual is in a quiet state of rest, thought-related activity in the brain does not cease. This activity can be recorded by functional magnetic resonance imaging (fMRI) and represented as constellations of anatomic regions in the brain that co-activate during cognition called resting state networks. Although there are a number of such networks, the default mode network (DMN) became the first, and now the most extensively studied of the many known resting state functional networks. Network activation has been associated with specific mentation including autobiographical memory, self-reflective thought, envisioning future events, mind wandering, and considering the thoughts and perspectives of others. Abnormal DMN activity – such as distractive mind wandering during tasks or excessive

rumination – has been associated with a number of psychological disorders such as schizophrenia, anxiety, depression, attention deficit hyperactivity disorder (ADHD), and Alzheimer's disease (AD).

As research strengthens the link between anatomical regions of the DMN and psychological disorders, much interest has been directed toward non-pharmacological means of harnessing the brain's inherent neuroplasticity and altering patterns of behavior within this network. One promising method of achieving this goal is through meditation training. Meta-analyses examining the specific neurocorrelates of meditation have shown reductions in DMN activity as a primary outcome of meditation practices. In addition, modulation of DMN activity through meditative training has been demonstrated to help individuals concentrate

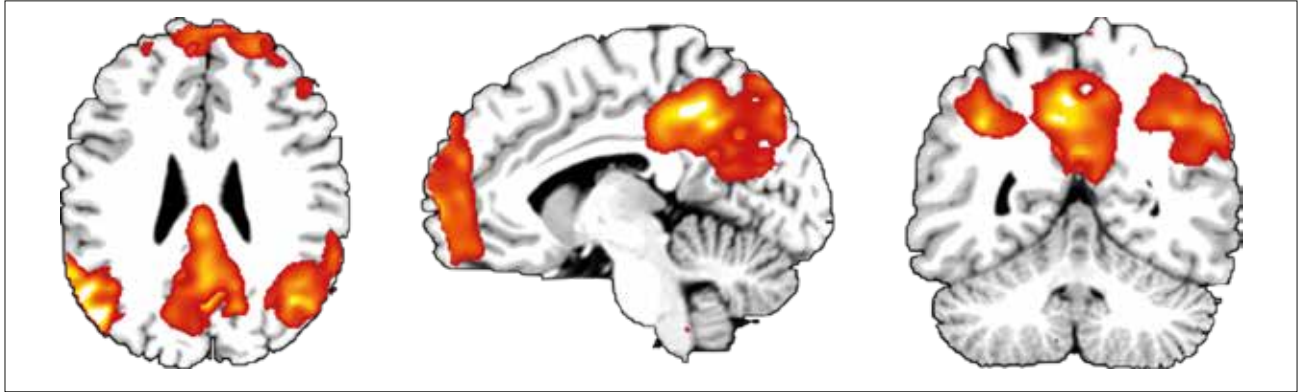


Figure 1. Data from five zen meditators showing differences in the Default mode network between focused attention meditation on breath versus resting state. Increases in red, decreases in activity in green.

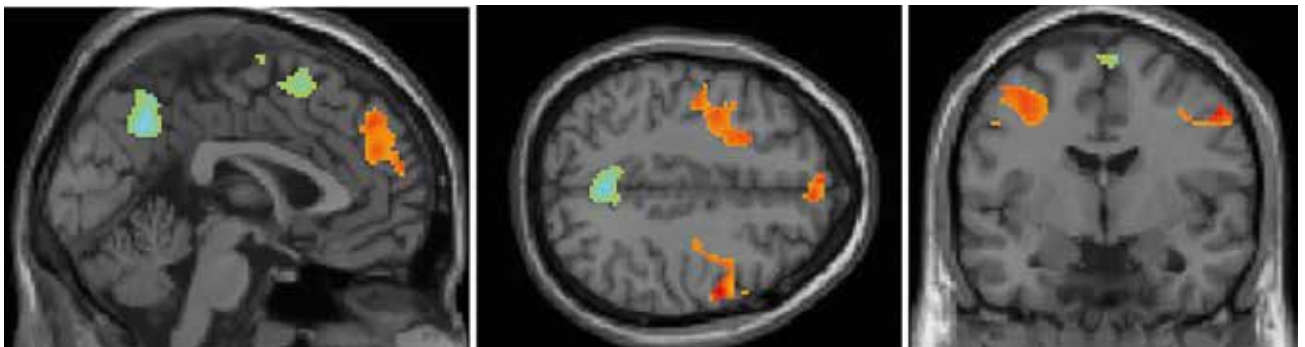


Figure 2. Activations in the default mode network for meditators during rest alone.

and increase their present awareness, thus reducing mind wandering activities and improving cognition. Functional magnetic resonance imaging (fMRI) has been used to successfully visualize changes in the DMN resulting from meditative practices such as Vipassana and Mindfulness-based stress reduction (MBSR). Although there is evidence that meditation practice alters DMN activity, the specific neurocorrelates based on the type of meditation practiced remain unclear. For example,

what regions of the brain are active when one focuses their attention on the breath? How does open awareness of one's thoughts affect emotional centers

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

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

PROJECT NAME

Ab Initio Mathematical Modelling of Mechanisms in the Human Brain

PROJECT LEADER

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

MAIN PROJECT PARTICIPANTS

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GRANTS

Swedish research council 2015-2018
FORSS 2014-2018

KEY PUBLICATIONS

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

Susanna A. Walter, Mikael Forsgren, Karin Lundengård, Rozalyn Simon, Maritha Torkildsen Nilsson, Birgitta Söderfeldt, Peter Lundberg, Maria Engström. Positive Allosteric Modulator of GABA Lowers BOLD Responses in the Cingulate Cortex. Plos One, 2016;1:e01148737.

Suzanne T. Witt, Marcel Warntjes, Maria Engström. Increased fMRI sensitivity at equal data burden using averaged shifted echo acquisition. Frontiers in neuroscience, 2016;10:544.

AB INITIO MATHEMATICAL MODELLING OF MECHANISMS IN THE HUMAN BRAIN

Brain activity can be visualized and time dependent signals of the brain at work can be recorded by functional magnetic resonance imaging (fMRI). fMRI is widely used in both research and health care but the relation between brain activity and the recorded signals remains elusive.

The aim of this project is to investigate different hypotheses for the relation between brain activity and the fMRI signal using mathematical modeling, and thereby increasing the under-

standing of how the brain works. This is done by “translating” these hypotheses to mathematical expressions, so called differential equations. These mechanistic models are then fitted to experimental data, which could be the fMRI signal but also measurements of blood flow, hemoglobin, or neurotransmitter concentrations. By fitting a mathematical model to experimental outcome, we can evaluate if the model can or cannot explain data. Once we know that the model can explain data, we can use

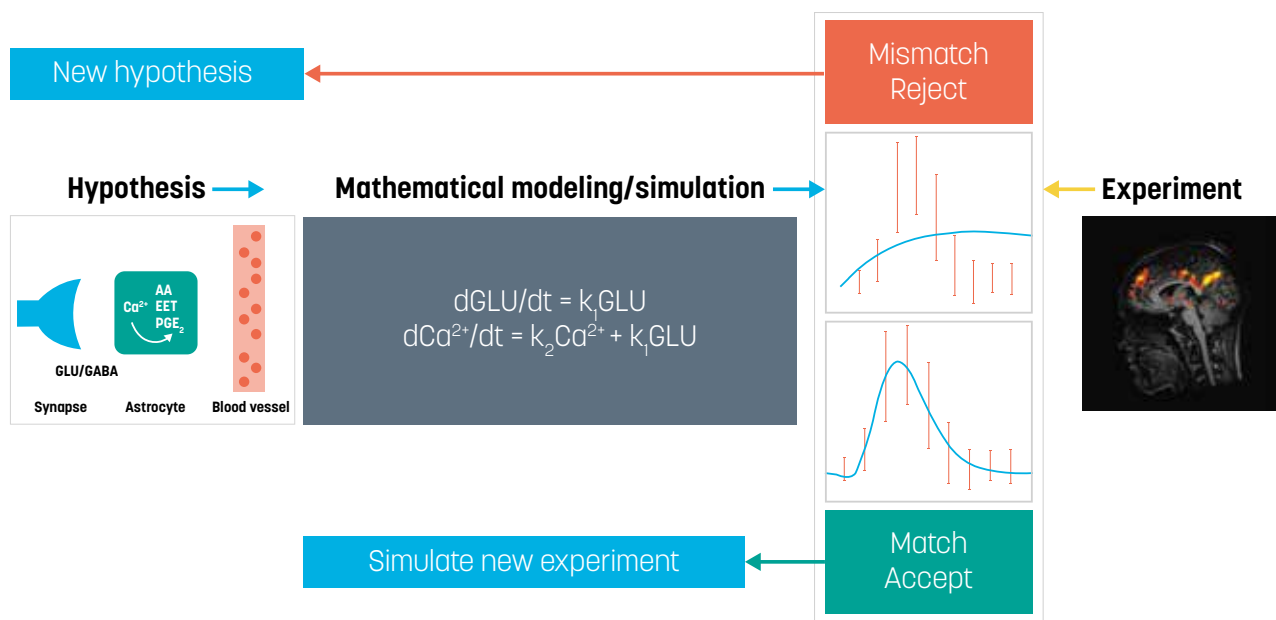


Figure 1. (ModelingOutline): Schematic overview of the project showing a simplified workflow from hypothesis to mathematical modeling, experimental data and hypothesis rejection or acceptance.

the model to predict brain function in response to different stimuli.

In the first phase of the project we have investigated the “metabolic” and the “neurotransmitter” hypotheses for the mechanism behind the fMRI signal. According to the metabolic hypothesis it is assumed that increased energy demand drives blood flow changes in activated areas of the brain. According to the neurotransmitter hypothesis it is assumed that neurotransmitters, released when the brain is activated,

trigger changes in the brain’s blood flow. We have shown that neither of these hypotheses alone can explain the fMRI signal. The metabolic hypothesis is necessary to explain the transient decrease in the fMRI signal immediately after a stimulus and the neurotransmitter hypothesis explains the response peak that occurs 6-8 seconds after a stimulus.

Presently, we are investigating the mechanisms of negative fMRI signals commonly observed in e.g. the default mode network, which is activated at rest

but normally deactivated during tasks that require attention. Preliminary data show that negative fMRI signals can be explained by neural inhibition. In the future we will use the mathematical models to investigate brain function in clinical studies. For this purpose the project is directly linked to “Sleep abnormality network description: Modeling and analysis in neuroimaging”, which investigates patients with sleep disorders.

DECODING AND LANGUAGE COMPREHENSION IN YOUNG VERY LOW BIRTH WEIGHT ADOLESCENTS

PROJECT NAME

Neuroimaging of Decoding and Language Comprehension in Young Very Low Birth Weight Adolescents

PROJECT LEADER

Nina Nelson Department of Clinical and Experimental Medicine, Division of Pediatrics

MAIN PROJECT PARTICIPANTS

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

Children that are born preterm with a very low birth weight have an increased risk of developing impairments in the cognitive and behavioral domains. One of the potential problems they may develop is in language, and as our school system is heavily based on reading, any reading problems would affect development in other cognitive domains. However, there are no research results that clearly states if the reading problems are related to general neural impairment or if there is reason to suspect a change in neural wiring of language processing regions that happened during development.

The aim of the study was to investigate if language problems related

to preterm birth with very low birth weight could be attributed to an inadequate phonological processing system. To phonologically sound out words is how we learn language and reading, and a faulty phonological processing system would have effects on other aspects of learning as it delays and perhaps interferes with the whole learning process.

We investigated language processing in adolescents of 12-14 years of age that were born about around 30 weeks (normal gestation time is around 38-40 weeks) with a birth weight under 1,500 gram (normal birth weight is above 2,500 gram).

We obtained functional magnetic resonance images (fMRI) during three

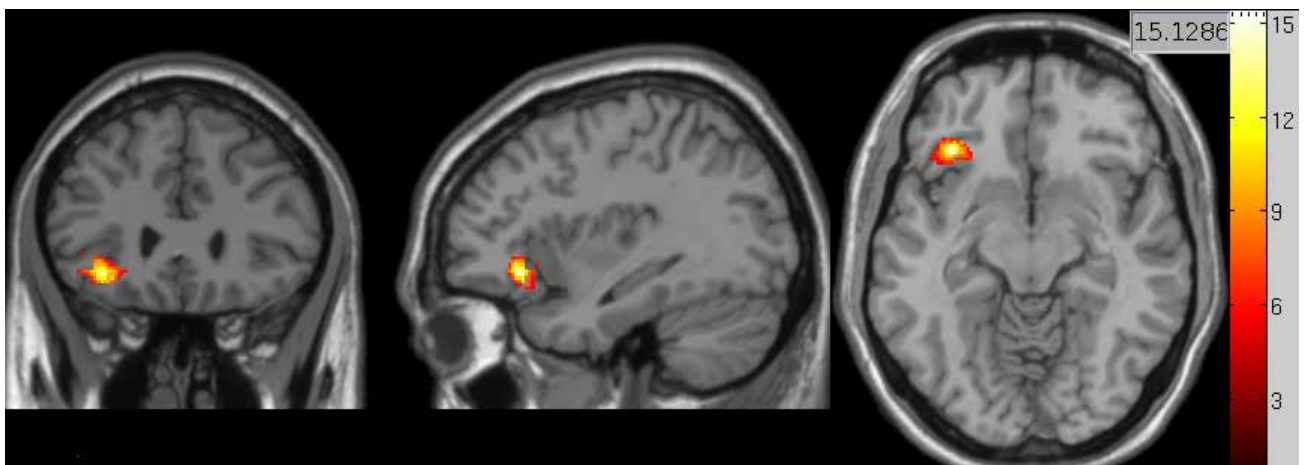


Figure 1. Increased activation in left inferior frontal gyrus during phonological processing for adolescents with very low birth weight compared to adolescents with normal birth weight. We think that this region during development after being born with very low birth weight has either obtained a different functionality or different connection with other language processing regions, to compensate for language processing difficulties.

different types of language processing, and investigated the relation of neural activation during fMRI scanning. We investigated phonological processing of how a word sounds, orthographic processing of how a word is spelled, and semantic processing of in which semantic category a word belongs.

Our results showed that adolescents with very low birth weight indeed have different neural activation during different types of language processing

when compared to normal birth weight term-born controls. We observed a difference in neural activation between birth weight groups for phonological as well as semantic processing in the left inferior frontal gyrus. Different parts of this region are involved in either phonological or semantic processing, and our results support the hypothesis that children born with very low birth weight do not have a normal phonological processing system, and have to com-

pensate by recruiting adjacent regions. In addition, we found that the very low birth weight group had impaired performance on the WISC Block Design test that tests for spatial processing, and a lower brain volume in concordance with previous studies. We did not find a difference in performance between birth weight groups during either of the fMRI language processing tasks.

PAIN DISRUPTS CORTICAL CONNECTIVITY IN CHRONIC WIDESPREAD PAIN

Of all patients that have a chronic pain condition a considerable group (up to 25%) will develop a more widespread pattern of chronic pain. Chronic widespread pain, which is considered the worst chronic pain condition affects predominantly women, and results in many negative effects such as work absence and a poor quality of life.

An important subgroup of chronic widespread pain is fibromyalgia syndrome; these patients also develop hyperalgesia which is an increased sensitivity to pain. It is known from literature that there is a change in functional and structural neural connectivity in patients with chronic widespread pain, however the picture is as of yet very unclear. A major factor that is insufficiently understood is the effect of psychological comorbidities commonly increased in these patients such as anxiety and depression.

Our interest is to investigate functional connectivity in patients with chronic widespread pain, and if their functional pattern reacts differently to pain than it would in healthy controls. We therefore investigate short-term neuroplasticity, namely the immediate changes that can be observed in the functional connectivity patterns after receiving acute pain for about 20 minutes. Our ultimate goal is to investigate the effect of psychological strain in the form of anxiety and depressive symptoms on this neuroplasticity effect of the functional connectivity pattern in patients with chronic widespread pain.

Functional connectivity can be investigated as a direct relation between brain regions, or as communication between connected regions in a so-called functional network, or even as collaboration between networks. Well-known functional networks include perceptual and motor systems, and

PROJECT NAME

Pain Disrupts Cortical Connectivity in Chronic Widespread Pain

PROJECT LEADER

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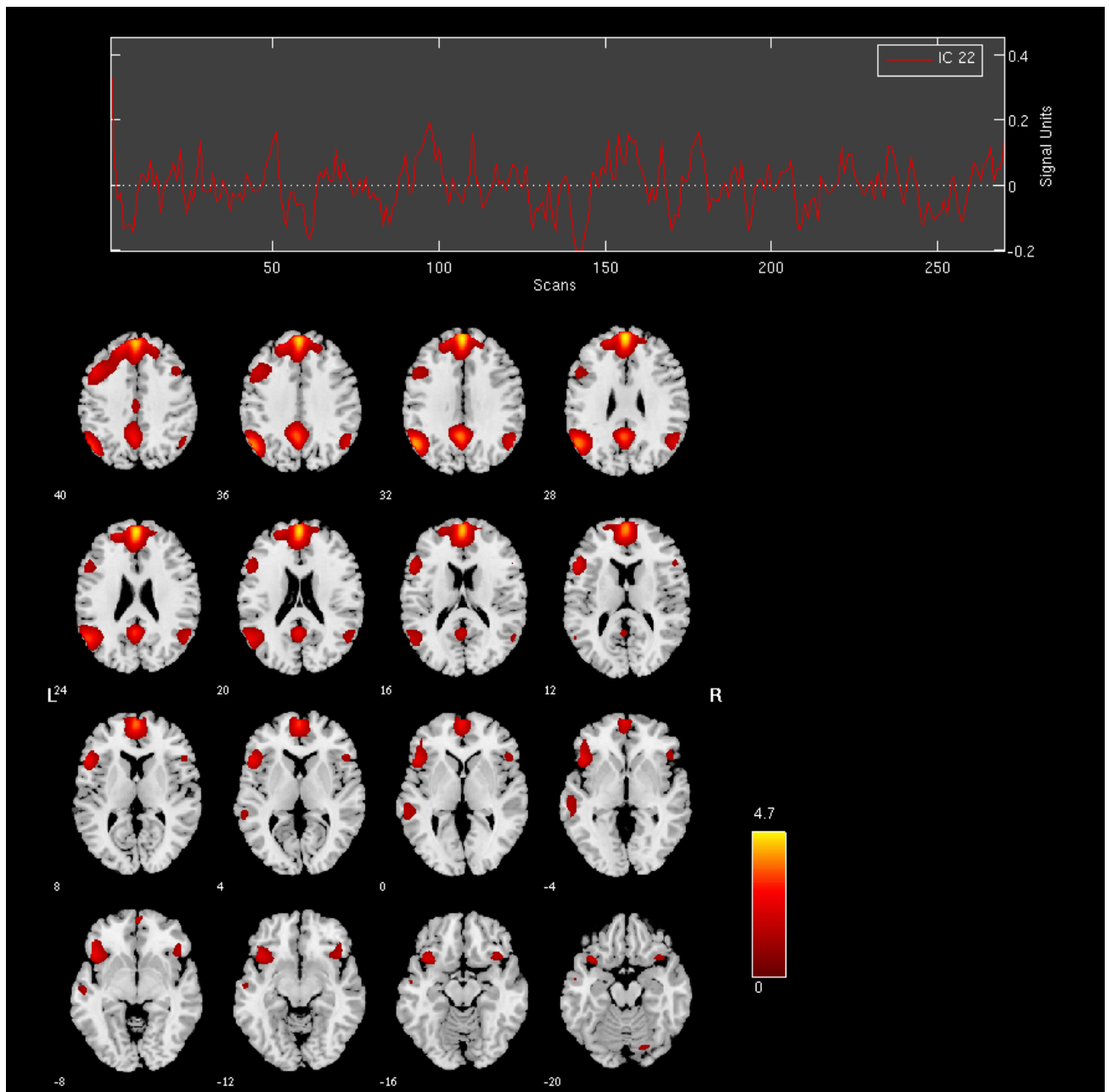


Figure 1. The Default Mode Network in our study population, on top the change in activation (in arbitrary signal units) over time during scanning (scans) for the default mode network. In healthy subjects, the salience network would be active only when the default mode network is not, in people with chronic widespread pain the activation of both networks overlaps more.

attention networks such as the salience network that processes important or attention-grabbing events in- or outside of the body. Another important network is the default mode network, which is involved in introspective functions of a person that is not engaged in a specific task or actively perceiving the external world.

Literature suggests that chronic pain is related to a disrupted default mode network, and interference between the

default mode network and the salience network. These networks are normally not active at the same time as introspection naturally is diminished when the person is paying attention to salient stimuli.

Thus far, we have observed functional connectivity changes between regions associated with the default mode network and regions associated with the salience network. We found that patients with chronic widespread

pain react differently to pain compared to healthy controls. Patients with increased psychological strain, defined as increased symptoms of anxiety and depression, had a different connectivity pattern. Also the pain sensitivity of a patient was related to functional connectivity differences. Future research will further investigate the effect of psychological strain on functional connectivity.

