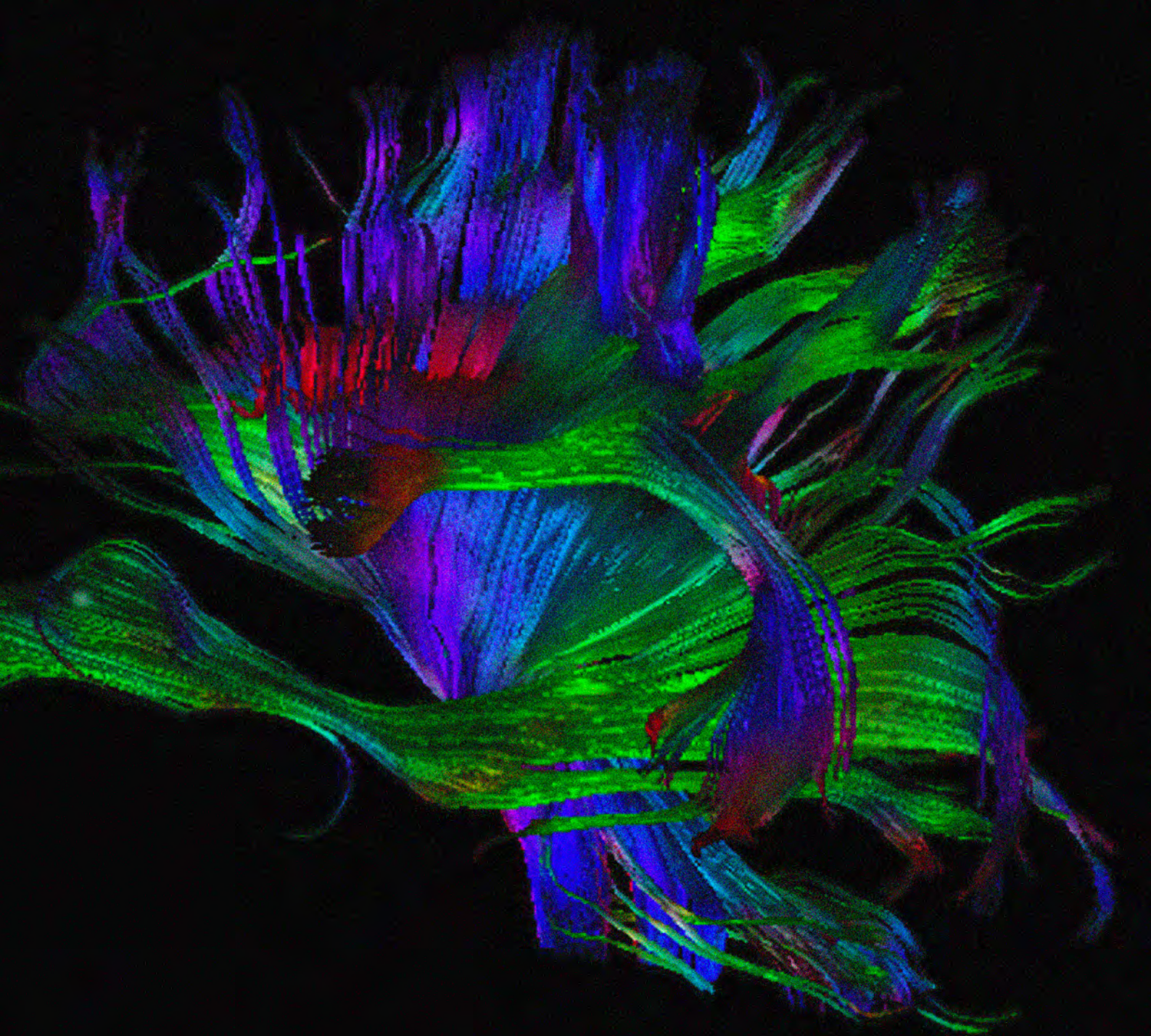


Welcome to the exciting world of CMIV

ANNUAL SCIENTIFIC REPORT 2019

The image shows a tractogram that visualizes the nerve tracts of the brain. The tractogram is based on data from diffusion MRI, which is a technique that uses the diffusion of water molecules to reveal details about tissue architecture.



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Production: Futurniture
Photography: CMIV, John Sandlund, Thor Balkhed
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During 2019, CMIV had a turnover of more than SEK 56 million. The financial result was SEK 2.7 million.



Preface

In 2019, CMIV's expanded premises were filled with additional creative forces that enabled interdisciplinary research, creativity and patient benefit to flourish. But the road has been paved with unexpected obstacles.

Yet another time, CMIV has been under construction, but this time due to the neurosurgical clinic installing a new intraoperative MRI scanner on the wing just above CMIV. This forced CMIV to move out of our heart, the coffee room. After a few months with outsourced coffee we could in the fall gather all the creative forces again and exchange ideas in the recycled now overcrowded CMIV coffee room.