SHORT-TERM NEUROPLASTICITY OF FUNCTIONAL CONNECTIVITY AFTER LEARNING

PROJECT NAME

Short-term Neuroplasticity of Functional Connectivity After Learning

PROJECT LEADER

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MAIN PROJECT PARTICIPANTS

India Morrison

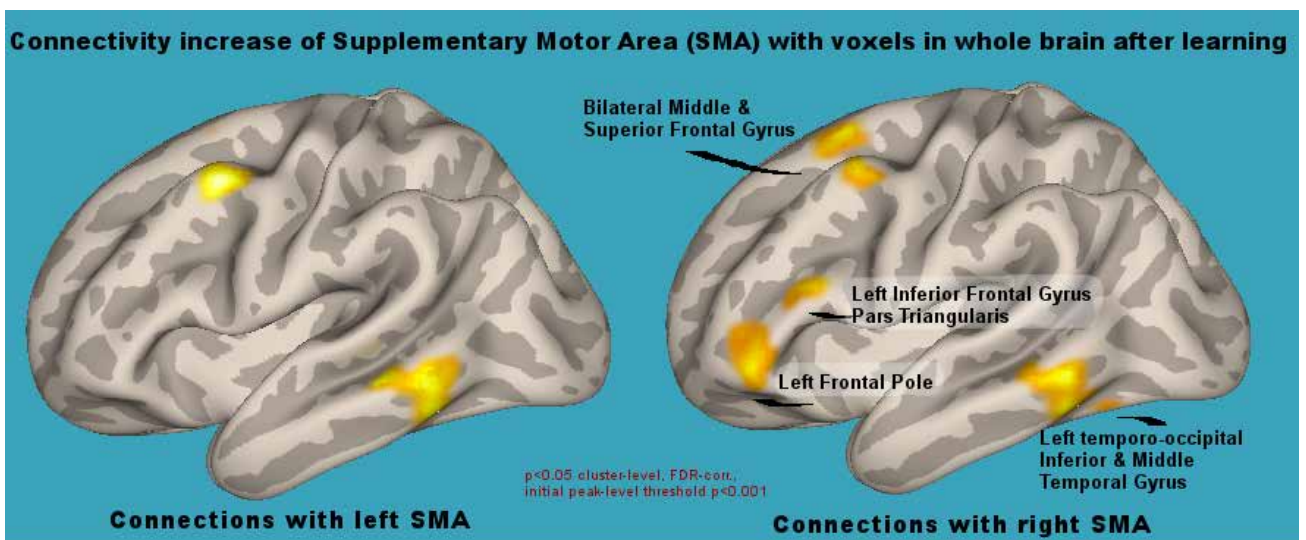
GRANTS

FORSS pilot project

Neuronal connections are not static but dynamic as our brain adapts and learns throughout life. Our goal with this project is to visualize how learning effects almost directly affect the functional connectivity of the brain on a macro-scale. This neuroplasticity has been demonstrated after learning motor, spatial, or perceptual tasks. However, cognitive training is often only visible after a longer period.

We investigate neuroplasticity on a

macro-scale by measuring the fluctuation of intrinsic functional connectivity patterns over the whole brain with functional magnetic resonance imaging (fMRI). Intrinsic functional connectivity patterns are visible when a person is not performing a specific task but is just lying, perhaps relaxing in the MR-scanner. Our brain stays active, and we might think about our day or plans ahead of us, or whatever pops up in the brain directed by either internal



or external cues. In a healthy person, functional networks activate and deactivate, and over a period of time all of these intrinsic neural networks in the brain, be it perceptual, motor, language, introspection, or attentional networks, have been activated. Another way of measuring functional connectivity changes is by simply measuring functional connectivity between regions of interest.

Our pilot-project investigated intrinsic

functional connectivity neuroplasticity during an inference task, which is cognitively demanding. After a while, the participant gets better at the task, and due to the nature of the task we expect a slow learning effect. Indeed, we found changes in functional connectivity after only 20 minutes of task performance. The changes observed were in mid-frontal and inferior frontal regions that are involved in inference processing. We believe that the results

of this pilot project show that training in a complex cognitive task initially results in a redistribution of task-evoked connectivity. This confirms the existing theory and shows that we can be successful in evoking short-term functional neuroplasticity. Future projects will include short- and long-term neuroplasticity after pain modulation or after intervention strategies aimed at direct pain reduction or pain reduction through coping training.

PROJECT NAME

Clinical, psychosocial and imaging studies of fatigue in multiple sclerosis

PROJECT LEADER

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

MAIN PROJECT PARTICIPANTS

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GRANTS

Swedish Research Council (VR)

KEY PUBLICATIONS

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

Flensner G, Landtblom AM, Söderhamn O, Ek AC. Work capacity and health-related quality of life among individuals with multiple sclerosis reduced by fatigue: a cross-sectional study. *BMC Public Health*. 2013 Mar 15;13:224. doi: 10.1186/1471-2458-13-224.

Engström M, Flensner G, Landtblom AM, Ek AC, Karlsson T. Thalamo-striato-cortical determinants to fatigue in Multiple Sclerosis. *Brain & Behaviour*, 2013 November; 3(6): 715-728.

CLINICAL, PSYCHOSOCIAL AND IMAGING STUDIES OF FATIGUE IN MS

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

ment), physiological (coupling to heat sensitivity), clinical (effect on cognition) and interventional (cryotherapy) point of view.

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

We have used functional magnetic resonance imaging of the brain (fMRI) to investigate the neuronal activity involved in the enhancement of cog-

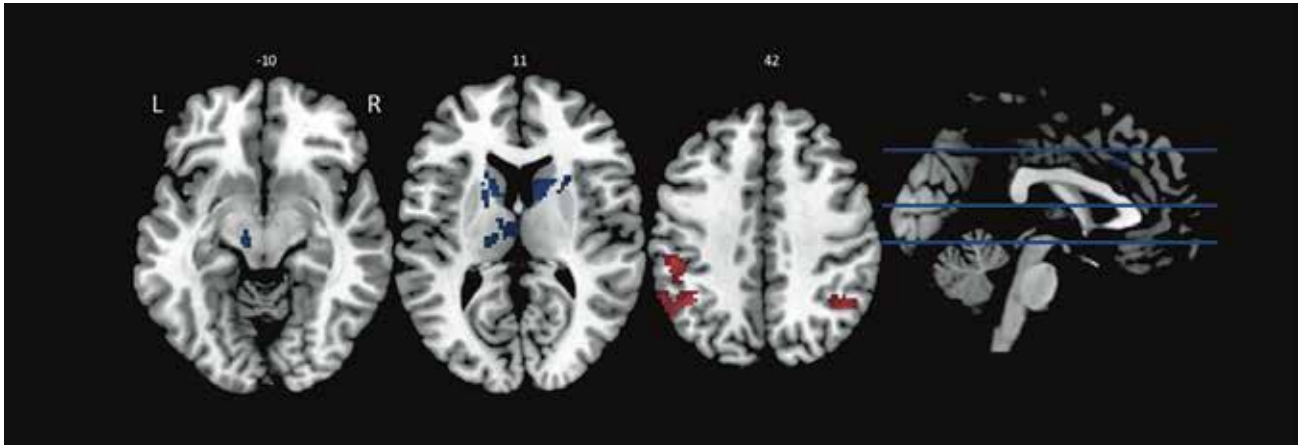


Figure 1. Differences in brain activation between MS participants and healthy participants in regions of interest in the brain. The red colour represents areas that were more activated in MS participants compared to controls, and the blue colour represents areas that were less activated in MS participants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

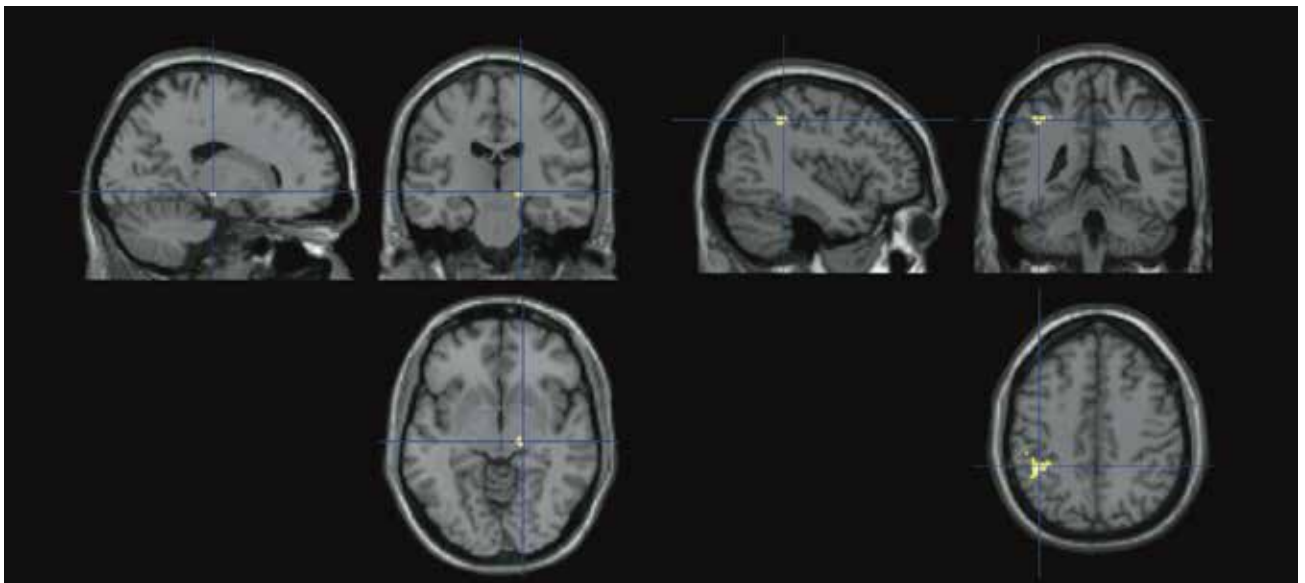


Figure 2. Brain activation with positive correlation to perceived fatigue during the working memory task. The images show activation in regions of interest: the right substantia nigra and the left posterior parietal cortex.

nitive problems due to fatigue among patients with MS. In fMRI, changes to the blood flow in the brain are measured. Increased blood flow corresponds to increased activity in that area of the brain. The patients were performing verbal tasks during the scan. A control group of healthy participants were also investigated. The patients were then examined in the same way after having a treatment with cryotherapy, i.e. having put on an active cooling garment with running cold water to lower the body temperature. The measurements

were repeated to see if the cooling had improved the cognitive functions.

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

It is important to describe fatigue to

gain acceptance for this decapacitating symptom. It is of great relevance to continue to investigate the physiological mechanisms behind the symptom. The results of this study have identified areas of the brain that are involved.

Analysis of results after intervention with a cooling garment is now terminated. Here the fMRI analysis revealed some responders who are of great interest. We now prepare a manuscript that contribute to the work of determine the physiological background of MS fatigue.

CLINICAL, IMAGING AND MEMORY INVESTIGATION IN KLS PATIENTS

PROJECT NAME

Clinical, imaging and memory investigation in KLS patients

PROJECT LEADER

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

MAIN PROJECT PARTICIPANTS

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GRANTS

Kleine Levin Foundation, USA

KEY PUBLICATIONS

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

Engström M, Hallböök T, Szakacs A, Karlsson T, Landtblom AM. Functional magnetic resonance imaging in narcolepsy and the Kleine Levin syndrome. *Front neural* 2014 Jun 25;5:105

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

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

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

Within a larger project (see Engström's report the SANDMAN project), we have investigated other sleep disorders in addition to KLS. The

results show differences between KLS and narcolepsy regarding the impact on memory. KLS has the potential to seriously affect working memory in the long run, but in narcolepsy there is a fluctuating problem to mobilize memory function.

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

Our results show that there are areas in the brain that are activated differently in patients with KLS compared with healthy individuals. The differences between patients with KLS and healthy controls were demonstrated in the resting state. In activated state during the working memory test, patients

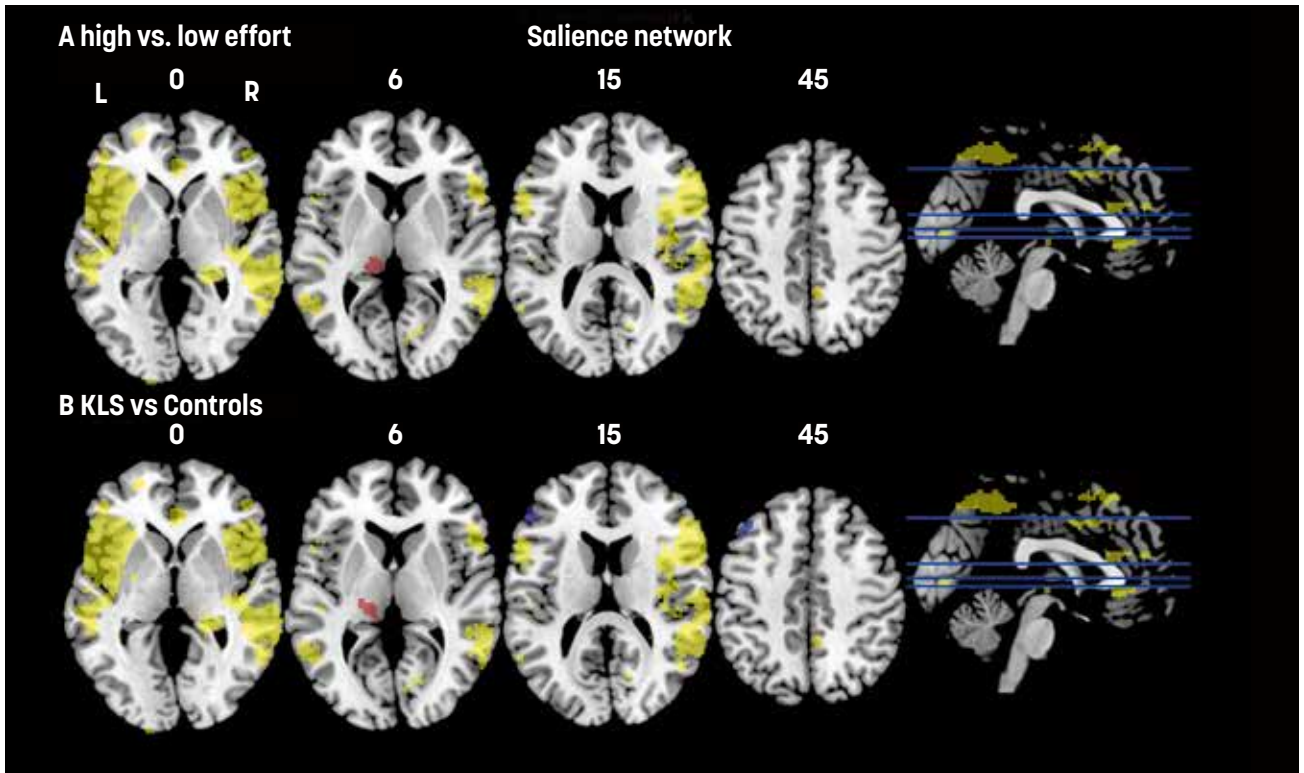


Figure 1. Functional connectivity in the salience network. Neural processing is often performed by an integrated network of several regions in the brain. Functional connectivity studies investigate the interaction of regions within these networks. Yellow areas show the network in selected slices. Red and blue areas show connectivity differences. (A) Red colour denotes regions that are more strongly coupled to the network at a high effort level compared to a low effort level. Blue colour denotes regions that are more strongly coupled to the network at a low effort level. (B) Regions that are more strongly (red) respectively more weakly (blue) coupled to the network in patients with periodic idiopathic hypersomnia (KLS) compared to healthy individuals at the high effort level.

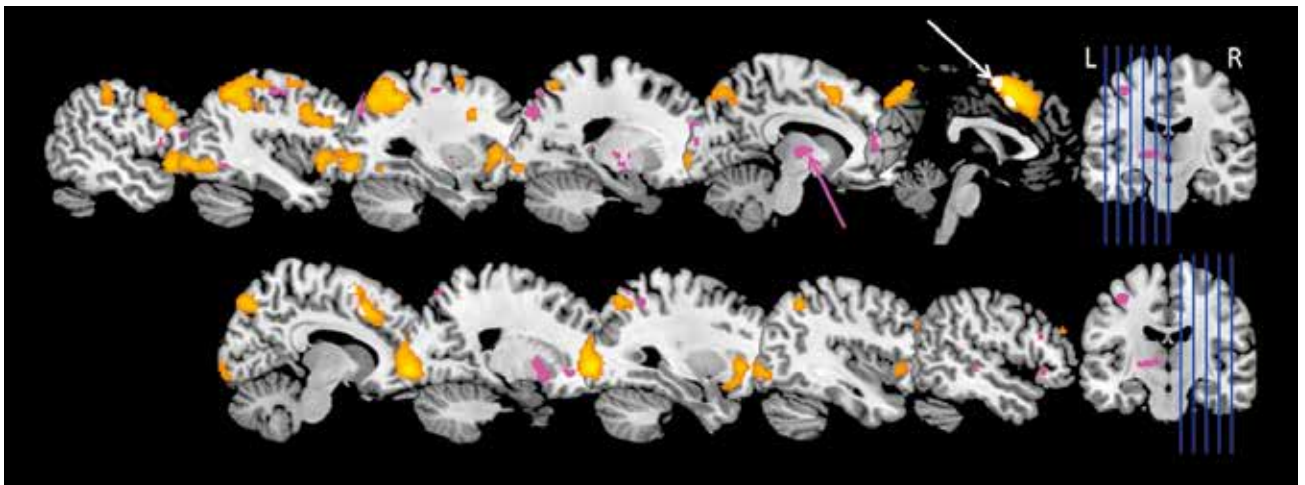


Figure 2. Typical working memory activation in healthy individuals and thalamic hyperactivation in KLS patients. In other parts of the brain KLS patients had less activation than healthy individuals.

with KLS showed increased activation in some parts of the brain while other parts were less activated compared with healthy individuals. The differences in activation in these areas could be used to part the KLS patients from the healthy individual in most of the cases; hence the techniques have the potential

to be developed into diagnostic tools of KLS. In addition, we have observed and reported that cerebral centers for regulation of eye movements are involved, using fMRI, and this corresponds to clinical symptoms.

In KLS, additional studies regarding genetics are now being evaluated. We

also intend to expand the studies into physiology i.e. the role of body temperature and certain CSF metabolites in relation to sleep episodes in collaboration with Uppsala University and Helsinki University.

PROJECT NAME

Clinical and Imaging studies of multiple sclerosis

PROJECT LEADER

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MAIN PROJECT PARTICIPANTS

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GRANTS

Swedish Research Council (VR)

KEY PUBLICATIONS

Tisell A, Leinhard OD, Warntjes JB, Aalto A, Smedby Ö, Landtblom AM, Lundberg P. Increased concentrations of glutamate and glutamine in normal-appearing white matter of patients with multiple sclerosis and normal MR imaging brain scans. *PLoS One*. 2013 Apr 17;8(4):e61817. doi:10.1371/journal.pone.0061817.

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Warntjes M, Tisell A, Landtblom AM, Lundberg P. Effects of gadolinium contrast administration on automatic brain tissue segmentation of multiple sclerosis patients. *Am J Neurorad* 2014;35(7):1330-6

CLINICAL AND IMAGING STUDIES OF MULTIPLE SCLEROSIS

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

Together with inflammation, destruction of the insulating covers of nerve cells and the formation of lesions in the central nervous system are the main characteristics of MS. However, not all MS patients have the typical lesions in the brain. In fact, MS could be seen as

a generic group for a variety of disease patterns and this perspective may help the endeavors to find more specific treatment in the future.

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

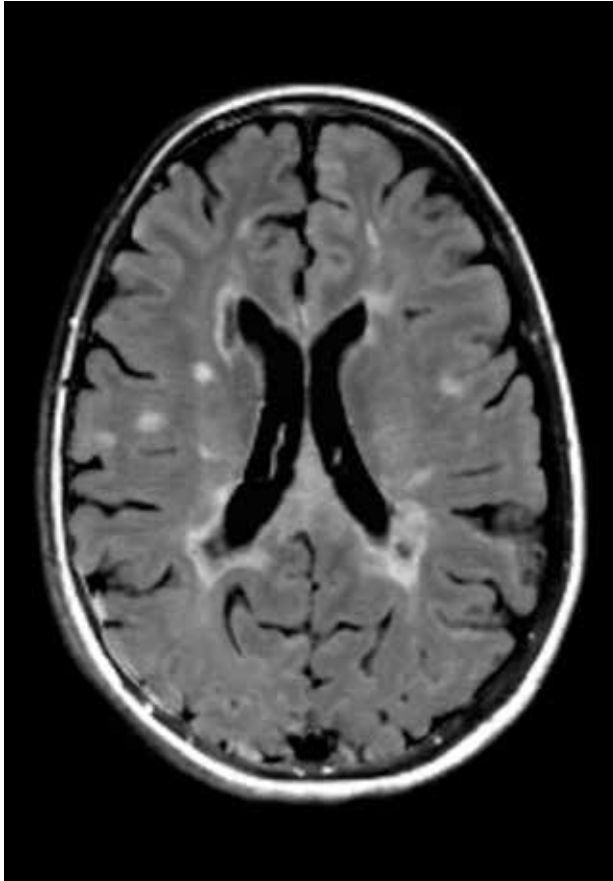


Figure 1. Image of the brain using MRI with conventional technique, showing lesions in the brain which can be a sign of MS, arteriosclerosis or insignificant signs in a healthy person over the age of 40.

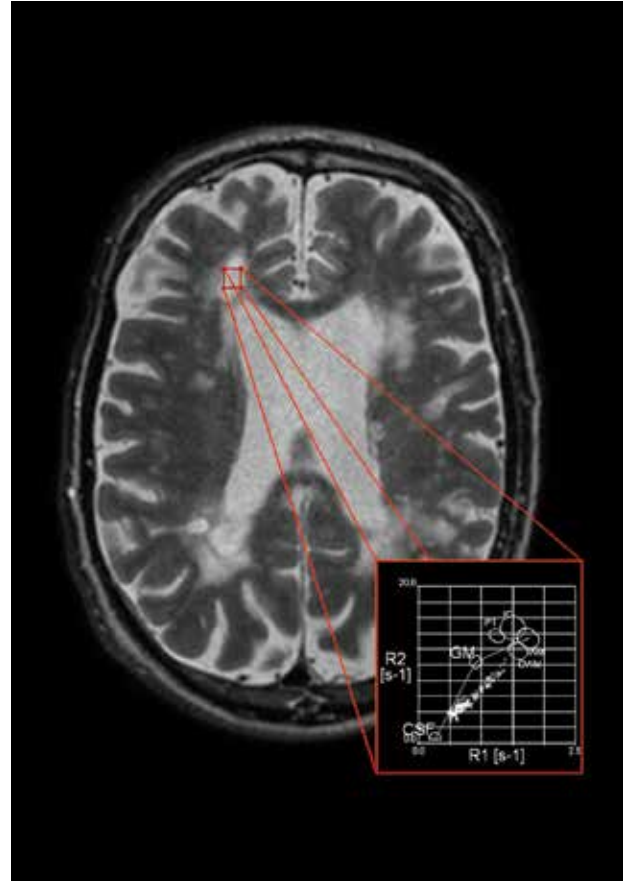


Figure 2. MR based method to discriminate between different types of brain lesions. Image by Örtér and Warntjes, 2008.