Nevertheless, many new research projects were initiated during the year and research activities developed. Without the fantastic collaboration between all stakeholders: university, health-care, industry, individual research groups and support staff, this step

would not have been possible to take.

The digital pathology research field is growing and the results have led to clinical benefit not only in Sweden but also outside the country's borders. In terms of equipment, the access to computing power has taken a huge step forward by installing a genuine "supercomputer" in CMIV's premises in collaboration with the National Supercomputer Center (NSC) at Linköping University.

Increasing external research fundings have enabled the launch of several new research projects. Professor, Anders Ynnerman and Professor Markus Heilig have both been appointed as Wallenberg Scholars in 2019. Professor Håkan Olausson received SEK 34.5 million to study the ultrafast pain-signaling system from the Knut and Alice Wallenberg Foundation.

The flagship projects of 2019 are two outstanding projects that visualize the broad competence among the CMIV

researchers. They represent CMIV well in showing different areas and how we work close to the clinic combining technical and medical knowledge.

In the first flagship project "Imaging for Stereotactic Neurosurgery" imaging tools for stereotactic brain surgery and deep brain stimulation (DBS) are developed. The second flagship project "Analytic Imaging Diagnostic Arena" (AIDA) is a national arena for research and innovation in medical image analysis. AIDA's objective is to develop AI-based decision support solutions for imaging diagnostics that reach all the way to clinical use. The arena has evolved during the year and a new national research data hub has been setup.

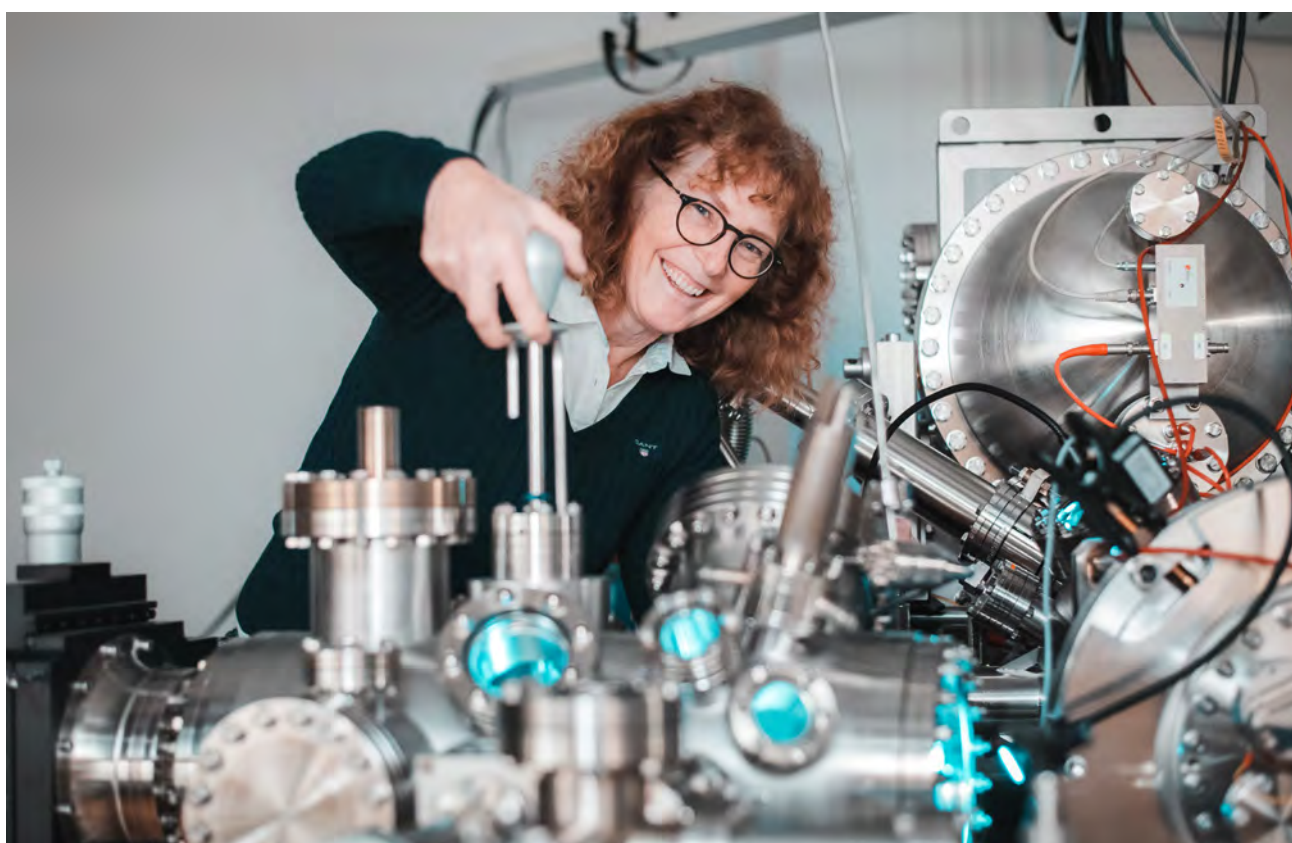
All in all, 2019 has been another great year at CMIV.