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

With magnetic resonance (MR) techniques we can measure the levels of different metabolites in the brain using 1H-MRS. High levels of some substances reflect healthy tissue whereas others reflect damage. Using this method we

have followed MS patients treated with the pharmaceutical Copaxone. Copaxone has been shown to decrease the lesions and slow down the progression of the disease. The results showed that the treatment slowed down the biochemical development of the disease.

Unspecific lesions in cerebral white matter can be seen both in MS and cerebral arteriosclerosis and is therefore often hard to use as basis for a diagnosis. A possibility to discriminate these lesions regarding their origin would

be a valuable tool for diagnosis and we have therefore performed a pilot project aiming to develop an MR method to determine such differences using QMR. Results of this study including 20 patients revealed a trend, that may help in differentiating these two conditions and this will be investigated further. The project is now being expanded through cooperation with Uppsala University, where another 50 patients will be examined during the following year.

PROJECT NAME

Working Memory in Visual Noise

PROJECT LEADER

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MAIN PROJECT PARTICIPANTS

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GRANTS

Swedish Research Council 2016-2020

KEY PUBLICATIONS

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

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WORKING MEMORY IN VISUAL NOISE

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

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

working memory in trim by requiring continual activation in communicative situations, episodic memory declines because of disuse.

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

Acoustically noisy situations are often visually noisy, i.e. the visual signal may be degraded in various ways, and it is

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

Video gaming enhances cognition

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

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

language knowledge and video gaming experience influence the dynamic relation between episodic and working memory.

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

NEUROAFFECTIVE EFFECTS OF ELECTROCONVULSIVE THERAPY FOR MDD

PROJECT NAME

Neuroaffective Effects of
Electroconvulsive Therapy for Major
Depressive Disorder

PROJECT LEADER

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

MAIN PROJECT PARTICIPANTS

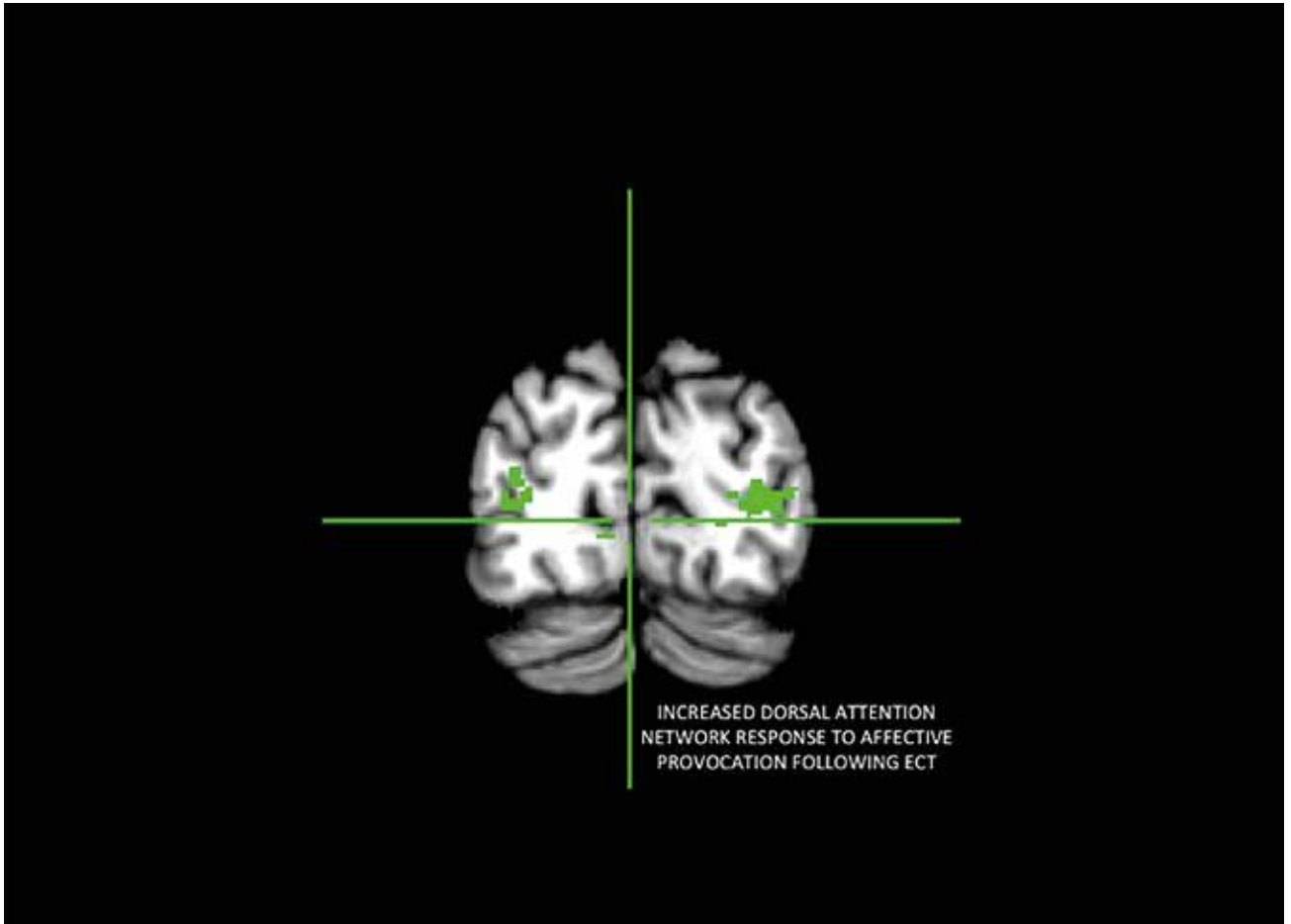
Paul Hamilton, Pia Nordanskog, Åsa Axén,
Robin Kämpfe

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

In acute cases of MDD, individuals can become entirely incapacitated or worse; pose a significant danger to themselves. In such acute cases, immediate amelioration of depressive symptomatology is required. Only a small handful of currently implemented courses of treatment can achieve

such immediate effects—among these treatments, the most broadly applied is electroconvulsive therapy (ECT).

While effective, ECT is burdensome, requiring the patient to be anesthetized and to receive electrical stimulation sufficient to cause a grand mal seizure and concomitant side effects, including significant (but transient) autobiographical memory impairment. Given this, it is desirable to investigate the neural underpinnings of ECT's therapeutic effects so that we might develop equally effective treatments that are less burdensome to patients.



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

Preliminary analyses of functional neuroimaging data show intriguing functional changes in the brain as a result of ECT. Before ECT, for example, depressed patients show a pattern of affective flattening in which they react

little, either neurally or behaviorally, to affective provocation with pictures. After ECT, however, depressed patients show robust response in the brain’s visual attention network (see Figure 1) to emotionally provocative stimuli.

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

strongly activate these structures as they anticipate failure at this challenging task.

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

EFFECTS OF rTMS ON ALCOHOL USE AND NEURAL RESPONSES IN ALCOHOL-DEPENDENT PATIENTS

PROJECT NAME

Effects of rTMS on Alcohol Use and Neural Responses in Alcohol-Dependent Patients

PROJECT LEADER

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

MAIN PROJECT PARTICIPANTS

Irene Perini, Andreas Löfberg, Hanna Karlsson, Paul Hamilton, Robin Kämpfe, Åsa Axén

GRANTS

The Swedish Medical Research Council
EU-funded Horizon 2020

Craving and an impaired ability to stop alcohol use despite adverse consequences are key features of alcohol addiction. Functional brain imaging studies have shown that insula activity in response to drug cues is positively correlated with cravings. In addition, it has been shown that high insula activity during a simple decision-making task is associated with relapse to methamphetamine use. This observation is consistent with the notion that disrupted insula function contributes to impaired decision making, resulting in continued drug use despite negative consequences. This notion is consistent

with the finding that chronic cocaine users have grey matter loss in the insula. Similar reductions in insular volume and cortical thickness have been reported in alcoholics. Modulation of insula activity may therefore represent a novel therapeutic approach in addiction, but non-invasive methods to modulate the activity of this structure have until recently not been available.

The ability of repetitive transcranial magnetic stimulation (rTMS), a non-invasive tool for neuromodulation, to reduce craving and cue reactivity in addiction has been suggested by small pilot studies in alcohol, cocaine and

opiate users. In these studies, rTMS has typically been applied to the dorsolateral prefrontal cortex (DLPFC), a superficial structure that can be targeted by the conventional “figure eight” TMS coil design. However, this design does not allow deeper structures to be targeted. No study has therefore to date evaluated whether modulation of insula activity using rTMS would reduce alcohol craving and use. The present study uses a novel coil, designed to allow “deep TMS”, to examine whether stimulation of the insula offers a novel alcoholism treatment.

The study objectives are to investi-

gate the effects of repetitive transcranial magnetic stimulation (rTMS) targeting the insula on alcohol use and neural responses in alcohol-dependent patients.

The study population consists of treatment seeking alcohol dependent subjects who have first completed standard alcohol withdrawal treatment if needed. Participants first undergo an MRI scan to collect resting state and structural data, and then receive one of two treatments: Active (10Hz) rTMS; or sham stimulation, both targeting the insula bilaterally. rTMS sessions will be conducted five times per week, for 3 weeks, for a total of 15 sessions. A

second MRI scan is obtained at the end of the treatment phase to assess changes in resting state connectivity, and to evaluate insula activity in tasks known to activate this structure.

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

BRAIN CORRELATES TO AFFECTIVE PROCESSING IN TYPICAL INDIVIDUALS AND CLINICAL GROUPS

PROJECT NAME

Brain correlates to affective processing in typical individuals and clinical groups.

PROJECT LEADER

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MAIN PROJECT PARTICIPANTS

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GRANTS

The Swedish Medical Research Council
EU-funded Horizon 2020 project

The aim of this project is to contribute to the understanding of the intense affects and difficulties with affect regulation that is noted clinically in adolescents with non-suicidal self-injury (NSSI) disorder and Autism Spectrum disorder (ASD) compared to healthy controls.

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

In order to address these aims the

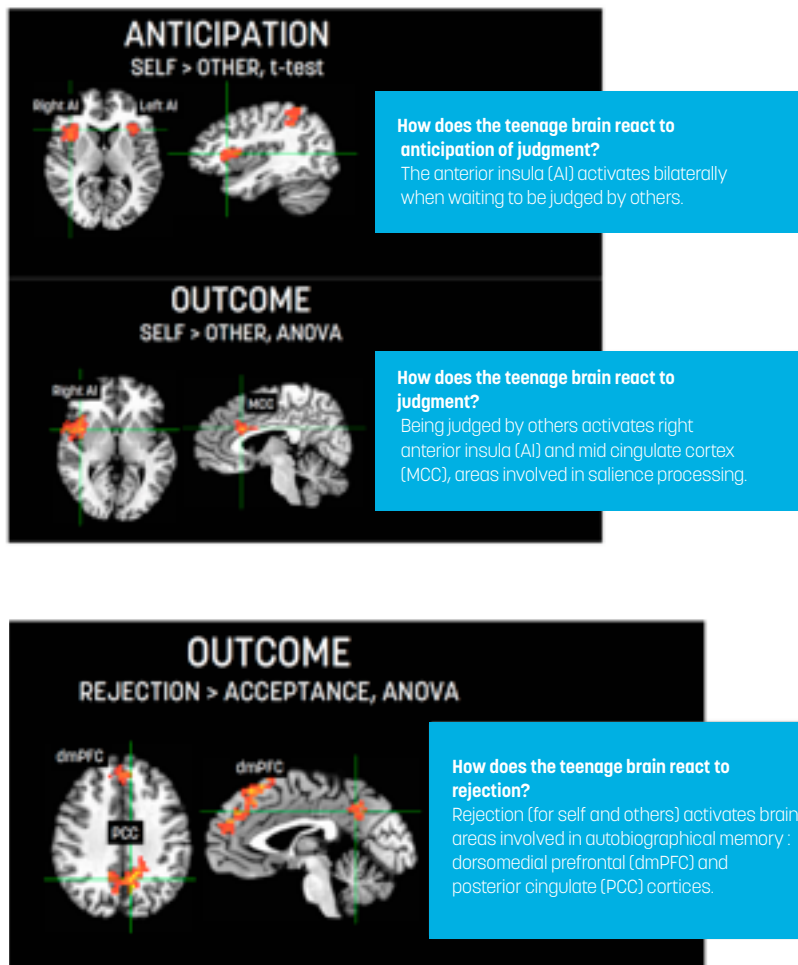
following paradigms are tested in the Magnetic Resonance Imaging (MRI) scanner:

Matching of images

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

Online game paradigm

Adolescence is an especially vulnerable time for social pain and distress. Neural



Preliminary findings are available for the healthy adolescents group. Two images show preliminary findings of the online game task in healthy teenagers. Healthy participants activate the salience network when they feel judged by others and also when they anticipate other people's judgment (Figure1). The salience network activates to direct our cognitive resources towards what's mostly important and relevant to us. During rejection the healthy subjects activate areas involved in recalling personal life events (Figure2).

systems are not fully developed for processing emotional reactions, and in clinical samples these systems may also have been affected by trauma. Rejection or other negative social interactions are some of the most powerful stressors for humans. Here the subjects participate in a novel paradigm, which mimics everyday interactions in a social media context. The paradigm induces the feeling of being accepted or rejected by other participants. It also investigates brain correlates to seeing others being

liked or disliked. This task is based on two relevant aspects in the adolescents' world. Firstly, the importance of feeling included in a group and secondly, the importance of social media when it comes to acceptance or rejection.

Touch paradigm

Light touch to the skin by a conspecific is the affiliative behavior that is important for the development of a close attachment between mother and child. This type of social-affective touch is one

of the strongest signals of a successful attachment bond between parents and offspring during early childhood, and later life in close relationships. Lightly touching the skin activates two different systems of neurons that signal to the brain. Here tactile soft brush strokes are delivered to the skin of the right dorsal forearm in a proximal-distal direction. After each stimulation the subjects are asked to rate the pleasantness and intensity of stroking on a visual analog scale (VAS).

PROJECT NAME

Statistical Analysis of fMRI Data

PROJECT LEADER

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Swedish Research Council

KEY PUBLICATIONS

Eklund, A., Nichols, T., Knutsson, H., Cluster failure: why fMRI inferences for spatial extent have inflated false positive rates, *Proceedings of the National Academy of Sciences of the United States of America*, 113, 7900 - 7905, 2016

Sidén, P., Eklund, A., Bolin, D., Villani, M., Fast Bayesian whole-brain fMRI analysis with spatial 3D priors, *NeuroImage*, 146, 211-225, 2017

Eklund, A., Nichols, T., Andersson, M., Knutsson, H., Empirically investigating the statistical validity of SPM, FSL and AFNI for single subject fMRI analysis, *IEEE International Symposium on Biomedical Imaging (ISBI)*, 1376 - 1380, 2015

STATISTICAL ANALYSIS OF fMRI DATA

Functional magnetic resonance imaging (fMRI) is a popular tool for studying human brain function, as it can non-invasively image the human brain without any ionizing radiation. Despite the popularity the statistical methods used have rarely been validated using real data. Validations have instead mainly been performed using simulated data. From a statistical perspective, analyzing fMRI data is a challenging task for several reasons. One reason is that the fMRI 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 such as head motion, breathing and pulse.

In this project we extend, validate and improve existing statistical models for fMRI data, such that weak brain activity patterns can be detected and the brain activation images can be trusted.

In our latest work, published in PNAS, we used resting-state fMRI data from 499 healthy controls to conduct a total of 2,880,000 random group analyses, to compute the empirical false-positive rates for the software

Spatial distribution of false clusters for SPM

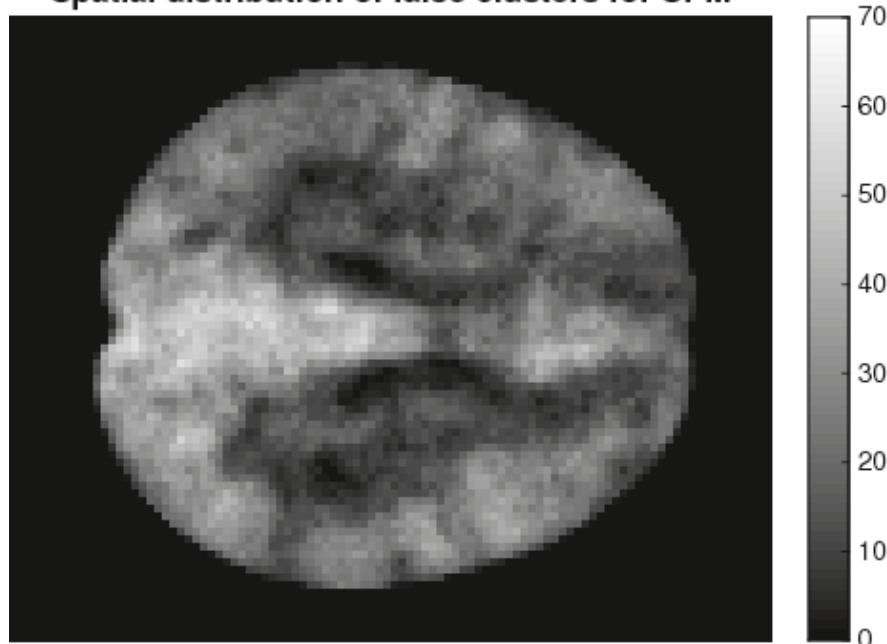


Figure 1. The map shows voxel-wise incidence of false clusters for the SPM software package. Image intensity is the number of times, out of 10,000 random group analyses, a significant cluster occurred at a given voxel.

packages SPM, FSL, and AFNI. The analyses comprise 1,000 one-sided random analyses repeated for 192 parameter combinations, three thresholding approaches, and five tools in the three software packages. The tested parameter combinations are common in the fMRI field.

We considered both two-sample and one-sample designs. Because two groups of subjects are randomly drawn from a large group of healthy controls, the null hypothesis of no group differ-

ence in brain activation should be true. Moreover, because the resting-state fMRI data should contain no consistent shifts in blood oxygen level-dependent (BOLD) activity, for a single group of subjects the null hypothesis of mean zero activation should also be true.

Using this null data, we estimated the incidence of significant results. In theory, we should find 5% false positives (for a significance threshold of 5%), but instead we found that the most common software packages for

fMRI analysis (SPM, FSL, AFNI) can result in false-positive rates of up to 70%. By comparison, a non-parametric permutation test, which is based on a lower number of assumptions, yielded nominal false-positive rates for almost all settings. The main reason for the high degree of false positives was found to be that the fMRI noise has a more complicated spatial structure than previously believed.

TISSUE CLASSIFICATION USING DUAL ENERGY CT AND ITERATIVE RECONSTRUCTION

PROJECT NAME

Tissue Classification Using Dual Energy CT and Iterative Reconstruction

PROJECT LEADER

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

MAIN PROJECT PARTICIPANTS

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GRANTS

Cancerfonden 2013-2015, 2016-2018
Swedish Research Council 2017-2020

KEY PUBLICATIONS

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

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

Malusek, A., Magnusson, M., Sandborg, M., and Alm Carlsson, G. A model-based iterative reconstruction algorithm DIRA using patient-speci tissue classification via DECT for improved quantitative CT in dose planning, accepted for publication in *Medical Physics* 2017

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

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

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

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

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

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

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

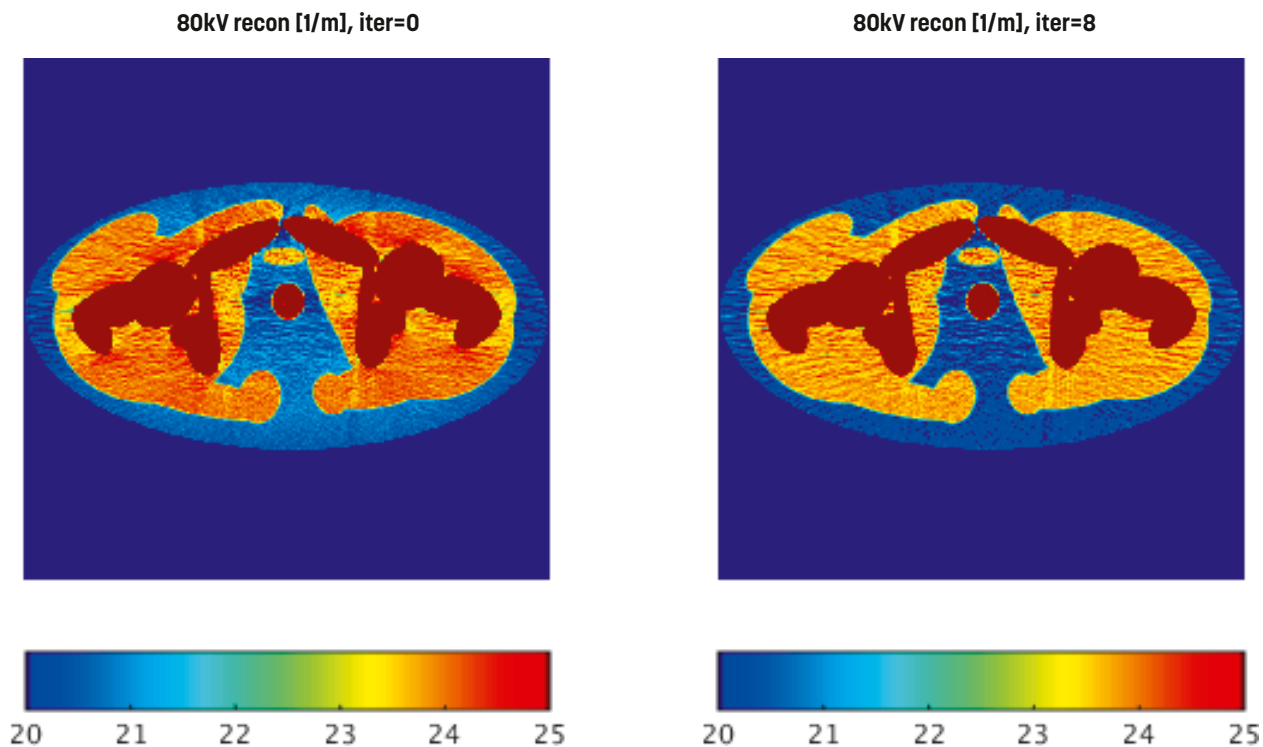


Figure 1. Suppression beam hardening artifacts in the human pelvic region from iteration 0 to iteration 8 in DIRA.

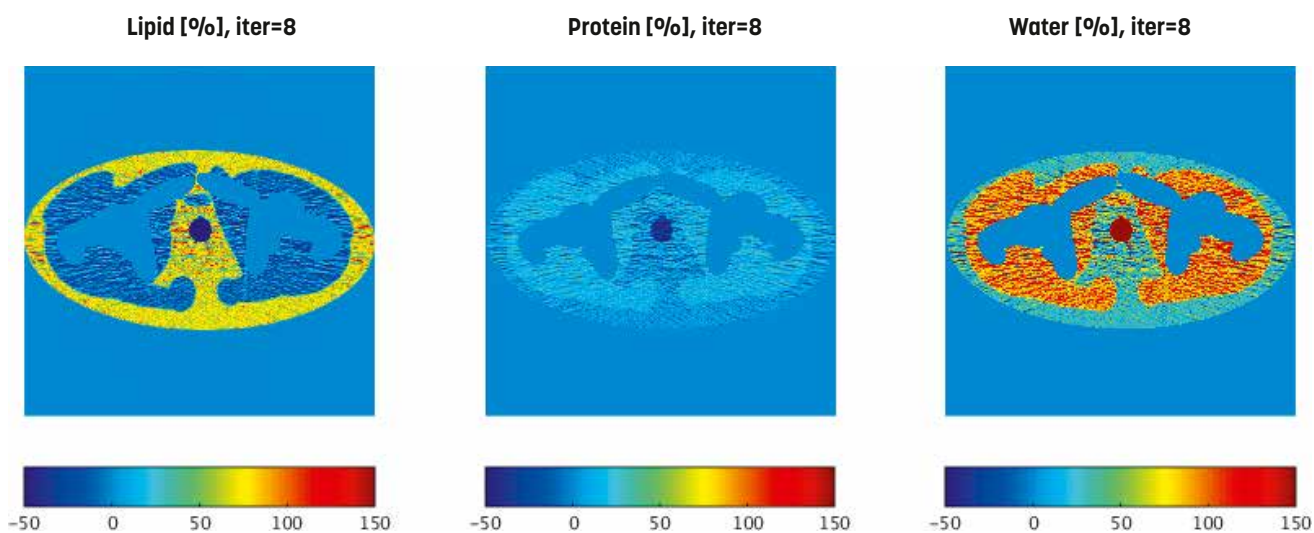


Figure 2. Soft tissue classification into lipid, protein and water (LPW) after 8 iterations of DIRA.

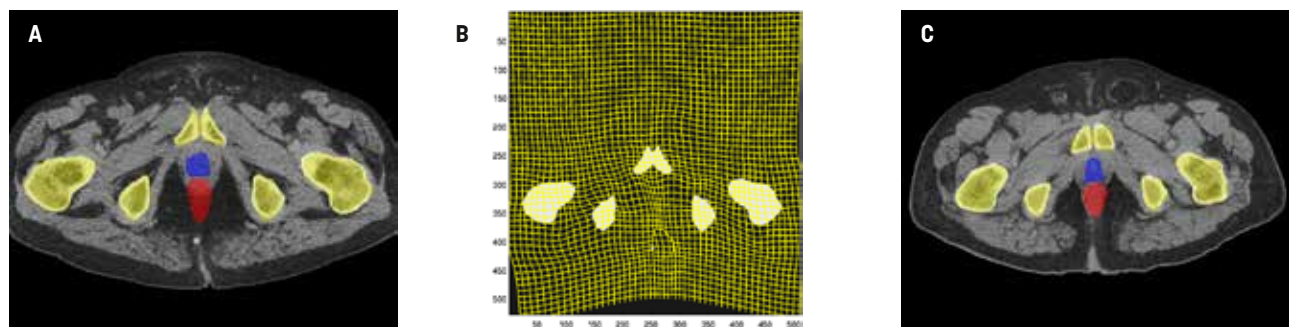


Figure 3. a) Automatic segmentation of the male pelvis to bone (yellow), prostate (blue) and rectum (red) using our algorithm JJ2016 (Master thesis by Julius Jeute). (b) Transformation field calculated using the morphone algorithm and applied to the atlas bones. (c) Automatic segmentation of a different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

OPTIMISING RADIOGRAPHIC TECHNIQUES – DOSE VERSUS IMAGE QUALITY

PROJECT NAME

Optimising radiographic techniques – dose versus image quality

PROJECT LEADER

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

MAIN PROJECT PARTICIPANTS

Guðrun Alm Carlsson, Erik Tesselaar, Alexandr Malusek

KEY PUBLICATIONS

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

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

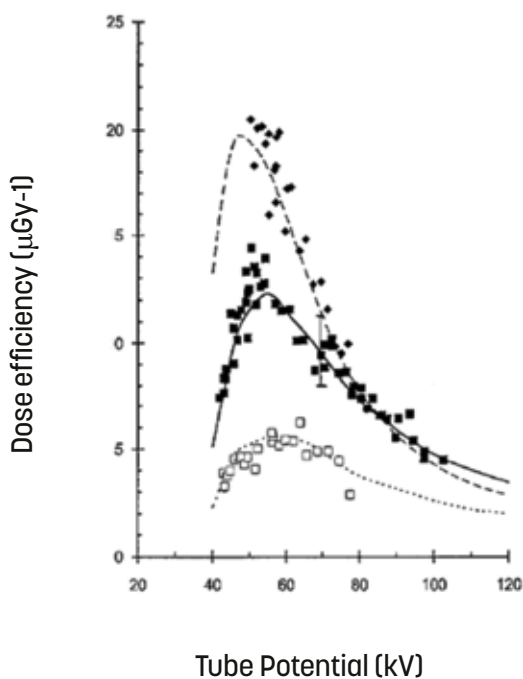
Alexandr Malusek, Michael Sandborg, and Guðrun Alm Carlsson. Accurate KAP meter calibration as a prerequisite for optimization in projection radiography. *Radiat. Prot. Dosim.*, 169, 353-359 (2016)

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

The procedure for this is called dose

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

Our aim is to develop and use a computer simulation model of the complete x-ray imaging system. To achieve this goal, we are validating a model called the virtual x-ray machine by exploring the correlation between subjective radiologists' assessment of image quality and the objective estimates from a so-called model observer. The validated model observer's assessment is then used to search for radiation dose-



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

efficient settings of the x-ray machine. This cost-efficient strategy provides unique opportunities not only for evaluating today's x-ray machines, but also future machines before expensive prototype systems are built. The whole medical imaging process can be optimised including image acquisition, image processing and pathology detection.

An example of a model observer is the signal-to-noise ratio when imaging the reduced blood flow in a coronary artery. The signal-to-noise ratio measures the

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

The figure illustrates important results from our model observer. The y-axis shows that the dose efficiency

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

FINDING HIGH RISK OSTEOPOROSIS PATIENTS WITH DUAL ENERGY CT

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

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

Our idea is to use dual energy abdominal CT scans made for different indications at CMIV, including the lumbar spine and/or the hips to describe the risk for having osteoporosis and by that finding high-risk patients earlier.

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

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

We also analysed the amount of

PROJECT NAME

Finding High Risk Osteoporosis Patients with Dual Energy CT

PROJECT LEADER

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

MAIN PROJECT PARTICIPANTS

Eva Klintsröm, Benjamin Klintström, Martin Sedlmair and Philipp Hoffmann (Siemens Healthcare)

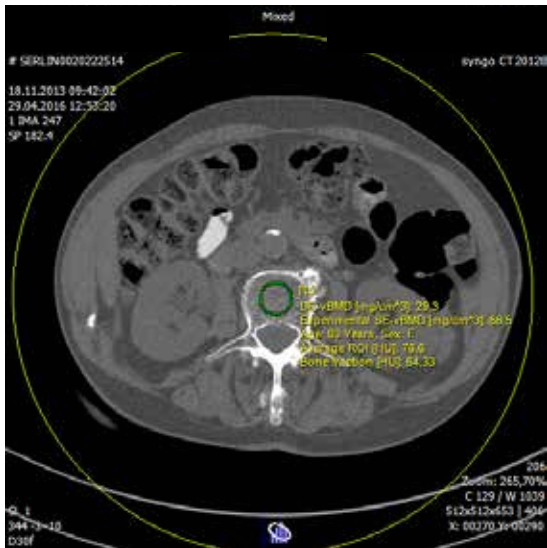


Figure 1. Results of the vBMD (volume BMD), measured by eXamine, the software application developed together with Siemens. The analysis is done on a dual energy scan without contrast.

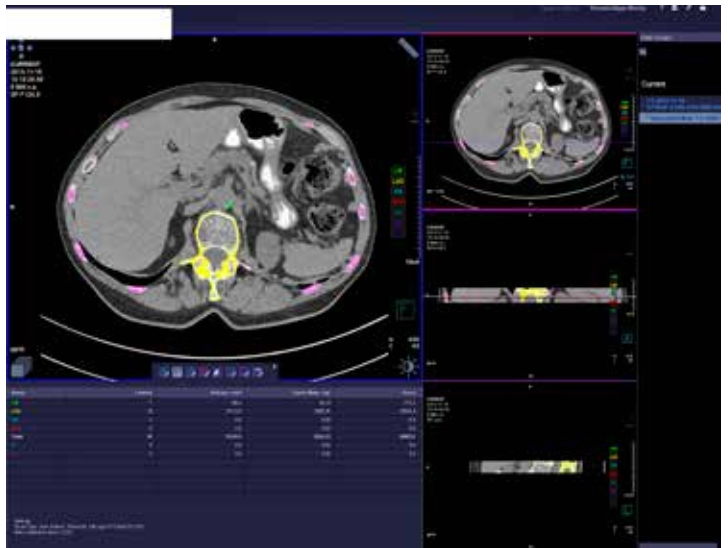


Figure 2. Results of the CaScoring analysis of the aorta with quantification of the amount of CaHA (Calciumhydroxyapatite) in the aorta. The results were used to proof that DXA scans are false too high in individuals with aortic calcifications compared to vBMD obtained in the same patients.

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

In the second part of the project we

have a collaboration with the RMV (Rättmedicinäverket). The goal of the project is to optimize CBCT (cone beam CT) techniques in order to be used more widely to detect high risk patients for osteoporotic fractures. CBCT is today mainly used in dentistry to make high resolution images of the mandibles and teeth. But recently CBCT is used more and more for examination of extremities. In the future we think applications of CBCT like in the new Multitome

RAX from Siemens (a robotic radiology system for skeletal and lung examinations) can be used to make high resolution scans of the radius of fractured patients in the emergency setting and ideally even the lumbar spine in order to find high risk patients earlier. We also think it might be possible to use CBCT technique to obtain a DXA scan in the same session as the acute examination.

ANALYSIS OF CT LIVER PERFUSION

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

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

radiation dose and enhancing image quality in CT.

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

Patients with hepatocellular carcinoma (HCC) planned for a transarterial chemoembolization treatment (TACE) will be scanned with our CT perfusion protocol as well as with a 4 phase CT (non contrast, late arterial, venous and late phase) before TACE and 3-4 weeks after TACE treatment.

The image quality of the four phase CT will be compared to the images of the perfusion CT. We will also analyse

PROJECT NAME

Analysis of CT Liver Perfusion

PROJECT LEADER

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MAIN PROJECT PARTICIPANTS

Per Sandström, Bergthor Björnsson,
Wolf Bartholomae, Lilian Henriksson,
Petter Quick

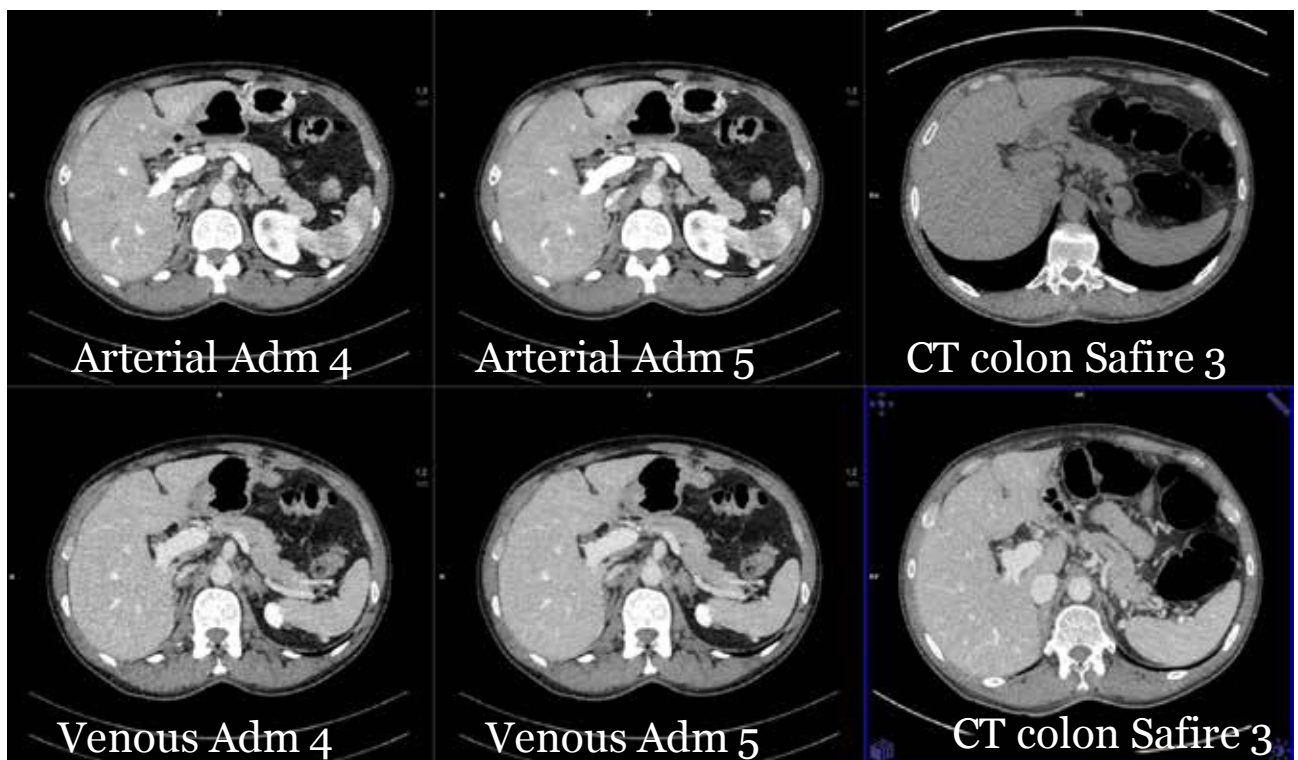


Figure 1. Results of the vBMD (volume BMD), measured by eXamine, the software application developed together with Siemens. The analysis is done on a dual energy scan without contrast.

the results of the CT perfusion software and compare these with the visible results to analyse if the quantitative information can increase the radiologist confidence in deciding if lesions are HCC or nodules as well as the question about residual tumour after TACE treatment.

In the first part of the study we concentrate on lowering the radiation dose. In the second part we will examine if lesions are missed or under-diagnosed

with the fixed time points of a four phase CT, compared to the continuous CT perfusion scan. We will then investigate if fewer sequences in a perfusion scan might be sufficient for the quantitative information. The last part will investigate if LI-RADS scores are changed when evaluating liver nodules only visibly as compared with adding the help of the quantitative perfusion information.

In summary, the goal of this project

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

PROJECT NAME

Methods for high-quality illumination in interactive volume graphics

PROJECT LEADER

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

MAIN PROJECT PARTICIPANTS

Daniel Jönsson, Joel Kronander, Timo Ropinski

GRANTS

The Swedish Research Council 2011

KEY PUBLICATIONS

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

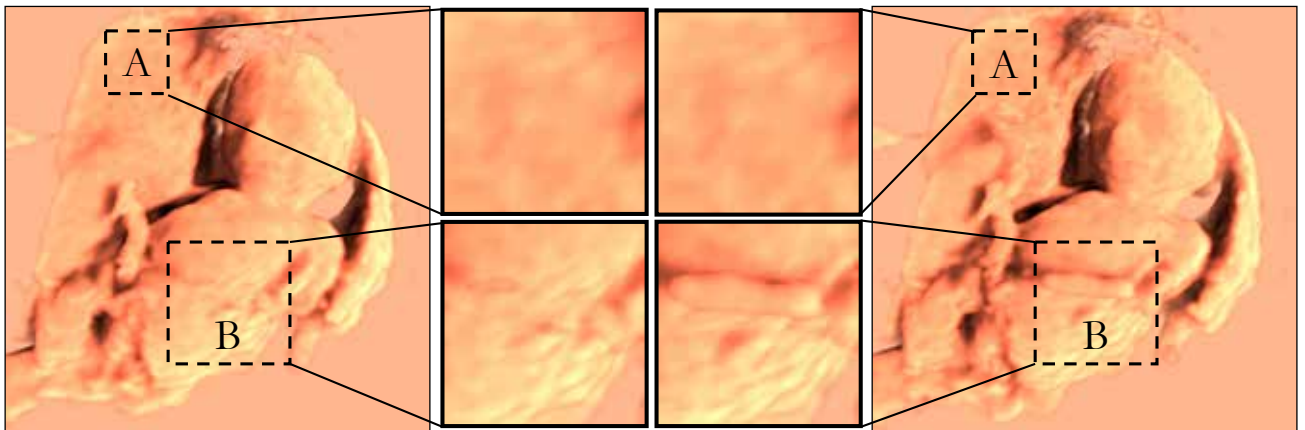
Interactive Visualization of 3D Scanned Mummies at Public Venues, Anders Ynnerman, Thomas Rydell, Daniel Antoine, David Hughes, Anders Persson, Patric Ljung, ACM Communications, Volume 59, Number 12, pages 72-81 - 2016

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

METHODS FOR HIGH-QUALITY ILLUMINATION IN INTERACTIVE VOLUME GRAPHICS

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

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



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

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

By utilizing recent advances in hardware we have also shown how to per-

form selective light updates and reduce the memory footprint of a widely used light transport algorithm. This enables the user to interactively create advanced light setups with low memory overhead.

In our latest work, we have extended our methods to time-varying CT, MRI and ultrasound scans, thus enabling examination of organ functions with accurate shading. We show that the key to allow high quality illumination for time-varying data is to utilize the

correlation between the changes in the data over time, illustrated in the figure below. By efficiently incorporating the information about changes in the data, we can reduce the light transport computation to the changing areas and thereby reach interactive performance. This work received an honorable mention for the best paper award at IEEE Visualization 2016.

PROJECT NAME

Optimized flows and IT tools for digital pathology

PROJECT LEADER

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

MAIN PROJECT PARTICIPANTS

Senior research leaders: Claes Lundström, Darren Treanor, Martin Hallbeck, Peter Lundberg, Stergios Kechagias, Daniel Forsberg

Post-docs: Martin Falk, Nazre Bataol

PhD students: Dharshana Jayewardene, Jesper Molin, Anna Bodén

Research assistants: Jeronimo Rose
Main clinical partners: Anna Bodén, Karin Skoglund, Arrigo Capitanio, Helén Richard, Christine Johansson, Sofia Jarkman

GRANTS

VINNOVA 2012-2014, 2015-2017

KEY PUBLICATIONS

Transfer Function Design Toolbox for Full-Color Volume Datasets
Martin Falk, Ingrid Hotz, Patric Ljung, Darren Treanor, Anders Ynnerman, Claes Lundström
IEEE Pacific Visualization Symposium 2017

Scale Stain: Multi-Resolution Feature Enhancement in Pathology Visualization
Jesper Molin, Anna Bodén, Darren Treanor, Martin Fjeld, Claes Lundström
arXiv preprint arXiv:1610.04141

Slide navigation patterns among pathologists with long experience of digital review
Jesper Molin, Marten Fjeld, Claudia Mello Thoms, Claes Lundström
Histopathology 2014.