Anders Persson
DIRECTOR OF CMIV

Highlights

As always a lot of things have happened over the past year. The CMIV infrastructure was expanded with the supercomputer and the Swedish Research Council granted funding for a project regarding photon counting CT. Here you can read about these and many more highlights of the year.



SEK 17.9 Million to Research on Nanoprobes

CMIV RESEARCHERS Kajsa Uvdal, Professor in Molecular Surface Physics and Nanoscience, and Anders Persson, Professor in Medical Image Science, has together with an interdisciplinary team of researchers at Linköping University received a grant from the Swedish Research Council. The SEK 17.9 mil-

lion grant will be used for an initiative to develop tailor-made, targeting nanoprobes and endogenous contrast agents for photon counting computer tomography in medical imaging, by a new interdisciplinary approach. The objective is to obtain improved treatments for heart disease and cancer. ■



SSF Grant to CMIV Researcher

THE SWEDISH FOUNDATION for Strategic Research has awarded grants amounting to SEK 200 million for research projects in the interface between technology and medicine.

Karin Wårdell, professor of bio-medical engineering, received SEK 35 million for the project “Multimodal Guidance in Neurosurgery”. The aim of the project is to combine several types of technology, such as fiber-optic measurement systems, magnetic resonance imaging, and advanced image processing, to improve the treatment of neurological injuries such as brain tumors, head trauma, and brain hemorrhage. The scientists hope that the project also will lead to new knowledge about the human brain. ■

SCAPIS

IN DECEMBER 2018 the last examinations in the large national study Swedish CARDioPulmonary bioImage Study (SCAPIS) were finalized. This means that the project moved into the analytic phase where all the collected data from the six research sites were merged in one database. From this database it is possible to perform research on the whole material of a little over 30,000 participants. In Linköping around 5,000 volunteers participated in the study. Since the study moved into the analytic phase the administration of the local database research is handled at CMIV.

Together with SCAPIS and AI Innovation of Sweden the national arena AIDA has launched the SCAPIS AI platform pilot project. The project, which comprises a total of 8 million SEK, is financed in half by Vinnova and will last for two years.

The SCAPIS AI platform project aims to simplify the use of data from SCAPIS for AI development by providing a secure research environment with access to relevant infrastructure. The need for the platform primarily concerns imaging data, but AI methodology will also be applied to other types of data, as required by researchers. ■



The Swedish Society of Medicine on Tour

FOR THE FIRST TIME the Swedish Society of Medicine arranges meetings outside of Stockholm in the new initiative “The

Swedish Society of Medicine on Tour”. First up was a visit to Linköping and CMIV. The CMIV Director Anders Persson spoke about the imaging diagnostics of the future and showed the participants around the premises.

The Swedish Society of Medicine is an independent scientific and professional organization for Swedish doctors, medical students, and allied healthcare professionals.

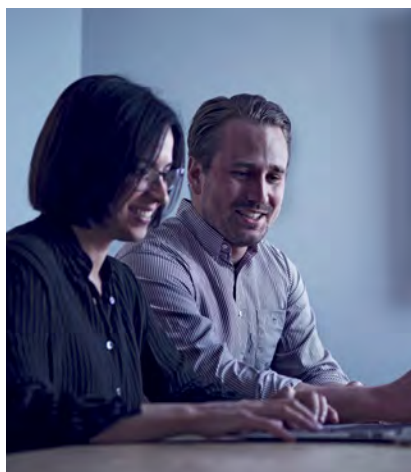
It is a nonprofit organization and a forum for discussing and developing health and health care by promoting Medical Research, Ethics, Education and Quality. ■



Almedalen 2019

DURING ALMEDALEN Week this year CMIV participated in East Sweden Arena. The topic discussed was how AI can move from vision to actual patient benefit. The event ended with a panel debate with representatives from CMIV, health-care, industry, politics and Vinnova.

The Almedal Week is an annual event in Visby on the Swedish island Gotland. The week is a democratic meeting place for politics and social issues. ■



Successful Year for CSAN

THE CENTER FOR Social and Affective Neuroscience, CSAN, unites research groups in adult psychiatry, child and adolescent psychiatry, neurobiology, clinical neurophysiology and neuro-economics. Many of the researchers are also part of CMIV.

CSAN had a successful year. In the fall the Knut and Alice Wallenberg Foundation awarded Professor Håkan Olausson with SEK 34 million to investigate ultrafast pain receptors. In the Swedish Research Council's funding in medicine and health sciences the group leader Markus Heilig received a SEK 9 million grant for translational research of why some people continue to consume alcohol despite experiencing negative consequences. In the same call Professor Håkan Olausson was awarded SEK 7 million for social touch and pain signaling. Postdoc Rebecca Böhme received a starting grant of 6 million SEK.