OPTIMIZED FLOWS AND IT TOOLS FOR DIGITAL PATHOLOGY

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

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

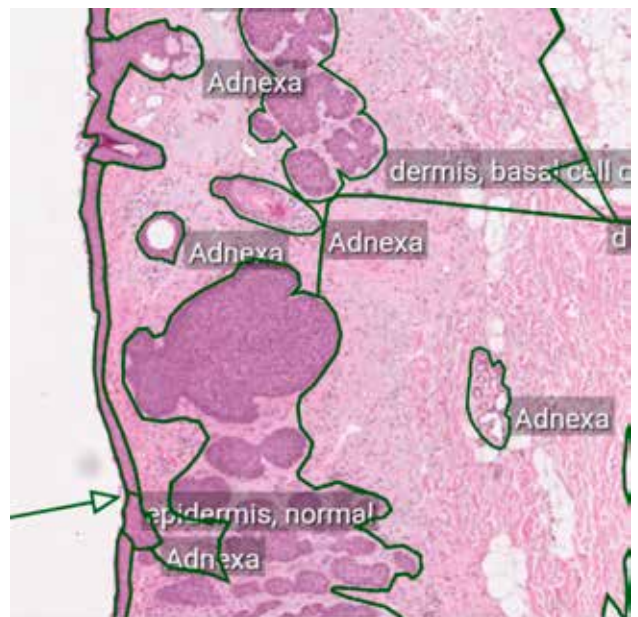
In order to realize this potential,

cross-disciplinary research efforts are needed that can combine clinical expertise with knowledge in image analysis and human-computer interaction.

This project aims to design an optimal workflow for digitized pathology, to develop IT tools such as the pathologist's workstation, and to bring the resulting innovations out into the clinical reality. Apart from CMIV the project consortium currently consists of Sectra AB, eleven regional care providers, Equalis, Interactive Institute Swedish ICT, and LRI Imaging AB. The main funding source is VINNOVA (the Swe-



Investigating a gland candidate in a colorectal adenocarcinoma (red highlight, left). Clipping the 3D slide stack with a cut plane reveals that the gland extends over the entire stack (right).



Normal skin tissue is annotated in an ambitious project aiming to create a database over normal tissues to be used in future image analysis projects.

dish Innovation Agency). CMIV efforts within the project are primarily focused on a number of research initiatives.

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

Analyzes of the pathology depart-

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

The CMIV research agenda in digital pathology tackles image analysis challenges such as correlating findings between radiology and histology in

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

QUANTITATIVE MRI AS A GROUND-BREAKING TOOL FOR POST MORTEM IMAGING DIAGNOSES

PROJECT NAME

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

PROJECT LEADER

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

KEY PUBLICATIONS

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

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

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

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

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

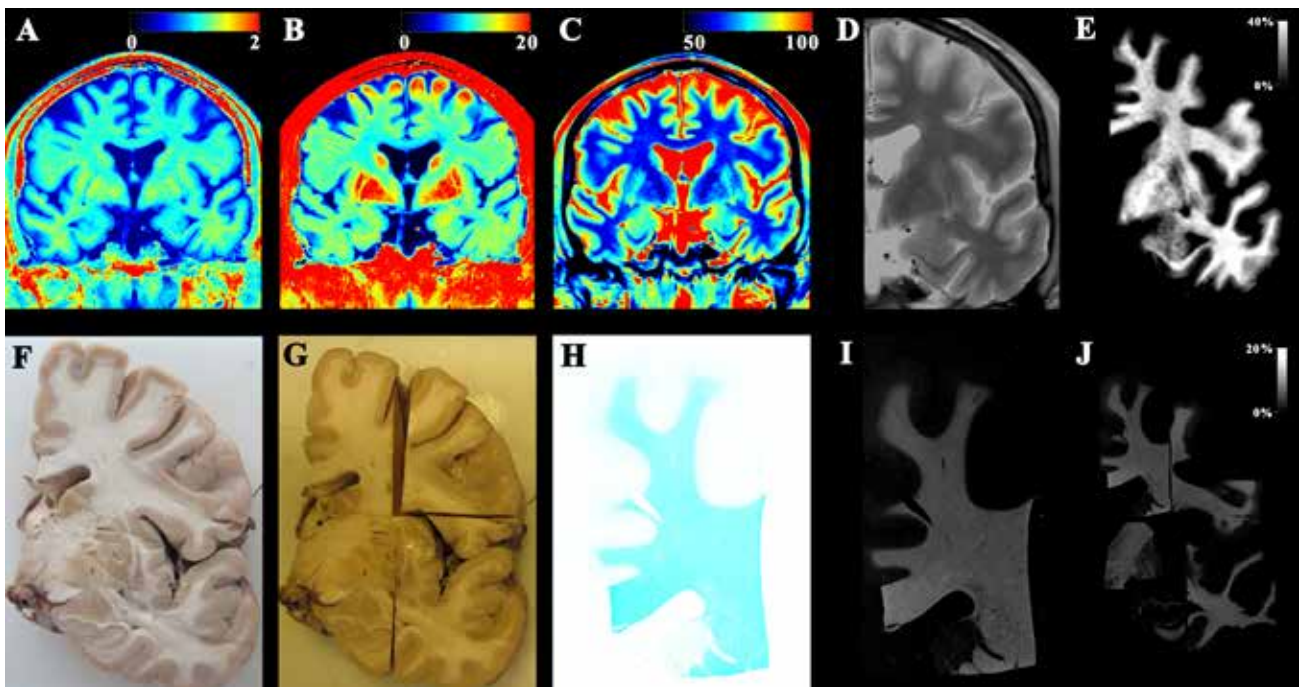
A substantial advancement required for post-mortem imaging to equal classic autopsy is related to post-mortem quantitative MRI. This approach is based on a recently developed MRI sequence that allows for rapid quantification of parameters called relaxation times and proton densities. These parameters can be measured by placing measuring fields in regions of interest in MR images.

It was found that each relevant pathology such as infarction, inflam-

mation or tumors exhibit unique combinations of parameters. Therefore, the measured values can provide the radiologist and the forensic pathologist with relevant information for the determination of the cause of death.

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

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



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



FROM RESEARCH TO CLINICAL PRACTICE

Ever since the start in 2002 the CMIV foundation has been the collaboration between university, health care and industry with focus on bringing technology and medicine together to create patient values. Each part contribute with important knowledge that is otherwise lacking. This work method has proven successful over and over again.

In general, collaboration with the surrounding world is important for any university. The interaction with health care, industry and people around us inspire creativity and strengthen the relevance of the research. It keeps us on our toes. In specific, collaboration is vital when working on the border between research areas where no one has all the answers on their own.

Bringing an idea from research to implementation in clinical practice is not done in a heartbeat. Apart from being a long process it also requires extensive knowledge from multiple fields. At CMIV we are using novel technology in medical applications thus complicating the process further as these fields are not naturally mixed. To succeed in our endeavors the technical and medical faculties are collaborating within the university and at the same time externally with health care and industry. In this constellation the university faculties are providing a solid research platform with extensive knowledge in technology and medicine while the health care have insight in clinical practice routines and what would actually result in improved patient care. The industry is essential when it comes to packaging the results into a safe product that can be used in routine care.

CMIV has ongoing research collaborations with Siemens, Philips, Sectra and Bayer. This ensures that we can work with the latest technology and have access to novel software under development and the vendors receive feedback, validation as well as new developments in return.

The research process is not always a straight line between a new idea and implementation. As described in the examples below some projects do follow the line with a CMIV researcher having an original idea and develop that through extensive basal research followed by clinical verification. Finally the researcher creates a spin-off company that can take the idea to the market in a product that is implemented in clinical practice. However, some projects are based on validation of software provided by an existing medtech company. Yet another might originally come from a CMIV research idea but comes back for validation as a product. There are also numerous projects that never reach commercialization but are implemented in clinical routines directly, producing patient benefits in silence.

The following section will present some of our projects that has reached all the way to the patient.

HEART CT

Traditional examination of the coronary arteries to discover narrowings involves an invasive method where a catheter with a camera is inserted through a vessel in the groin. During the examination the pressure may be measured to decide whether the discovered narrowing requires adjustment. The procedure is expensive and involves an increased risk for the patient.

At CMIV a large study is ongoing in collaboration with the Cardiac center at Region Östergötland. All heart patients in the region who are referred to computed tomography (CT) of the coronary arteries are currently included in the study. The result of the study shows that there is a potential for 40-60% of the patients to be spared an invasive procedure as the CT shows that no narrowing needs to be adjusted. During the study optimizations of the protocol has been made to lower the radiation dose and the amount of contrast agents used. CMIV has the most extensive follow-up in the world on this type of study and has been able to use it to perform a solid validation of the method.

A development of the heart CT projects involves new software from Siemens that allows virtual measurement of the pressure in the coronary arteries.



This will further limit the number of patients that need an invasive procedure. A validation study performed at CMIV shows that the virtual method is as precise as the invasive method in determining the pressure.

These kinds of validating studies are very important, even though they do not involve an original research idea or results in a new spin-off company. Instead it creates values for healthcare in a more direct way. This study is unique in its way of combining original research with validation.

New deep ground breaking research at CMIV have for the first time made it possible to use already acquired CT cardiac data and to simulate the blood flow

in the heart. This provides the ability to obtain new functional information without affecting the CT examination and the radiation dose to the patient. The method gives the potential to simulate “what if” scenarios.

SYNTHETIC MRI

Conventional MRI produces images that must be subjectively assessed by the radiologist. The images lack an absolute scale and it is therefore impossible to compare images directly. About a decade ago CMIV researcher Marcel Warntjes developed a new method that allows a quantitative measure of the signals received from the MRI. These measures directly reflect physical prop-

erties of the patient and are therefore independent of the MR scanner.

To allow radiologists to easily interpret the new, quantitative maps, a method has been implemented called ‘Synthetic MRI’. By using this technique, conventional images are synthesized based on the maps. This means that radiologists have access to a large range of conventional image contrasts and absolute numbers in a scan time as short as 5 minutes. Moreover, a computer can automatically add clinical relevant information such as tissue segmentation and volume calculations.

The invention was brought into a spin-off company called SyntheticMR, where it evolved into a full-scale prod-

uct. All major MRI vendors have now implemented the technique into their scanners and it is available as a plug-in software to the Sectra PACS.

New developments, mainly focused at computer aided diagnose, are still validated at CMIV together with radiology departments throughout Sweden and the rest of the world.

BODY COMPOSITION MRI

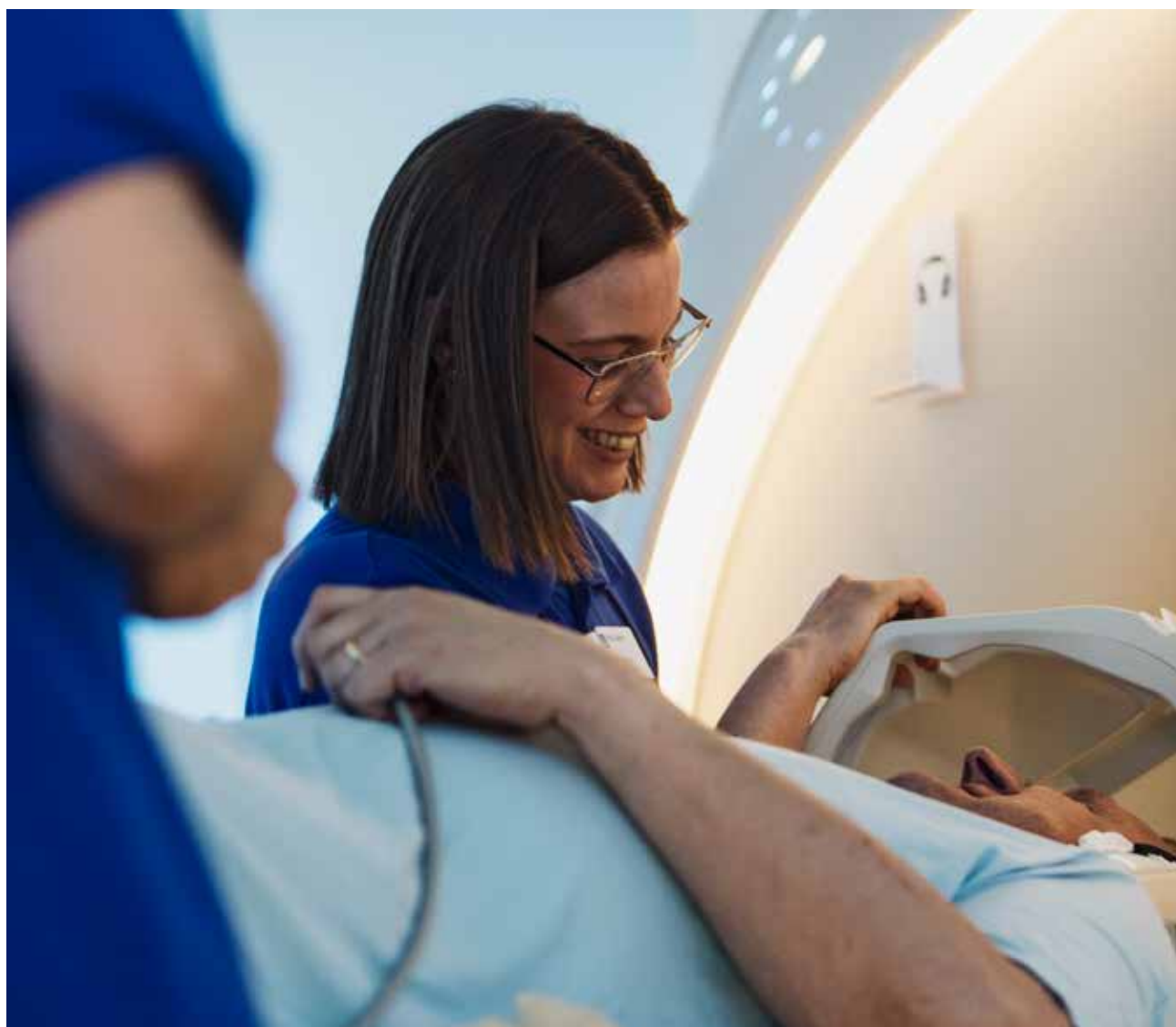
The composition of body fat is an important risk factor for many life-style diseases, such as heart disease, stroke and diabetes. The body mass index neither tell the whole story as it does not reveal the distribution between fat and muscle tissue nor where the fat is located. Visceral fat is a strong risk factor while subcutaneous fat might even be protective. Finding better tools to evaluate which individuals are at risk and allow large-scale research is



important.

CMIV researchers Magnus Borga and Olof Dahlqvist Leinhard have developed an image analysis method that can quantify the volume of fat and muscles in the body from a regular MRI scan. The method is automatic which makes it possible to analyze big datasets and is

therefore perfect for big data research studies. The method is also used in clinical applications for individual patients. The two researchers created the spin-off company AMRA where they developed their findings into a cloud-based service. The customers send in MRI data and get the body



“The research process is not always a straight line between a new idea and implementation.”

composition measurement back.

Research is continuing at CMIV to refine the method further and in parallel, large collaboration studies with other universities over the world is made possible.

DIGITAL PATHOLOGY

Pathology is an important cornerstone in health care, analyzing tissue samples to provide enough information for a diagnosis. Digitization of the pathology workflow is essential to ensure increased quality of care and shortened waiting times for the patients. The government funded project DigiPat has in a perfectly balanced collaboration between industry, university and health care created new workflows and digital tools that are now being used in clinical practice. The most concrete product of the project is the pathologist's workstation developed by the medtech company Sectra in close collaboration with CMIV and the Swedish pathology

departments involved in the project.

This is a successful example of when the industry is involved from the beginning, taking part in the research and development until the results are ready to be taken to the market. All parts in this collaboration are equally important. The strong collaboration is continuing with the goal to develop image analysis tools that can be used in clinical practice.

POST MORTEM IMAGING

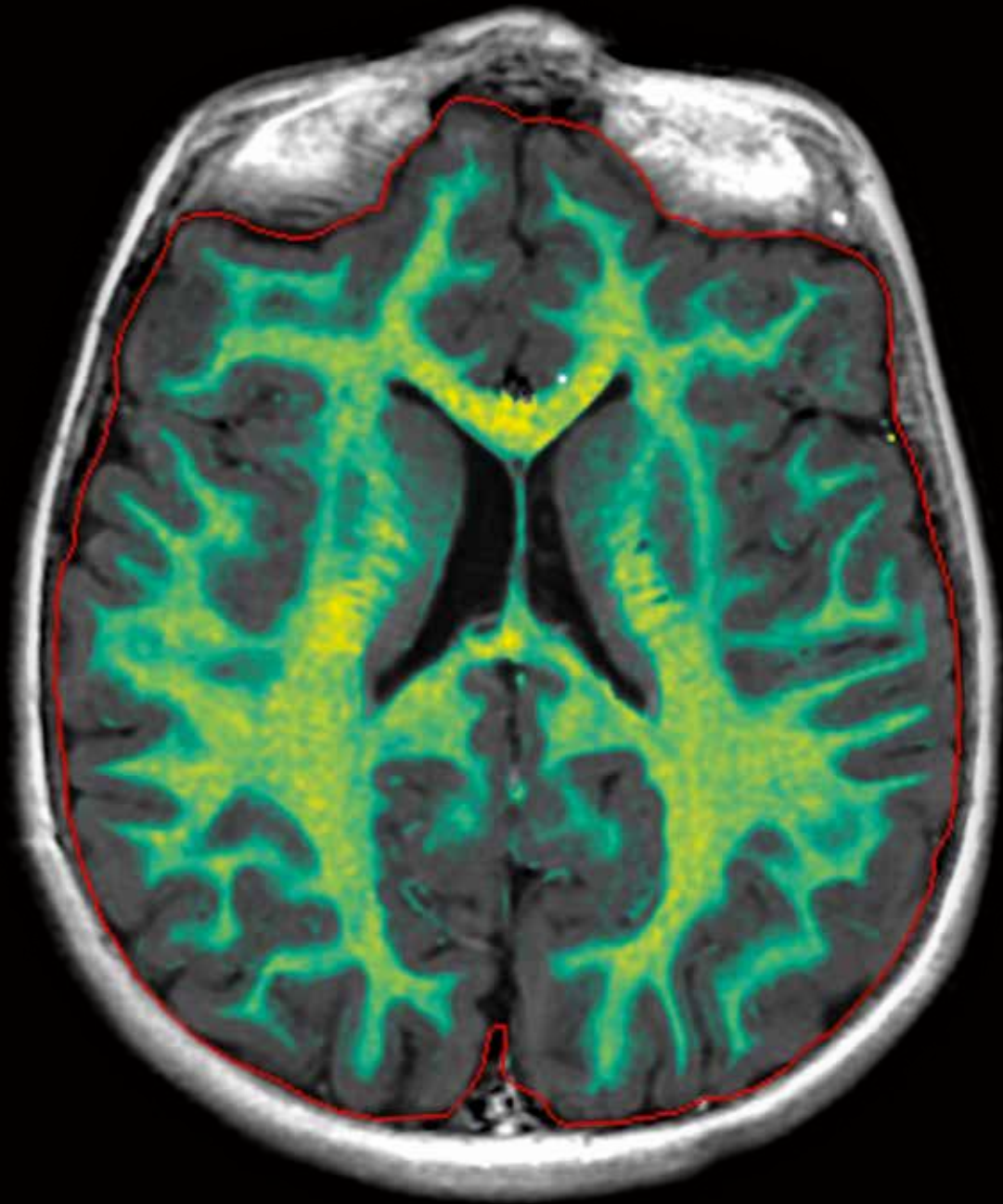
Since 2003 CMIV performs postmortal imaging of murder victims to complement the forensic autopsies made at the National Board of Forensic Medicine (RMV) on behalf of the police, district attorney or court. Mostly homicides are analyzed and the imaging gives the police an early report allowing the traditional autopsy to wait for the crime scene investigation to finish.

This project has optimized the total workflow for the post mortem imaging

and developed a new type of software that can handle full body datasets and three-dimensional visualization. The software was developed in collaboration with the Interactive Institute ICT and Visualization Center C and eventually evolved into the visualization table now manufactured by Sectra.

The number of autopsies performed is decreasing and natural deaths are rarely investigated. The virtual autopsy is therefore not only a useful complement to the traditional autopsy in the forensic investigation. It could be used instead of autopsy for natural deaths that would otherwise not be investigated to improve medical education, quality assurance and reliable mortality statistics.

Ongoing research is now concentrated on imaging methods that can identify common lethal conditions as heart attacks without the need for an autopsy.





THE CMIV RESEARCH SCHOOL

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



ASSESSING MUSCLE VOLUME USING MAGNETIC RESONANCE IMAGING

SUPERVISORS

Magnus Borga, Olof Dahlqvist Leinhard, Ola Friman

PROJECT

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

BACKGROUND

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

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

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

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

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

water is shown in figure 1.

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

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

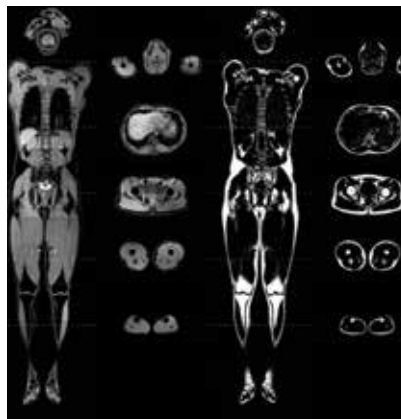


Figure 1. A paired magnetic resonance image where the left shows all the water within a whole body and the right shows all the fat.

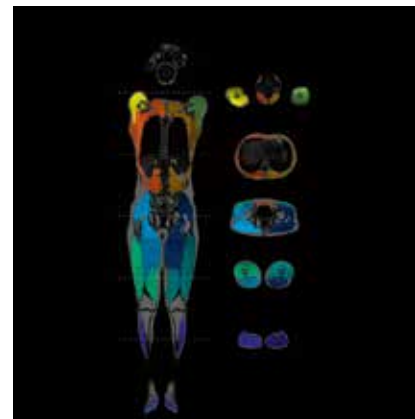


Figure 2. A typical result from the automatic method. The different muscle groups are shown in different colors. Grey color indicated that the automatic method has not considered that tissue as muscle tissue.

QUANTITATIVE WATER-FAT IMAGING

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

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

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

We have created an inexpensive method for analyzing water and fat separated images as well as protocols for speedy MRI acquisition. We can cover the abdomen in 5-6 min, and the entire body in less than 10 min, making it possible to add the sequences to existing protocols without much cost. After



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

the data acquisition the abdominal fat can usually be measured without user interaction, by a system which learns from prior examinations. However, no bodies are identical to each other, so we have developed tools for those few cases where the automatic method fails, and by using those tools the abdominal fat can be measured in 1-3 min. For every new case the method learns a bit more about the possible variations, so it will handle those variations better in the future.

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

SUPERVISORS

Magnus Borga
Olaf Dahlqvist Leinhard

BACKGROUND

MSc from Linköping University

DETERMINING HEPATIC FUNCTION IN DIFFUSE AND FOCAL DISEASE USING MULTIMODAL MRI

SUPERVISORS

Bengt Norén (co-supervisor), Gunnar Cedersund (co-supervisor), Olof Dahlqvist Leinhard (co-supervisor), Peter Lundberg (supervisor)

PROJECT

Non-Invasive Liver Biopsy (NILB)
Liver Intrinsic Function Evaluation (LIFE and 4LIFE)
Hepatic Inflammation and Fibrosis (HIF)

BACKGROUND

Master of Science (MSc; 2006-2011), Engineering Biotechnology, Systems Biology, Linköping University

Applications Engineer (October 2012-Present), Wolfram MathCore AB

Research Assistant/Engineer (2009-2012), County Council of Östergötland, CKOC, Department of Radiation Physics

The liver is one of the largest organs in humans and it handles many vital tasks such as nutrient processing, toxin removal, and protein assembly. In our modern society the number of people suffering from chronic liver diseases is on the rise and there is an ever growing need to develop novel diagnostic techniques that can be used for accurate and non-invasive investigation of the liver. Such diagnostic techniques are the primary focus of my research.

The conventional methods for diagnosing liver disease suffer from several drawbacks. One primary method is based on analyzing a small sample of the liver, which is extracted from the patient with a sharp needle. This very small sample is about 0.1% of the whole liver and thus not necessarily representative of the entire liver as disease is often heterogeneously spread. As with any invasive method, there is an added risk of complications that might require hospitalization.

A common problem with many liver diseases is that they develop undetect-

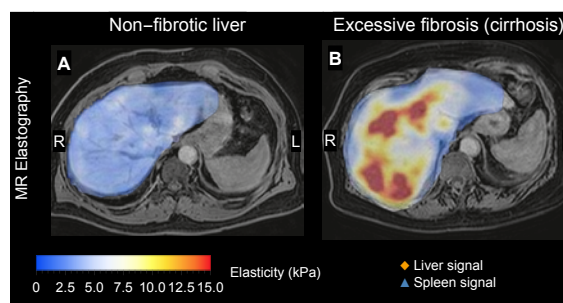
ed, and patients often seek medical care at a late stage in the disease process. Importantly, as the disease progresses there is ultimately a loss of liver function, and diagnostic tools that can accurately measure this loss are in high demand. For instance, when surgeons plan resective liver surgery they need to be sure that there will be enough 'liver function' after the surgical intervention, so that the risk of liver failure is minimal.

In our projects we use a set of novel magnetic resonance (MR) imaging methods in order to determine liver function and excess scar tissue (fibrosis). Liver function is measured by injecting a contrast enhancing agent into the blood and image the liver for 10-30 minutes. The contrast agent is taken up by the liver cells, but only in areas of the liver that are healthy enough. That is the healthy areas of the liver are very bright in the images as compared to the areas suffering from disease. Once the images are processed we use mathematical models to determine liver function. Scar tissue can be detected by applying

mechanical motion to the liver and measure how these wave propagate in the organ. A diseased liver is stiff and allows the waves to propagate further.

The goal of my projects is to be able to present a comprehensive understanding of the overall

status of the liver by combining our set of liver specific MR methods. This would help, for instance, surgeons planning liver surgery, or to doctors treating patients.



Two patients suffering from non-alcoholic fatty liver disease. One patient does not have fibrosis (panel A) and one has excessive fibrosis, known as cirrhosis (panel B). By measuring the mechanical motion we can calculate elasticity maps, which are very good for measuring the amount of fibrosis.

THE CARMA STUDY

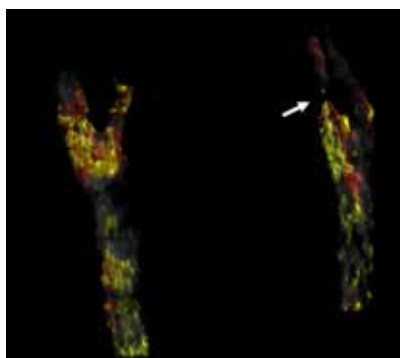
The most common cause of death in Sweden as well as in the rest of the world is cardiovascular disease. The primary cause is myocardial infarction and stroke, which most often stem from rupture of atherosclerotic plaques.

Our research group focuses on high-risk patients with atherosclerotic plaques in the carotid arteries. According to current guidelines these patients are to be offered cardiovascular risk management (CVRM) programs that combine pharmacological treatment of high cholesterol, blood pressure and diabetes with lifestyle modification. Even though the clinical benefits of CVRM are beyond dispute, we have previously shown that in patients with high-grade carotid stenosis, current CVRM is deficient in all aspects.

During 2016 we initiated the CARMA-study, a prospective study of 50 patients with carotid atherosclerosis. The study uses a repeated-measures design where assessments will take place at baseline, and after one year. The objective is to improve CVRM with the goal of increasing our mechanistic understanding of its beneficial effects. To this end, we will measure the effect of CVRM on plaque composition using our novel, quantitative magnetic resonance imaging (qMRI) method to measure the extent of two features inside plaques that are associated with the risk of plaque rupture: lipid rich

necrotic core (LRNC) and intraplaque hemorrhage (IPH). Because there is a well-established link between systemic inflammation and the presence of atherosclerotic plaques we will also study the relationship between LRNC and IPH as measured by qMRI versus circulating markers of inflammation.

One third of patients with high-grade carotid stenosis are treated with surgery to reduce risk of recurrent stroke. One of the major indications for surgery is stenosis $\geq 70\%$. However, recent studies show that stenosis severity alone is an insufficient criterion to determine if a plaque has a high risk of causing stroke. The plaque components, as described above, are more accurate predictors of plaque rupture. We anticipate that plaque component assessment with qMRI will refine the diagnostics in the future, and contribute to the selection of patients that will benefit the most from surgery.



SUPERVISORS

Ebo de Muinck, Toste Lanne, Joep Perk, Petter Dyverfeldt

PROJECT

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

BACKGROUND

Medical school, Linköping University, medical degree 2011

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

MAGNETIC RESONANCE IMAGING OF PERFUSION AND DEFORMATION IN CARDIAC DISEASE

SUPERVISORS

Jan Engvall, Tino Ebbers, Anders Persson

PROJECT

Cardiovascular blood flow assessment, Determining Optimal non-invasive Parameters for the Prediction of Left Ventricular morphologic, Early detection of cardiac effects induced by treatment for breast cancer, Heart4flow

BACKGROUND

Nursing degree from the University College of Health and Caring Sciences, Uppsala, in 1996

Bachelor degree 2000, Master of nursing in 2003, Linköping University.

Region Östergötland, Department of Medicine, Norrköping, 1996-1999,

Department of Radiology, Norrköping, 1999-2004.

2004-present CMIV, Linköping, radiographer responsible for the MRI scanners.

The treatment of myocardial infarction has advanced enormously in the last decade but is still one of the leading causes of death. The larger the scar is, the more likely that patients develop heart failure. When an exact determination of infarct size is required, magnetic resonance (MR) is the best method. An important parameter that has to be determined at the cardiac MRI exam is the inversion time, which is critical for scar imaging. We have developed a simulation of relaxation that in effect allows any inversion time to be used in scar imaging. The synthetic scar images showed a good agreement with the conventional images in terms of scar size.

Scar size determines systolic pumping function. The contraction of the left ventricular muscle can be analyzed in terms of cardiac strain, which provides an additional aspect on systolic contraction beyond what can be obtained from the determination of ejection fraction. We have developed "Displacement Encoding with Stimulated Echoes" (DENSE) which measures the displacement of the cardiac wall during systole. In my studies, DENSE has been validated for its ability to detect scars in 125 patients. The results showed that DENSE could detect major scars with

a sensitivity of 95% and a specificity of 80% with a clear cut off between healthy and scarred myocardium. The strain was well aligning with the left ventricular ejection fraction.

A competing MRI technique that can measure cardiac strain is "tagging", which can be analyzed with the software "HARmonic Phase", (HARP). Since HARP is considered the gold standard, we have compared DENSE with HARP as well as another MR strain method named "Feature tracking" in 90 coronary artery disease patients. DENSE outperformed both feature tracking and HARP showing better sensitivity, 96% versus 52% and 22% at a specificity at 80% for detecting major myocardial scar. Even ejection fraction and volumes correlated better with DENSE than with HARP and feature tracking.

Many diseases and treatments affect cardiac deformation. Therefore, it is interesting to follow a pathophysiological process with an accurate method like DENSE. The condition with insufficient aortic valves changes the cardiac function, the pressure and the flow pattern inside the heart with hypertrophy as a result. By monitoring patients after valve replacement with DENSE the remodulation could be more accurately described.

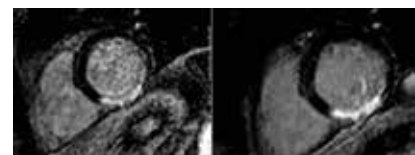
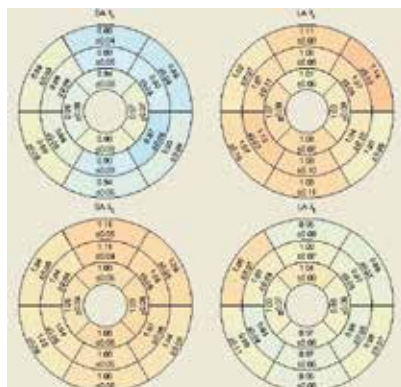


Image 1. Synthetic image of a myocardial scar using the adaptive inversion time technique to the left and the conventional late gadolinium image to the right.

Image 2. STAIzn values output as a bull's eye from DENSE data.

USING MECHANISTIC MODELING TO REDEFINE ACTIVITY IN fMRI

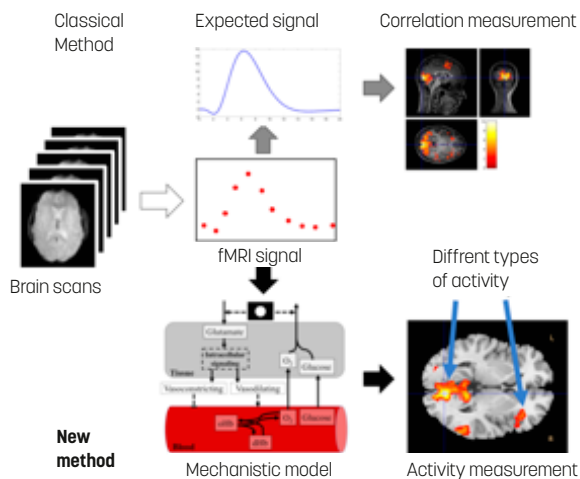
When we talk about brain activity, it is natural to think of the electrical signals that the neurons send to each other. But brain activity can also be thought of as an increased metabolism that occurs in order to support this increased signaling, or a chemical activation of the intracellular signaling pathways in neurons and astrocytes.

Many of these signals are hard to measure in humans. Functional magnetic resonance imaging (fMRI) detects changes in blood oxygen content in the brain. The oxygen content of the blood is affected by the neuronal activity through a series of physiological mechanisms called the neurovascular coupling, and is therefore considered to be a good approximation of the level of neuronal activity.

High correlation between the changes in oxygen level and the type of brain activity that is expected in a person performing a task is interpreted as high activity. If there is a low correlation or no correlation at all, it is interpreted as no activity. However, the oxygen chang-

es in the brain is not only influenced by neuronal activity leading to oxygen metabolism, but also by changes in blood flow and blood volume, and all these mechanisms are closely interconnected. Therefore, classical analysis of the fMRI signal cannot separate different types of brain activity, but merely state whether the correlation to the expected response is high or low.

In order to untangle the different types of activation in the brain, we have constructed a mathematical model representing the mechanism of the neurovascular coupling. The model can describe the fMRI signal response to a stimulus and predict new experiments. By fitting the model to the fMRI signal we can simulate the different types of activation. Using this model in our analysis of the fMRI signal we hope to be able to separate different types of activation in the brain, and use these results as potential biomarkers that can help doctors to diagnose patients and better understand the workings of the mind.



SUPERVISORS

Maria Engström, Gunnar Cedersund, Fredrik Ellinder, Susanna Walter

PROJECT

SAND:MAN

BACKGROUND

MSc from Linköping University

IMPROVED DIAGNOSIS AND MANAGEMENT OF HEART DISEASE BY 4D BLOOD FLOW ASSESSMENT; STENOTIC BLOOD FLOW

SUPERVISORS

Tino Ebbens (supervisor)
 Petter Dyverfeldt (co-supervisor)
 Jonas Lantz (co-supervisor)
 Carl-Johan Carlhäll (co-supervisor)

PROJECT

Cardiovascular blood flow assessment

BACKGROUND

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

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

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

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

The current gold standard for measuring the pressure drop is catheterization, but this is an invasive procedure and cannot be applied routinely. In practice, the pressure drop is instead estimated non-invasively based on

ultrasound measurements. This approach, however, does only work well for severe stenoses since mild pressure drops are masked by a pressure recovery phenomenon downstream of the stenosis. The irreversible pressure drop over the stenosis is directly related to the amount turbulence and a method monitoring this would be useful in detecting also mild stenoses.

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

AUTOMATED ASSESSMENT OF BLOOD FLOW IN THE CARDIOVASCULAR SYSTEM USING 4D FLOW MRI

Changes in intra-cardiac blood flow patterns appear to be early markers of cardiac disease. Altered blood flow patterns have been observed in many cardiac diseases, often as a result of early remodeling of the cardiac chambers. These alterations have turned out to be extremely difficult to predict based on anatomy. Blood flow velocity can be measured in the whole heart using 4D flow MRI.

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

As a first goal of the project, we developed an atlas-based segmentation method to automatically segment the major vessels of the cardiovascular system at each timeframe of the cardiac cycle, locate planes at predefined vessel positions, and calculate their corre-

sponding flow volume. The method was evaluated by comparison of flow volumes obtained at different locations in order to ensure that the values obtained were coherent with the expected cardiovascular inputs and outputs (See Fig. 1).

As one of the steps to achieve our final objectives, we proposed an improvement over the approach typically used for Phase-Contrast Magnetic Resonance Angiography (PC-MRA) data generation from 4D flow MRI. Namely, a technique for the generation of a temporally resolved Phase-Contrast Magnetic Resonance Cardio Angiography (4D PC-MRCA) that includes the geometry of the lumen of the vessels, as well as the heart over the entire cardiac cycle. The resulting 4D PC-MRCA at three timeframes, when compared to a PC-MRA can be seen in Fig. 2.

A combination of the techniques developed so far in the project can be seen in Fig. 3. Future works will focus on developing methods to automatically segment the chambers of the heart using 4D Flow MRI.

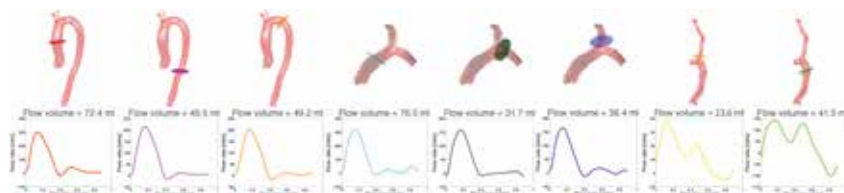


Figure 1. Segmented aorta, pulmonary artery and caval veins for one subject. Flow analysis planes located in different positions within each vessel are depicted, together with the volumetric flow rate obtained for each plane.

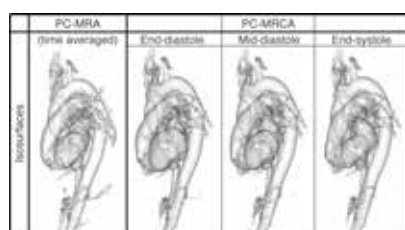


Figure 2. Isosurface renderings of a PC-MRCA at three timeframes of the cardiac cycle compared to a time-averaged PC-MRA.



Figure 2. 4D PC-MRCA (grey) at end-diastole (a) and end-systole (b), with vessel segmentations in colors: aorta (red), pulmonary artery (blue), caval veins (green).

SUPERVISORS

Tino Ebbers, Carl-Johan Carlhäll, Petter Dyverfeldt

PROJECT

Cardiovascular blood flow assessment

BACKGROUND

MSc Computer Science
Uppsala University, Sweden, 2010-2012

Computer Engineering
Simon Bolívar University, Venezuela,
2001-2006

ADVANCED MRI TECHNIQUES FOR FUNCTIONAL AND STEREOTACTIC NEUROSURGERY

SUPERVISORS

Hans Knutsson (supervisor), Mats Andersson (co-supervisor)

BACKGROUND

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

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

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

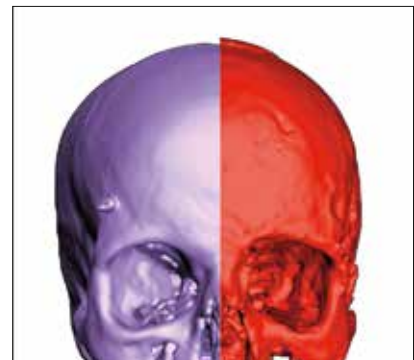
To take full advantage of this accuracy you need to know where to direct it, which is why you need imaging. This project deals with the imaging technique known as Magnetic Resonance Imaging (MRI). It was developed in the early 1970’s by the chemist Paul Lauterbur and the physicist Sir Peter Mansfield,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

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

Accurate and robust segmentation methods have several clinical uses. The most obvious is to aid in defining the target of a treatment and identifying nearby structures which must be protected. To evaluate the effects of

a procedure, new MR images are acquired and compared to the prior ones. Segmentation methods can facilitate this comparison by, for example, quantifying how much a tumor has shrunk. Yet another important application, specific to radiation therapy, is the need to accurately compute the radiation dose. This is something that typically requires additional X-ray imaging with little diagnostic gain, in particular for brain disorders. It is therefore desirable to do the dose calculations using only MR images. An important step in this direction is to use segmentation to identify tissue types that have different effect on the radiation (Figure).

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

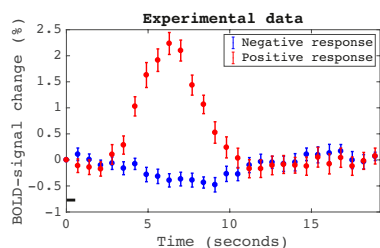


MATHEMATICAL MODELING OF BIOLOGICAL MECHANISMS UNDERLYING BRAIN RESPONSES IN fMRI

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

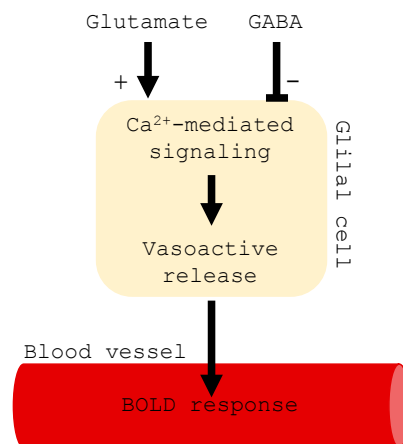
This regulation of blood flow can be seen in the blood oxygenation level dependent (BOLD) signal captured by functional magnetic resonance imaging (fMRI). Therefore, a connection between neural activity and blood flow changes, the so-called neurovascular coupling, exists.

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



elusive. Furthermore, the neurovascular coupling is shown to dysfunction in different neurological disorders.

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



SUPERVISORS

Maria Engström, Gunnar Cedersund, Fredrik Elinder, Susanna Walter

PROJECT

Methods for High-quality Illumination in Interactive Volume Graphics

PROJECT

Ab Initio Mathematical Modeling of Mechanisms in the Human Brain

BACKGROUND

Bachelor degree in engineering biology, Linköping University, 2011-2014

Research preparatory course I-II 2014-2015

EVALUATION OF OPTIMIZATION METHODS FOR ABDOMINAL COMPUTED TOMOGRAPHY

SUPERVISORS

Prof. Michael Sandborg
Co-supervisors:
Prof. Örjan Smedby
Prof. Anders Persson
Docent Hannibal Sakjer

BACKGROUND

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

Diagnostic Radiographer Nairobi, Kenya 1980-1985

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

Radiology Department in Linköping March 2014-present

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

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

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

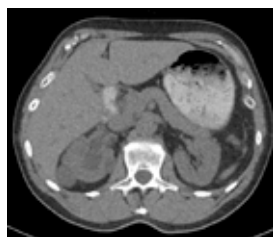
First we evaluated the dose reduction potential of an iterative (mathematical) reconstruction (IR) method, SAFIRE in a low-dose abdominal using SAFIRE strength 1. Image quality was improved with SAFIRE compared to Filtered Back Projection (FBP) and allowed

for a 5-9% dose reduction. The study revealed that the full potential of the algorithm had not been studied and further research was necessary.

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

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

FBP 98 mAs



ADMIRE 3 98 mAs



ADMIRE 5 98 mAs



Figure 1. Visual image quality demonstration with images obtained in the same patient at 70% dose level (98mAs) using dual source Siemens Somatom Force and reconstructed with Filtered Back Projection (FBP), ADMIRE 3 and ADMIRE 5.