In the beginning of the year Rebecca Böhme published the article "Distinction of self-produced touch and social touch at cortical and spinal cord levels" in PNAS. Findings in the study show that our brains seem to reduce sensory perception from an area of our skin when we touch it ourselves. The finding increases our understanding of how the brain distinguishes between being touched by another person and self-touch. ■

Wallenberg Scholars

ONE OF 22 SCIENTISTS who has been selected Wallenberg Scholars in 2019 is Anders Ynnerman, Professor in Visualization. He receives SEK 18 million for free research in the coming five years.

Markus Heilig is one of five medical doctors active in research appointed to be Wallenberg Clinical Scholars 2019. He receives a research grant of SEK 15 million to investigate why some, but not all, people become dependent on alcohol. The aim of the research is to develop a drug against alcohol dependence. ■



Markus Heilig



Anders Ynnerman

Aunt Minnie Highlights CMIV Research Project



IN MAY THE RADIOLOGY WEBSITE Aunt Minnie highlighted a multinational study lead from CMIV. The study evaluated an AI algorithm for estimating fractional flow reserve on coronary CT angiography (FFR-CT). The method had the same level of performance when used with CT tube voltages of either 100 or 120 kVp. The study was published in the American Journal of Roentgenology.

The team retrospectively assessed a prototype commercial machine-learning algorithm on more than 300 coronary CT angiography (CCTA) scans at different voltage levels. They found no statistically significant differences in the algorithm's performance and concluded that the technique is robust.

The research was also highlighted at ECR. ■

Medical Digital Twin Funded by Visual Sweden

IN THE BEGINNING of 2019 the platform project Medical Digital Twin, MeDigiT was funded by Visual Sweden. To begin with the project will continue until the middle of 2020.

The objective of the platform is to facilitate the use of individual-specific digital models in healthcare for better diagnostics, more individualized treatment of disease, and simplified and improved training of healthcare professionals. The aim of the platform is also to create and promote a network for knowledge and experience exchange between Linköping University, Region Östergötland and medical visualization companies. ■



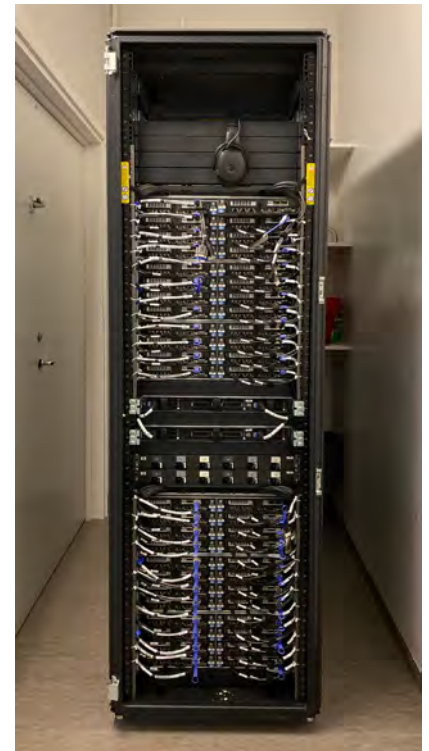
AIDA Showcase Event

TO MAKE IT EASIER for care providers to get an overview of AI solutions available on the market, AIDA decided to organize showcase events where care providers can meet a number of vendors and try out their products. The first event was held in October 2019.

It can be difficult for healthcare providers to get a grip on whether the AI solutions available on the market can make a real difference in their workflows. AIDA has a project type, Clinical Evaluation, that aims to assist care providers in crossing that threshold. The offering includes up to 50 % funding of costs and access to a unique “arena” with knowledge exchanges and a technical platform. ■



Speed dating with the vendors in the exhibition.



Real Super-computer now Part of the CMIV Infrastructure

ONE IMPORTANT addition to the CMIV infrastructure this year is the super-computer. The computer is built at National Supercomputer Center, nsc, at Linköping University. Nsc hosts the most powerful supercomputer in Scandinavia. CMIV’s own super-computer is placed inside the University Hospital firewall. ■

Deepened Collaboration with Mayo Clinic

CMIV HAS collaborated with Mayo Clinic for a few years and has now deepened the collaboration further around photon counting computed tomography. CMIV PhD student Mårten Sandstedt spent the autumn at Mayo Clinic to learn more and work on common research projects. ■