IDIOPATHIC SCOLIOSIS – DEFORMITY IN THREE DIMENSIONS

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

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

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

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

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

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



SUPERVISORS

Hans Tropp, Nils Dahlström, Daniel Forsberg, Per Aspenberg, Staffan Wirell

PROJECT

Quantitative musculoskeletal imaging for assessment of idiopathic scoliosis

ANALYSIS OF DIFFUSION MRI DATA

SUPERVISORS

Hans Knutsson, Anders Eklund

BACKGROUND

Bachelor of Engineering, Beijing University of Posts and Telecommunications, CHINA

Master of Science, University of Southampton, UNITED KINGDOM

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

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

To see how consistent diffusion tractography is over time we investigated the test-retest reliability, using 32 diffusion datasets from a single healthy

volunteer. We used two open source software's, FSL and Dipy, to run the analysis. A visual comparison of the results showed that diffusion along the cores of the corticospinal and cingulum gyrus tracts in the brain were common over the 32 datasets, for both FSL and Dipy.

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

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

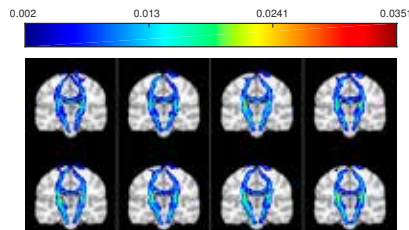


Figure 1. Tractography results for 32 diffusion datasets (in MNI space), for a maximum of 2 fibers per voxel, when using seed masks for the corticospinal tract. A threshold of 0.2% was used to remove less likely tracts. The results represent the proportion of times a streamline passed through a voxel.

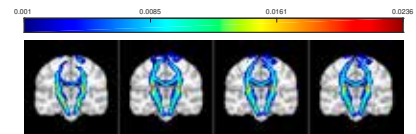


Figure 1. Averaged tractography results over the 32 datasets (in MNI space), for a maximum of 1, 2, 3 or 4 fibers per voxel (left to right), when using seed masks for the corticospinal tract. A threshold of 0.1% was used to remove less likely tracts. Using a maximum of 2 fibers per voxel leads to including more voxels in the tracts, compared to using a maximum of 1 fiber per voxel.

IMPROVED ASSESSMENT OF THE LINK BETWEEN HEMODYNAMICS AND VESSEL WALL DISEASE

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

MRI in general and 4D Flow MRI specifically offers the most powerful capabilities for in vivo flow assessment. 4D Flow MRI is a relatively new technique that allows quantitative assessment of the time-varying three-

dimensional flow fields of the cardiovascular system. Using this technique, new, and more accurate assessments of the patient's cardiovascular system can provide clinicians with deeper knowledge and aid in both diagnosis and treatment.

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

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

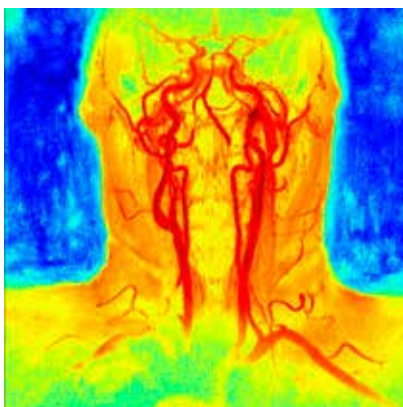


Figure 1. Stylized image of neck vasculature created using 4D Flow MRI imagery.

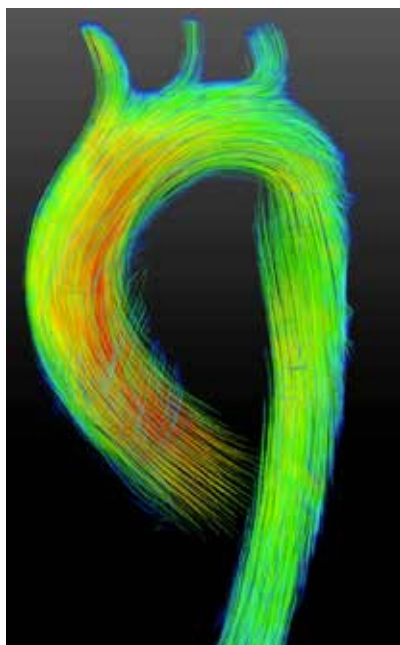


Figure 2. Streamline visualization of blood flow through the Aortic Arch in a healthy young volunteer created using 4D Flow MRI.

SUPERVISORS

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

PROJECT

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

BACKGROUND

Bachelor of Applied Science (B.A.Sc.)- Mechanical Engineering with Biomedical Specialization University of British Columbia, Vancouver, Canada

Graduated Spring 2012
Masters of Science (M.Sc.) - Biomedical Engineering Chalmers Institute of Technology, Gothenburg, Sweden
Graduated Summer 2014

QUANTIFICATION OF OSTEOPOROSIS WITH COMPUTED TOMOGRAPHY

SUPERVISORS

Örjan Smedby, Torkel Brismar,
Rodrigo Moreno

PROJECT

Quantification of osteoporosis with
computed tomography

Fractures related to osteoporosis are common in Sweden, in particular among women. This means suffering for the individual and great costs for the community. In order to be able to minimize the number of fractures, it is important to detect osteoporosis at an early stage. The technique most frequently used for diagnosing osteoporosis is DXA (dual energy X-ray absorptiometry). With this method it is possible to measure the mineral content, but it is not possible to describe the internal structure of the bone. There are several studies showing that also the internal structure of the bone is of great importance for bone strength and risk for bone fractures.

The aim of this project is to investigate the possibility to use the X-ray method computed tomography (CT) to image and measure the internal structure of bone, which would give a more complete picture of the osteoporosis. The aim is to find methods to measure osteoporosis and bone structure in patients. We started, however, with imaging small pieces of bone from the human forearm.

We have used 15 pieces of bone, all cubes with a side of 10-15 mm. The cubes were placed in test tubes filled with water, and the tubes were placed in a paraffin cylinder to mimic soft tissue.

Imaging was performed with different types of CT methods and compared with the results from a method called micro-CT, which is considered the reference method. Micro-CT can only be used on small samples and in animal testing.

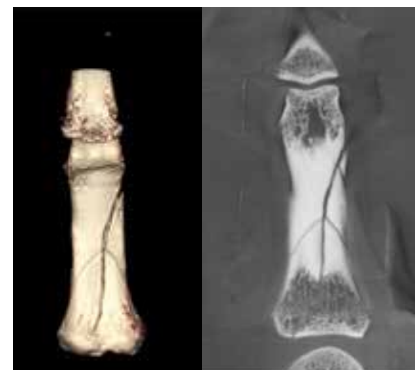
After imaging with the different X-ray methods, extensive image analysis is required. This analysis aims to identify all the small bone structures inside the bone. We analyse how many, how thick, how far apart the bone parts are, how many branches they have, how many free ends there are and the total amount of bone. For this purpose, a segmentation method is used that makes it possible to differentiate bone from the other structures, like blood vessels, fat and marrow inside the bone.

One of the tested methods, CBCT (cone beam CT), showed a very high correlation with micro-CT when analysing the bone pieces. CBCT is most often used in imaging teeth, jaws and people in need for implants in the jaws. The machine can also be used in diagnosing finger fractures both ordinary imaging and 3D visualisation.

In future studies, we want to compare the bone structure in the jaws with DXA results on patients examined for osteoporosis.



Left jaw and ear cells imaged by CBCT.



Left fractured first finger, CBCT image and 3D from CBCT.

CLINICAL APPLICATIONS OF SYNTHETIC MRI IN THE BRAIN

Conventional magnetic resonance (MR) images are assessed visually by the radiologist for diagnosis or evaluation of treatment effects. With new MR sequences it is possible to quantitatively assess the physical properties of the tissue, which gives a more objective evaluation tool. Synthetic MR is a quantitative MR sequence developed at CMIV and has a scan time of approximately 6 minutes. In this PhD-project the aim is to apply this sequence in different clinical settings, mainly in patients with multiple sclerosis (MS) and primary brain tumors.

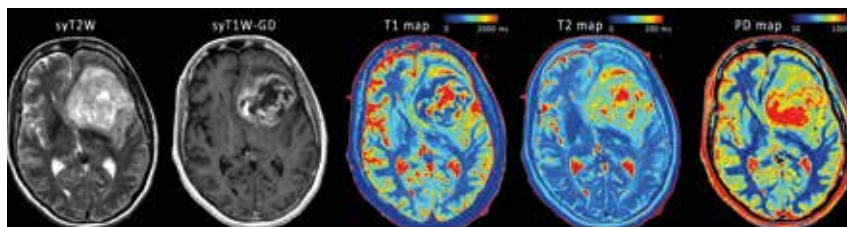
Contrast-enhancing MS lesions are important markers of active inflammation in the diagnostic work-up of MS and in disease monitoring with MRI during follow-up. Since intravenous contrast agents involve an expense and a potential risk of negative side effects for patients, it would be desirable to identify active lesions without using a contrast agent. Using synthetic MR we have showed that active brain lesions in MS patients differ significantly from non-enhancing lesions, but that there is also a great overlap, which makes it difficult to rely on quantification alone.

Patients with high grade malignant gliomas (primary brain tumors) are treated with surgery, chemo- and

radiotherapy and then followed with MR-examinations to evaluate treatment response and to detect early signs of tumor recurrence. Almost 25% of the patients react to the oncological treatment with edema and contrast-enhancement in the affected area of the brain, and although this pattern is benign it is difficult to distinguish visually from tumor recurrence.

Since the conventional image is non-specific, radiologists use quantitative methods in these cases, for example MR Spectroscopy, MR Perfusion and PET-CT, but there are still cases where it is unclear if the patient has tumor recurrence or treatment related changes. Since synthetic MRI is a quantitative MR-method it enables quantitative measurement of the tissue; relaxometry.

In this study we follow patients with malignant gliomas from diagnosis, during the follow-up after surgery and to oncological treatment. If it is possible to find tumor specific quantitative values, it might be possible to distinguish tumor 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 also 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.

PROJECT INFORMATION

SUPERVISORS

Elna-Marie Larsson, Peter Lundberg, Örjan Smedby, Marcel Warntjes, Anne-Marie Landtblom

PROJECT

Clinical Application of Synthetic MRI on Patients with Malignant Gliomas

BACKGROUND

Medical school Linköping University 1996-2002

Internship Enköping Hospital 2002-2005

Resident in Radiology 2005-2010,

Fellowship Neuroradiology 2010-2013,

Consultant Neuroradiologist, Department of Radiology, Linköping University hospital 2013-

EARLY CHARACTERIZATION OF HEPATIC INFLAMMATION, FIBROSIS AND FUNCTION

SUPERVISORS

Peter Lundberg, Gunnar Cedersund, Nils Dahlström, Stergios Kechagias

PROJECTS

Non-invasive liver biopsy (NILB)
Liver intrinsic function evaluation (LIFE)
Hepatic inflammation and fibrosis investigation (HIFI)

BACKGROUND

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

In the early stages of liver diseases the symptoms are often weak and ambiguous. Physicians are therefore often forced to do a liver biopsy to make a correct diagnosis. A biopsy however, has several drawbacks. Firstly, it is an invasive procedure that carries a risk for complications. Secondly, the biopsy also has a sampling error, since it only samples a tiny fraction of the liver. Therefore, there is a need for new diagnostic techniques.

Such new techniques can be based on magnetic resonance imaging (MRI). With MRI the diseased liver can be characterized by a number of different parameters: inflammation, fibrosis, iron loading, fat loading, and function.

In order to measure these parameters, we use a number of different MR-based methods. To measure fat, we use magnetic resonance spectroscopy, as well as Dixon imaging. We measure fibrosis using T1-mapping and magnetic resonance elastography (MRE).

MRE is a technique that measures the elasticity via an external vibrator by inducing shear waves into the

liver. When fibrosis is developed in the liver, the organ becomes stiffer which increases the elasticity. A major part of my project is to investigate if magnetic resonance elastography can also be used to measure inflammation in the liver. It is known that inflammation, as well as fibrosis, effect the elasticity but we want to be able to separate them.

These parameters are not only of interest when investigating the early stages of liver diseases. Measures of hepatic function can also be useful for liver surgeons deciding whether a patient has enough liver function to survive a resection, i.e. removing parts of the liver.

We measure liver function by using a contrast agent that increases the MR signal. The contrast agent used is liver specific, which means that it is only taken up by the liver cells. When liver function is reduced less contrast agent will be taken up by the liver cells and the signal from the liver will not increase as much. Once the images are processed, they are analyzed using mathematical modeling.

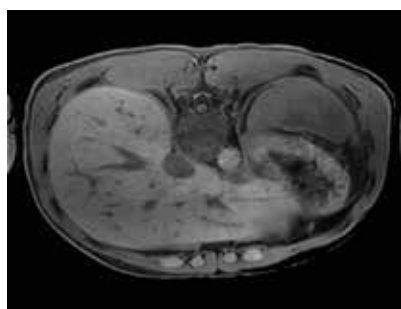


Figure 1. Image of a liver slice.

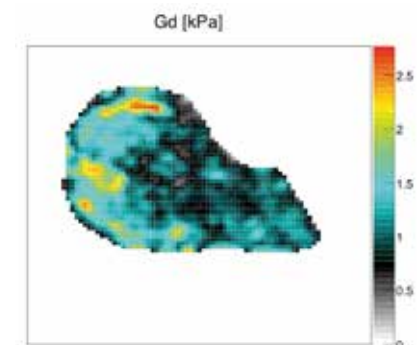


Figure 2. Elastogram showing the elasticity (Gd) of a liver slice.

NEUROTRANSMITTER IMAGING OF THE HUMAN BRAIN

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

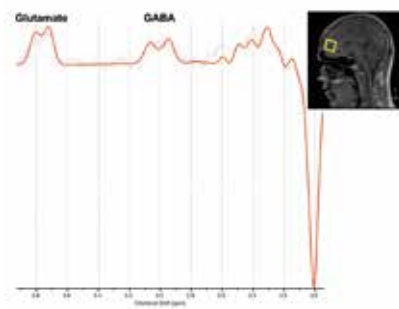
Magnetic Resonance Spectroscopy (MRS) is a non-invasive technique that can be used to study metabolic changes in the brain. However, the challenges are exceptional when measuring GABA, as the concentration of GABA is about 40,000 times less than that of water, and there is an additional overlap in the spectrum with signals from other metabolites. Because of this overlap, a special editing MRS-technique is necessary for the quantification of GABA.

Moreover, the MRS-technique has to handle effects from frequency drifts that occur when the MR-system is heated and signal artifacts such as those that originate from subject movements during the measurement.

Additionally, in clinical applications, it is desired to have minimal measurement time and measurement region, without any reduction of the quality of the measurement.

Therefore, it is important to develop a novel method that reliably quantifies GABA and other metabolites and at the same time handles all the factors described above.

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



The GABA and Glutamate signals that originate from the measurement region are visible in the resulting spectrum.

PROJECT INFORMATION

SUPERVISORS

Peter Lundberg, Anders Tisell,
Peter Zsigmond

PROJECT

Seeing Organ Function

BACKGROUND

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

Research preparing course I-II 2013-2014

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

QUANTITATIVE ASSESSMENT OF MYOCARDIAL TISSUE CHARACTERIZATION

SUPERVISORS

Tino Ebbers, Marcel Warntjes, Jan Engvall and Agnetha Gustafsson

BACKGROUND

Medical physicist Region Östergötland 2017-

PhD student in Cardiac Magnetic Resonance group 2013-

Medical physicist Region Östergötland, 2012 -2014

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

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

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

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

In an ongoing study we include patients with severe aortic stenosis who will undergo aortic valve replacement surgery (AVR). In this patient group the left ventricle must generate a higher pressure to effectively move blood forward into the aorta. The increased pressure will normally affect the left ventricular wall and induce myocardial fibrosis. Since the fibrosis is diffusely spread over the myocardium and thus affecting the whole myocardium, it is not possible to see the changes in a normal weighted MR image. In quantitative images, like T1 maps and T2 maps, it is possible to make a numerical measure and thus compare values with normal values in healthy volunteers. We are in this study interested to see whether magnetic resonance relaxation times, T1 and T2, can reflect changes in fibrotic tissue over time, from pre surgery to 12 months after the valve replacement.

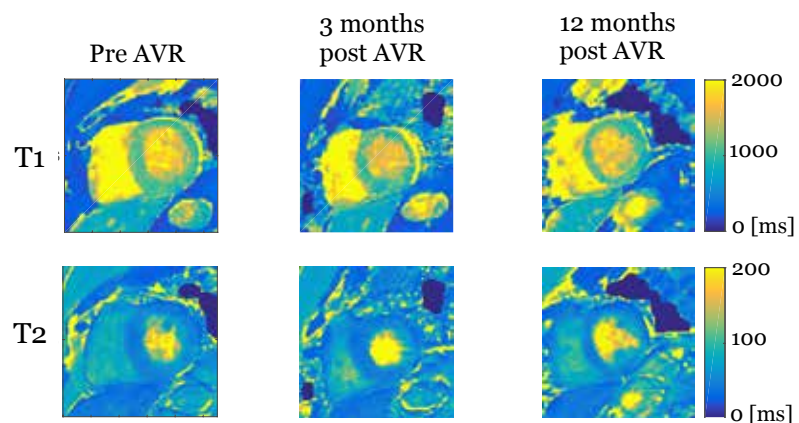


Figure 1. Illustration of mid-ventricular myocardial relaxation time maps with 3D-QALAS in a patient with severe aortic valve stenosis. Maps are acquired at three different time points: pre AVR, 3 months post AVR and 12 months post AVR.





DISSERTATIONS

During 2016 six of the CMIV PhD students have finished their studies and defended their dissertations. The PhD students and the research school are an important part of CMIV and we are proud to present their dissertations here.





CARINA STENMAN

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

STANDARDIZED ULTRASONOGRAPHY WITH CINE-LOOP DOCUMENTATION: DIAGNOSTIC VARIABILITY IN LIVER AND KIDNEY EXAMINATIONS

Ultrasound examination of the abdomen is often a first choice at radiology departments since it is a fast, safe and cost effective method. For diagnostic accuracy and economic benefits there is a need for new routines combining the benefits of a radiographer performing the examinations with strictly standardized protocols and documentation forms made by cine-loops. This will give the radiologist access to

all relevant information needed for an accurate post-examination diagnosis.

The overall objective of this thesis was to evaluate the diagnostic variability in examinations of the kidneys and liver that use a standardized ultrasound method along with video documentation of the entire examination and off-line review by radiologists. The thesis is based on four quantitative studies using standardized protocols for kidney, liver

and gallbladder examinations.

The satisfactory agreement shown in all four studies suggests that the new workflow method using standardized ultrasound examinations and stored cine-loops, performed by a radiographer or sonographer and analyzed off-line by a radiologist, is a promising technique.



STEPHANIE FRANZÉN

Linköping University, Department of Medical and Health Sciences, Division of Drug Research

THE ROLE OF HYPOXIA FOR THE DEVELOPMENT OF DIABETIC NEPHROPATHY: TEMPORAL RELATIONSHIP AND INVOLVEMENT OF ENDOTHELIN RECEPTOR SIGNALING

D iabetic renal disease is one of the most common causes of end stage renal disease. Recently, it has been proposed that intrarenal hypoxia is a unifying mechanism for chronic kidney disease, including diabetic renal disease. Several mechanistic pathways have been linked to the development of intrarenal hypoxia and diabetic nephropathy including increased angiotensin II signaling, oxidative stress and hyperglycemia per

se. Furthermore, pathological endothelin signaling has recently emerged as a possible contributing factor for chronic kidney disease and diabetic nephropathy.

By applying electron paramagnetic resonance oximetry in a mouse model of insulinopenic diabetes mimicking the human disease, we demonstrated intrarenal hypoxia already within the first couple of days after the onset of hyperglycemia, which is well before de-

tectable signs of kidney disease development. Furthermore, blockade of ETA or activation of ETB receptors significantly reduced intrarenal hypoxia in the diabetic kidney. These results demonstrate involvement of ETA receptor signaling in diabetes-induced intrarenal hypoxia and ETA blockade or ETB activation might provide new therapeutical targets to reduce kidney hypoxia and disease progression in diabetes.

JAKOB DE GEER

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

ON THE USE OF COMPUTED TOMOGRAPHY IN CARDIAC IMAGING

Cardiac computed tomography in general and Cardiac Computed Tomography Angiography (CCTA) in particular, is becoming increasingly useful in the work-up of coronary artery disease (CAD). The main strength of CCTA is the high negative predictive value and thus the ability to exclude significant stenosis. When more extensive atheromatous change is seen, there is a tendency of overestimation of stenosis significance, leading to a num-

ber of unnecessary invasive procedures. Several potential methods for increasing the diagnostic yield of cardiac CT are available. Previous studies indicate that approximately 40% of all Invasive Coronary Angiography (ICA) in patients with suspected CAD show normal findings, thus leading to no further intervention. This is unfortunate as ICA is an invasive, and thus expensive, technique that also carries with it a certain procedural risk. Hence, there are

both medical and economical gain to be made by improving the diagnostic yield of CCTA and, where possible, reducing the number of unnecessary ICA.

The overall focus of this thesis has been the exploration of potential methods improving the diagnostic yield of CCTA. These include image quality improvement and different functional applications, but also evaluation of the long-term prognostic value of CCTA.

FILIPÉ MIGUEL MARIA MARREIROS

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

GUIDANCE AND VISUALIZATION FOR BRAIN TUMOR SURGERY

Image guidance and visualization play an important role in modern surgery to help surgeons perform their procedures. In this thesis the focus is on neurosurgery applications, in particular brain tumor surgery where a craniotomy (opening of the skull) is performed. Once the skull is opened the shape of the brain may change, and

this deformation is known as brain shift. Hence, the magnetic resonance dataset acquired before the operation (preoperatively) no longer corresponds to the anatomy of the patient during the operation (intraoperatively). Moreover, the boundaries between healthy tissue and tumor are in many cases difficult to identify by the naked eye.