The CMIV Landscape

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

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

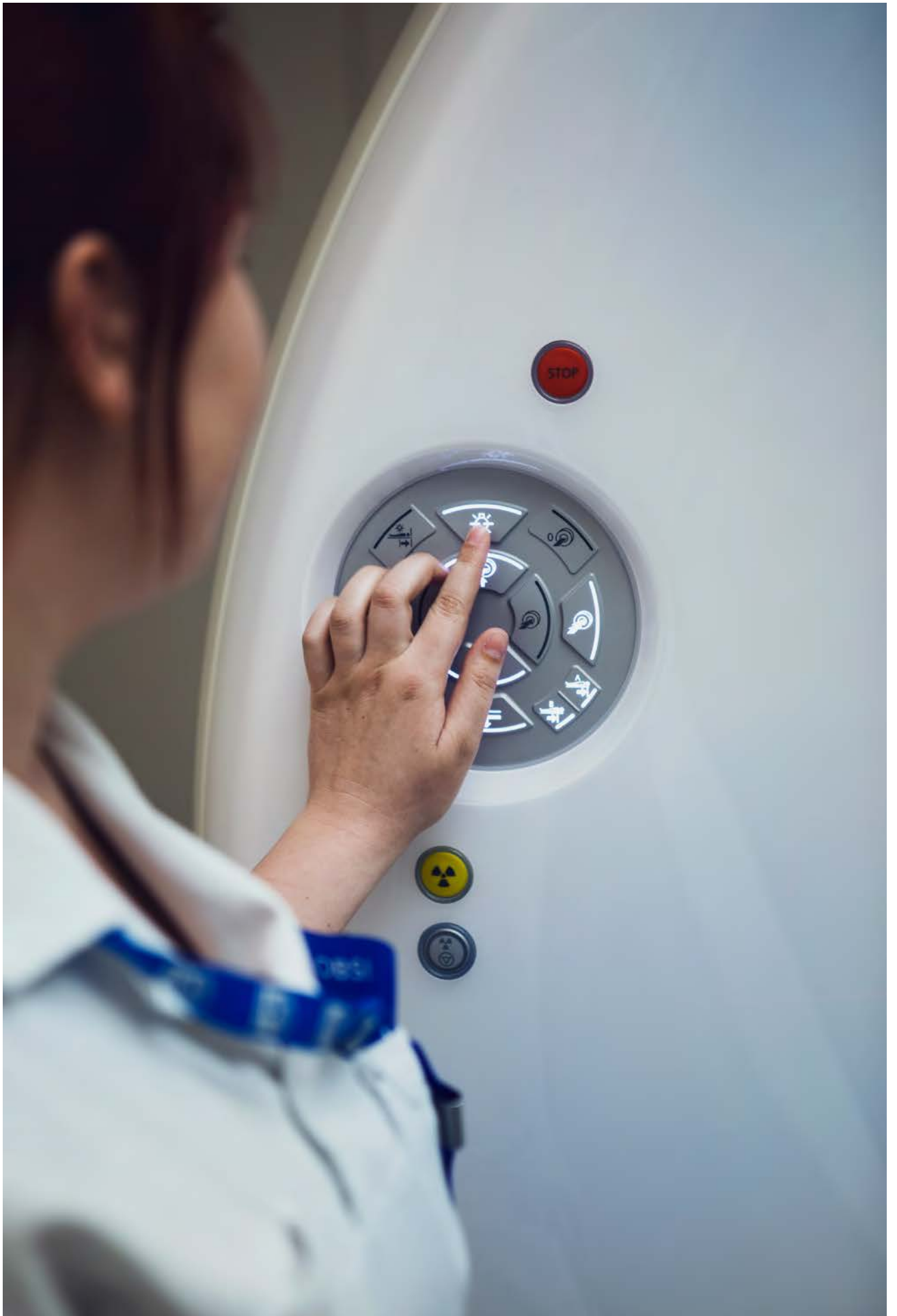
CMIV has a unique constellation in which research at the University provides healthcare with the opportunity of clinical benefits, while the industry gain from the research with e.g. spin-offs. The activities aim to combine different demands were the university seeks scientific publications in high quality journals and the county council expects

the research and development to come to patient benefit. CMIV's organization, fully embedded in the university hospital, creates conditions to successfully meet these requirements. Results from basic research at the university can be utilized in clinical research which can then result in scientific publications, and improved patient care.

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

research areas as artificial intelligence and precision medicine.

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





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

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

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

The categories used are divided in

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

Imaging Data Source

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

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

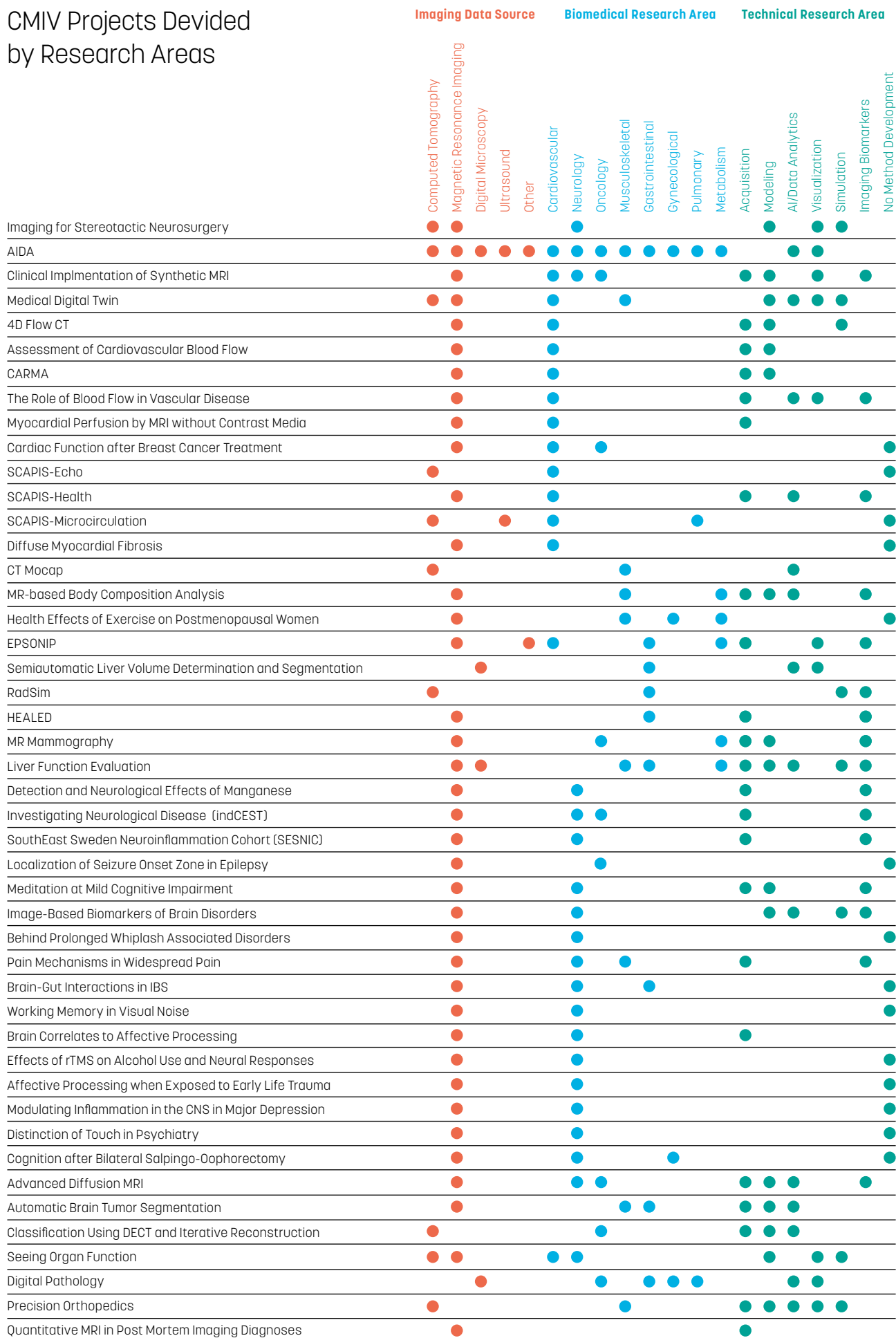
Biomedical Research Area

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

Technical Research Area

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

CMIV Projects Devided by Research Areas





CMIV researcher Magnus Borga. His research is focused on muscle and fat distribution in the body.

Flagship Projects

The 2019 flagship projects were selected by the CMIV scientific council. The chosen projects complement each other in modalities, project stage and medical area and therefore well represent the broad and multi-disciplinary research at CMIV.





Imaging for Stereotactic Neurosurgery

In Deep Brain Stimulation, DBS, electrodes are placed in the brain to deliver electrical stimulation that can block the abnormal nerve signals causing symptoms in Parkinson's disease. The surgery requires careful planning and imaging for the electrodes to be placed exactly right. This project works with MRI protocols for stereotactic neurosurgery and has developed a tool based on laser Doppler technique which can be used with the DBS probe to give more data on the surrounding tissue.



Parkinson's disease is a progressive nervous system disorder that effects the parts of the brain that control movement. The most common symptoms are tremor, rigid muscles and slowed movement. One way of reducing the symptoms is deep brain stimulation (DBS). In DBS surgery, electrodes are placed in specific brain regions to deliver electrical stimulation that can block the abnormal nerve signals causing the symptoms. The surgery requires careful planning and imaging in order for the electrodes to be placed exactly right. Even minor displacements might cause unwanted side effects.

In addition to Parkinson's disease DBS is used in essential tremor and dystonia. The procedure has been performed on around 160,000 patients worldwide and in Linköping around 30 patients are treated every year.

Before the stereotactic surgery a preoperative magnetic resonance imaging (MRI) is performed to guide the surgeon. Using the stereotactic frame and the coordinates from the MRI the surgeon can use a probe to produce a canal for the electrode to reach the exact location.

Karin Wårdell is Professor in biomedical engineering and has been working with MRI protocols for stereotactic neurosurgery for many years.