This project developed and evaluated 3D reconstruction, registration (rigid and non-rigid) and deformation methods with the purpose of minimizing the brain shift problem. Stereoscopic perception of the spatial position of enclosed objects was also studied using different rendering methods and parameter values.

DANIEL JÖNSSON

Linköping University, Department of Science and Technology, Division of Media and Information Technology.

ENHANCING SALIENT FEATURES IN VOLUMETRIC DATA USING ILLUMINATION AND TRANSFER FUNCTIONS

The visualization of volume data is a fundamental component in the medical domain. Volume data is used in the clinical work-flow to diagnose patients and is therefore of uttermost importance. The amount of data is rapidly increasing as sensors, such as computed tomography scanners, become capable of measuring more details and gathering more data over time. Unfortunately, the increasing amount of data makes it computation-

ally challenging to interactively apply high quality methods to increase shape and depth perception. Furthermore, methods for exploring volume data has mostly been designed for experts, which prohibits novice users from exploring volume data. This thesis aims to address these challenges by introducing efficient methods for enhancing salient features through high quality illumination as well as methods for intuitive volume data exploration. This work shows how

a multi-resolution grid can be used to encode the attenuation of light from all directions using spherical harmonics and thereby enable advanced interactive dynamic light configurations. Two methods are also presented that allow photon mapping calculations to be focused on visually changing areas. The results demonstrate that photon mapping can be used in interactive volume visualization for both static and time-varying volume data.

JESPER MOLIN

Chalmers University of Technology, Department of Computer Science and Engineering

DIAGNOSTIC REVIEW WITH DIGITAL PATHOLOGY: DESIGN OF DIGITALS TOOLS FOR ROUTINE DIAGNOSTIC USE

The role of the pathology lab is important in the future of cancer care. In order to further personalize the care for cancer patients, more precise review of tumor specimens is needed to guide clinicians between different treatment strategies. New digital imaging technologies is one promising possibility that might allow pathologists performing more and better work with the same amount of resources. Digital pathology is currently being imple-

mented worldwide.

This thesis summarizes four years of HCI and visualization research and provides an overall understanding of designing workstation software for pathologists. A human-centered design approach has been used to create a number of design interventions. The thesis covers three main areas of inquiry: Understanding pathologists' problem solving processes during diagnostic review, how to build different

digital tools to support those processes, and how to incorporate digital image analysis algorithms when building these tools.

Together, these design projects show how digital pathology images can be used to create tools to make pathologists more productive. This will make it possible for pathology laboratories to replace their diagnostic workflow using glass slides, with a workflow based on digital images.

EQUIPMENT

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

CT

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

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

improved spectral separation.

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

MRI


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

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

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

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

In addition, we have access to a GE



Signa 1.5T HDxt and Discovery 750 3.0T MRI system.

ULTRASOUND

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

PACS

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

For storage and handling of echocardiographic image data (for both research and clinical use), one of the

largest installations of the GE EchoPAC system in the world is available. A number of advanced diagnostic workstations are available for clinical and research purposes.

VISUALIZATION

CMIV has its own Virtual Reality theatre with a capacity of 70 persons. The theatre is built around Barco Galaxy NW-12 projector (12 000 lumens light output, WUXGA (1920x1200) resolution.) The NW-12 has an integrated active Infitec 3D stereo filter, allowing for optimal 3D visualization with passive stereo glasses. Using a Barco XDS 150 and an EXTRON DMS 3600 DVI switch, all computers at CMIV's network can be used for video conference system, allowing for 1080p HD conference meetings or video broadcasting. A Smartboard Interactive Whiteboard is available for interactive presentations

and meetings.

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

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

DIGITAL PATHOLOGY SCANNER

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





ORGANIZATION

CMIV is governed by its Board of Directors, with representatives from academia, health care 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.

RESEARCHERS

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Mischa Woisetschläger	IMH, Radiological Sciences
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Wolf-Dieter Zech	IMH, Radiological Sciences

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BOARD

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Jan Marcusson	Region Östergötland
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Maria Kvist	CMIV
Peter Lundberg	IMH, Radiological Sciences
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India Morrison	IKE, Neuro and Inflammation Sciences
Fredrik Palm	IMH, Drug Research
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Karin Wårdell	IMT, Biomedical Instrumentation

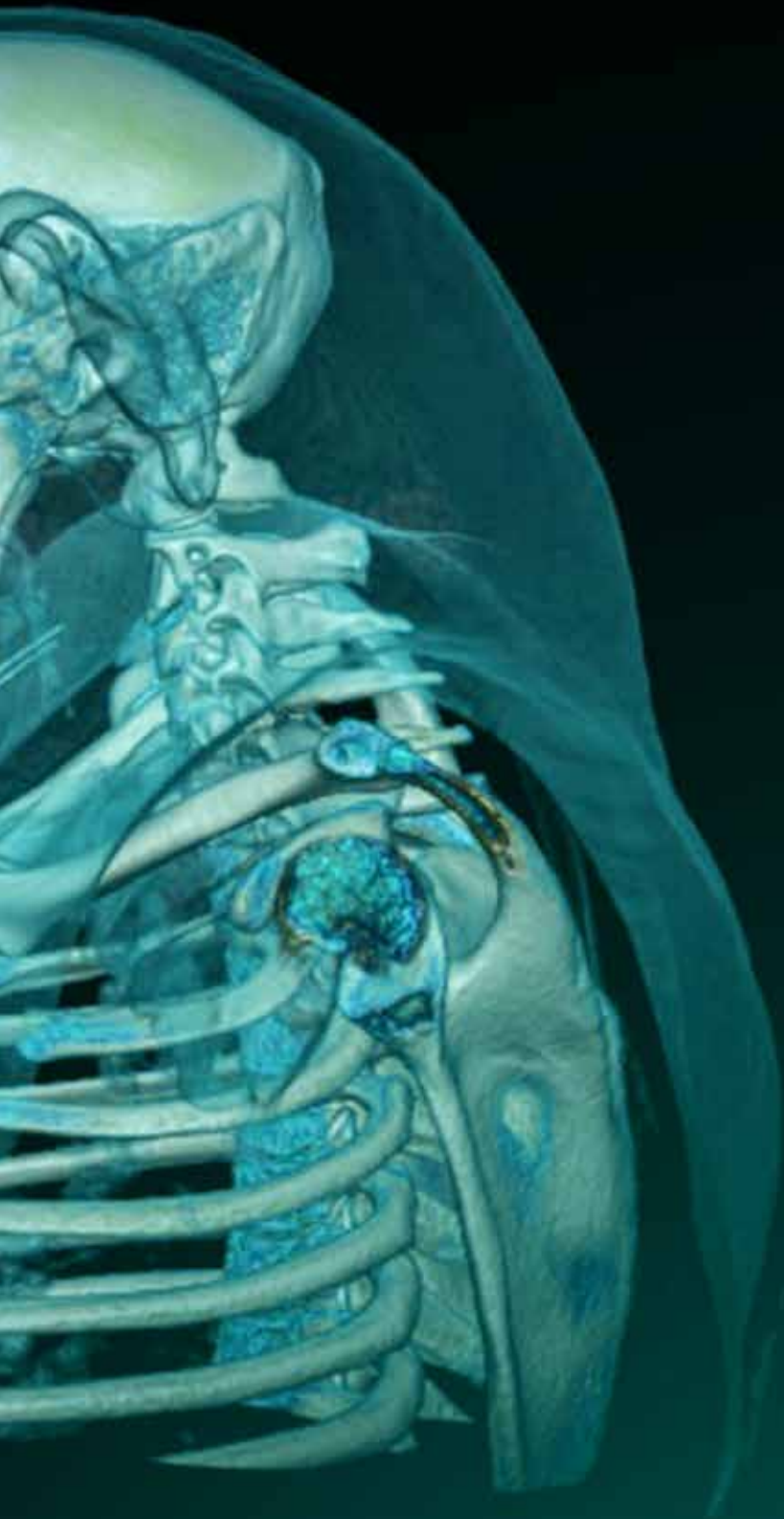
CORE STAFF

Anders Persson	Director
Maria Kvist	Coordinator
Marie Waltersson	Research Coordinator
Dennis Carlsson	IT Manager
Catrin Nejdeby	Coordinator
Marcel Warntjes	Clinical Scientist
Petter Dyverfeldt	Clinical Scientist
Suzanne Witt	Clinical Scientist

PUBLICATIONS

As the CMIV researchers are also affiliated to a home department at Linköping University or another university and their research is primarily registered there it can be difficult to overview. We have made an attempt at putting together a list with the publications produced during 2016. Although not complete it still shows a good representation of CMIV.





BIBLIOMETRIC ANALYSIS

The bibliometric analysis has been provided by the Linköping University Library, department of Publishing Infrastructure. The citation data used in the analysis has been supplied by CWTS, Leiden University; data source: Thomson Scientific/ISI.

Table 1
Norwegian Model

2010-2016		
	Number of publications	Number of fractions
Journal articles - refereed	388	186,1
Chapters - other academic	24	10,2

Comment: Proceeding papers are included if they have been published in an approved publication channel, and are counted as chapters or journal articles.

Results

Publication points	246,9
Average number of publications points per year	41,2
% author shares level 2	14%
Author shares, sum	196,3

% author shares level 2: Percentage of fractionalized publications published in journals / publishers of the highest scientific quality.

Table 2
Open access

Articles:	2016
Share of green open access	55%
Share of hybrid open access	5%
Share of gold open access	26%
Share of conference articles with green open access	31%

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

Table 3
Coverage in Web of Science

Publications in Web of Science (including Conference Proceedings Index)	Number of publications	Number of fractions
Articles, reviews, letters, proceedings papers	371	171,9

Figure 1
Number of fractionalized publications

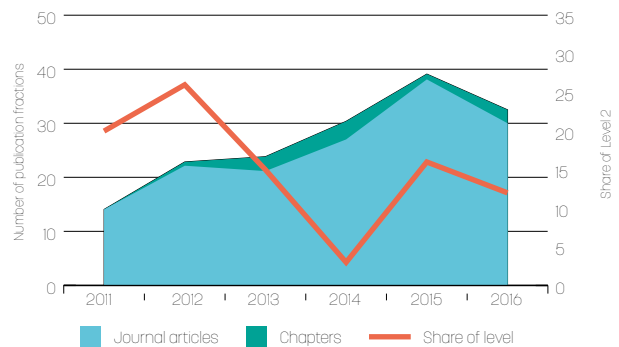


Figure 2
Open access articles

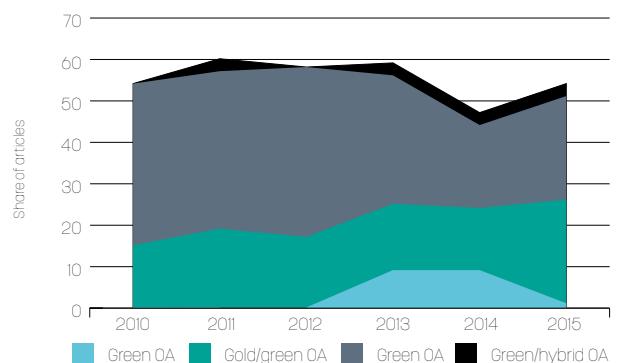


Figure 3
Number of fractionalized journal articles:
Coverage in WoS 88%

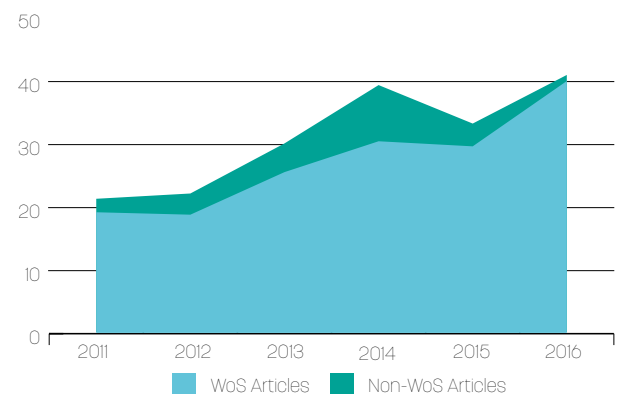


Figure 4
Impact

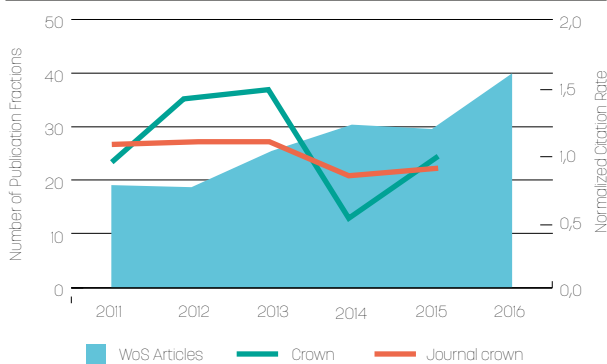


Figure 5
Fractionalized journal articles in WoS:
Co-authorships

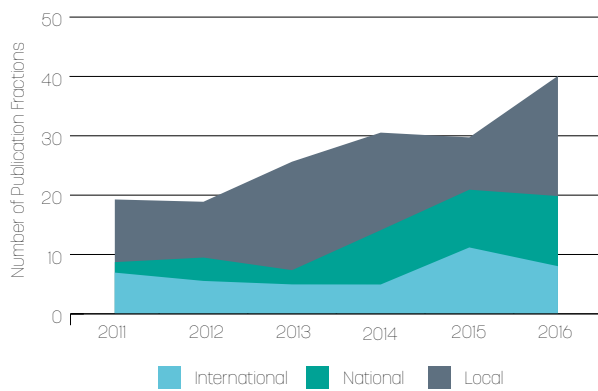


Figure 6
Interdisciplinary publications

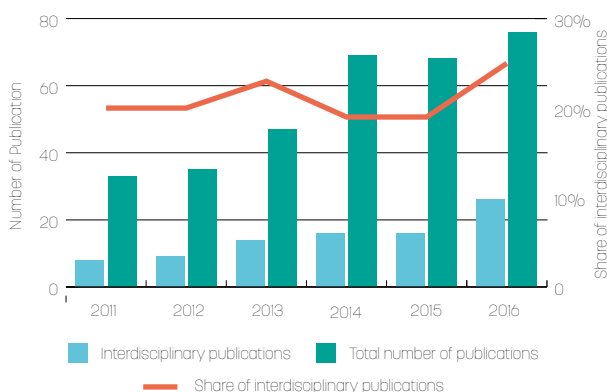


Table 4
Citation analysis

2011-2016		
"Publications in Web of Science (excluding Conference Proceedings Index)"	Number of publications	Number of fractions
Articles, reviews, letters	218	98,0

Results

2010-2015	
Field-normalized citation rate (crown)	1,06
Share of top 10 %	16%
Share of uncited publications	26%
Field-normalized journal citation rate (journal crown)	0,99
Journal Impact Factor (JIF) ranking, mean	0,66

Crown: A measure of the impact of the articles included in the analysis. Provides a comparison value with an international average for the same field, year and article type, and where the value 1 corresponds to a world average.

Share of top 10%: The percentage of publications that are among the 10% most cited in the subject area during the time period

Journal Crown: A measure of the impact of the journals that the department published in. JIF Ranking mean: All journals within each subject category are ranked based on the JIF, and the number indicates how the journal in question is placed in the rankings. Ex 0.8 indicates that the journal is among the 20% highest ranking.

Table 5
Co-authorship

2011-2016	
Share of articles with international co-authors	25%
Share of articles with national co-authors	24%
Share of articles with local co-authors	51%

Table 6
Interdisciplinary authorship (LiU faculties)

2011-2016	
Number	89
Share	21%

PUBLICATIONS 2016

CMIV affiliated researcher are written in bold

PEER-REVIEWED ORIGINAL ARTICLE

Abrahamsson A, Rzepecka A, **Romu T, Borga M, Dahlqvist Leinhard O, Lundberg P**, et al. Dense breast tissue in postmenopausal women is associated with a pro-inflammatory microenvironment in vivo. *Oncoimmunology* 2016;5(10). No of citations: 1 JIF: 7.644

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ANNUAL ACCOUNTS

During 2016 CMIV had a turnover of more than 40 million. The financial results for CMIV in 2016 was 4.5 million SEK in loss.

This fiscal year we've continued to develop our MRI research infrastructure by installing a new Siemens Magnetom Prisma. We have also made a review of our research backup and storage solutions, as well as the research workstations. The process of upgrading our Virtual Reality Theatre in the Wranne theatre was started during 2016 and we plan to install the

new equipment during 2017.

During 2016 CMIV had several on-going grant research projects. The VINNOVA-financed project "Optimized flows and IT tools for digital pathology" was started up early in 2015 and will continue until 2017. The smaller VINNOVA-financed pilot project "Bringing orthopedic implant surgery to the era of precision medicine" was finished during

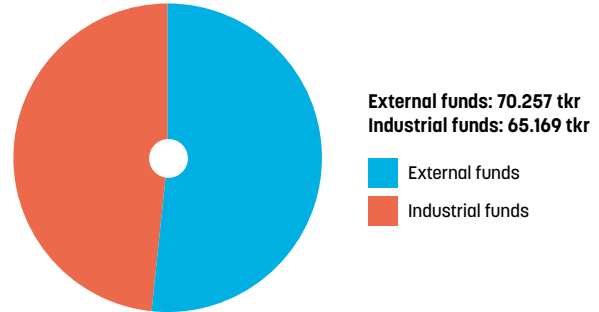
2016. This project will continue in a large scale during 2016-2019, with a new grant from VINNOVA. The project "Radsim: Simulation Based Training Program for CT Protocol, Iterative Reconstruction and Dual Energy Applications" continues until 2017. The project is funded by RSNA Research & Education Foundation.

Economic summary						
	2011	2012	2013	2014	2015	2016
TOTAL REVENUE	32 800	32 629	35 576	48 762	39 298	40 655
EXPENSES						
Staff expenses	-14 645	-15 102	-16 756	-19 507	-18 593	-16 978
Cost of premises	-1 975	-2 145	-2 034	-2 058	-2 869	-9 135
Misc. operating expenses	-9 549	-7 653	-8 876	-17 334	-11 483	-12 158
Depreciation expenses	-5 883	-4 938	-5 336	-5 629	-4 980	-6 781
Financial expenses	-403	-125	-185	-102	-123	-132
TOTAL EXPENSES	-32 455	-29 963	-33 187	-44 630	-38 048	-45 184
RESULT OF OPERATIONS	345	2 666	2 389	4 133	1 250	-4 519

Numbers in thousands of SEK

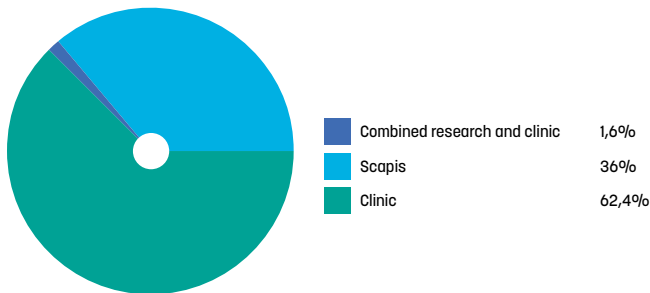
RESEARCH FUNDING

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

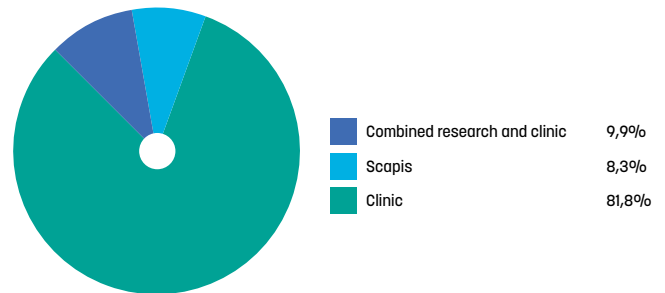


CT RESEARCH AND CLINIC

2016

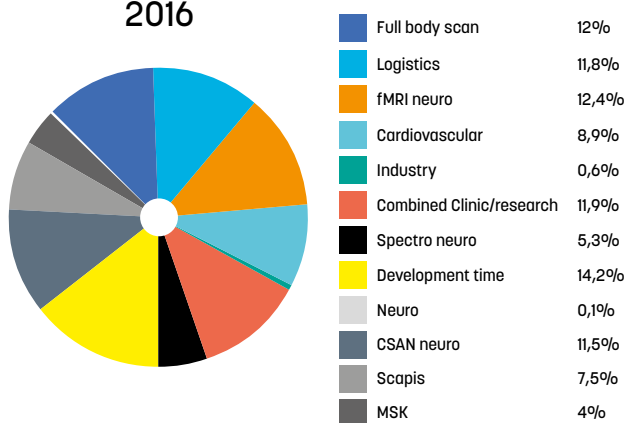


2015

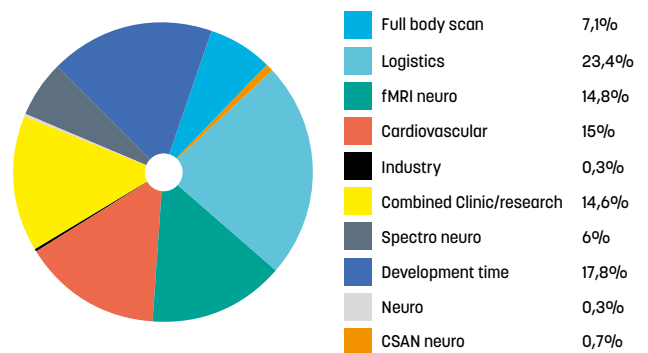


DISTRIBUTION OF RESEARCH ON THE MRI CAMERAS

2016



2015



CENTER FOR MEDICAL IMAGE SCIENCE AND VISUALIZATION