"The close collaboration with the clinic and the neurosurgeons means everything to my research."

Karin Wårdell

In addition, she has developed a tool based on laser doppler technique which can be used with the DBS probe to give more data on the surrounding tissue.

– The optical fibers can measure the blood flow in a small volume in front of the probe and warn the surgeon when the probe is about to pass a volume with high blood flow. We can also determine if the probe is in white or grey matter, Karin explains.

The data from the DBS probe, the preoperative MRI and a postoperative computed tomography (CT) or MRI are combined and used as input for patient-specific computer modelling and simulations of the electric field around the DBS electrode.

– The simulated electric field is visualized together with the preoperative MRI. This makes relative comparisons between simulations possible and the electric field can be related to the patient's own anatomy, Karin says.

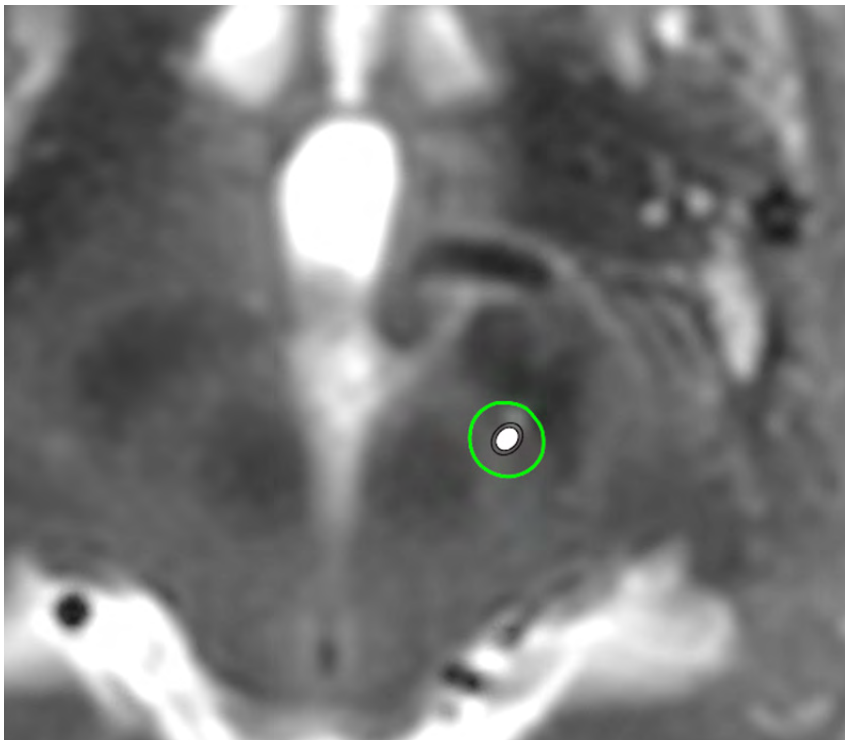
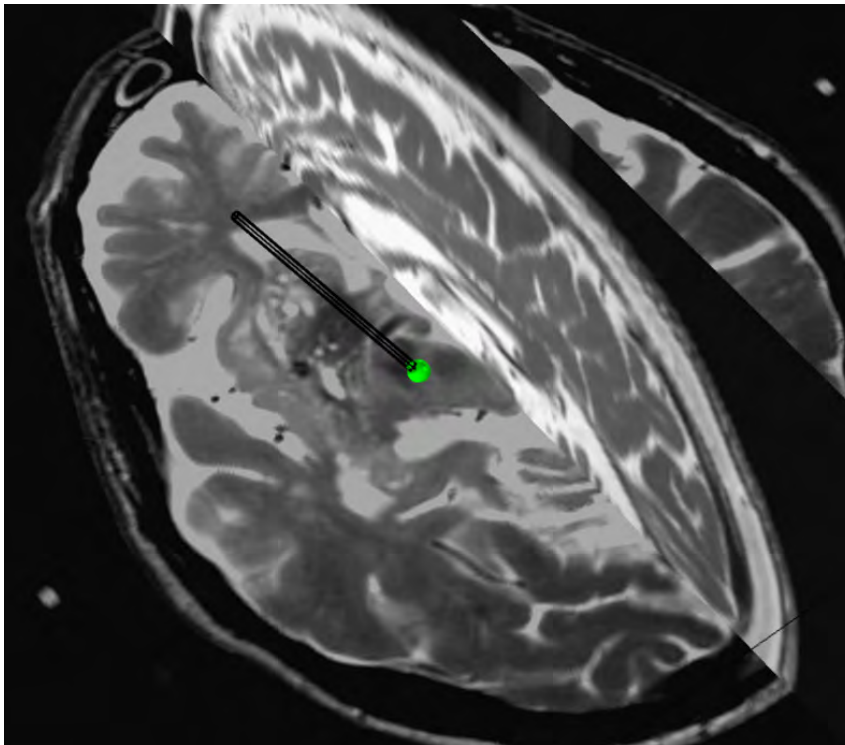
The research group is investigating if it is important to know what type of

tissue that surrounds the electrode. The results show that there is little difference between white and gray matter but if the electrode is placed close to interstitial fluid the electrical field may be distorted. This is highly relevant since Parkinson's patients often have Virchow-Robin Spaces, interstitial fluid-filled spaces, in the brain.

– We believe that placing the electrode too close to Virchow-Robin Spaces might be the reason for some of the side effects seen in DBS treated patient, Karin continues.

Three of the most common targets for DBS are located close to white matter tracts in the brain. These tracts can be visualized with diffusion MRI (dMRI). Karin's research group recently started up a project investigating if it would be possible to visualize these tracts and find out if the treatment is more effective when the electrode is placed in one of these tracts.

– You need to be able to show very thin white fibers and also when they intersect. We have developed a dMRI meth-



UPPER IMAGE: Example of simulation of DBS electric field (in green) in the zona incerta (Zi) for a patient with essential tremor. **LOWER IMAGE:** Zoom in of the target region where the Zi is an area between the subthalamic nucleus and the red nucleus.

odology for this using tractography and are working on refining the protocol to improve the visualization as much as possible, Karin says.

Karin is collaborating with research groups and neurosurgery clinics both in Sweden and in Europe.

– The close collaboration with the

clinic and the neurosurgeons means everything to my research. Without them it would be impossible to continue, Karin explains.

Some of Karin's research results have been commercialized, first a laser Doppler scanner developed during her PhD, and more recently the tech-

Computed Tomography

MRI

Neurology

Modeling

Visualization

Simulation

PROJECT INFORMATION

Project Name

Imaging for Stereotactic Neurosurgery

Project Leader

Karin Wårdell, Department of Biomedical Engineering, Neuroengineering Lab

Main Project Participants

Johannes Johansson, Fabiola Alonso, Teresa Nordin, Peter Zsigmond

Grants

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

Key publications

Johansson JD, Alonso F, Wårdell K. Patient-Specific Simulations of Deep Brain Stimulation Electric Field with Aid of In-house Software ELMA, 41st IEEE-EMBC, pp 5 212–5 216, 2019.

Zsigmond P, Hemm-Ode S, Wårdell K. Optical Measurements during Deep Brain Stimulation Lead Implantation: Safety Aspects, *Stereotact Funct Neurosurg.*, 95(6):392–399, 2018.

Alonso F, Latorre M A, Göransson N, Zsigmond P and Wårdell K. Investigation into Deep Brain Stimulation Lead Designs: A Patient-Specific Simulation Study, *Brain Sciences*, 6(3), 39; doi:10.3390/brainsci6030039, 2016.

nique for optical measurements in the brain.

– It is not often that something in your research turns out to be a potential product but when it does, I think it is my obligation to try to commercialize so that my idea can benefit others, Karin concludes. ■





AIDA

AIDA is a national arena for research and innovation in medical image analysis. AIDA is a cross-disciplinary collaboration aiming for largescale use of AI in healthcare. In the arena, academia, healthcare and industry meet to translate AI technology advances into patient benefit in the form of clinically useful tools. CMIV is the host and physical meeting place of AIDA but aims to assist all Swedish actors in this domain.

“We saw a need for more knowledge about how to translate AI innovations into actual use in clinical routine.”

Claes Lundström

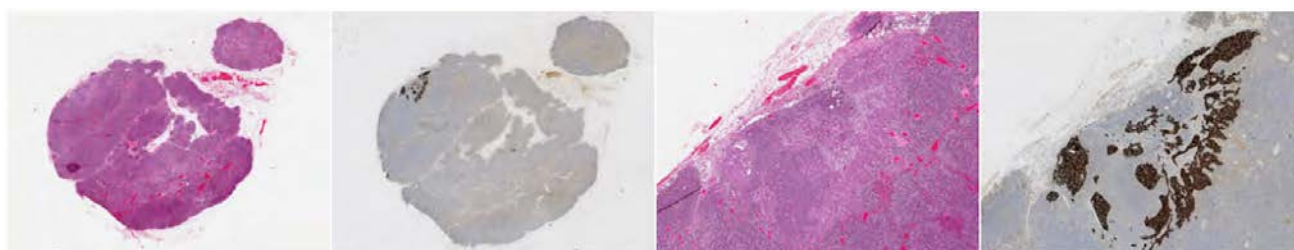


FIGURE. The image shows an entry in the AIDA Data Hub. The data set includes anonymized whole slide imaging of 396 full cases of axillary lymph nodes in breast cancer cases from the Department of Clinical Pathology in Linköping, Region Östergötland.

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

Analytic Imaging Diagnostic Arena (AIDA) is a national arena for research and innovation in medical image analysis. AIDA’s objective is to develop AI-based decision support solutions for imaging diagnostics that reach all the way to clinical use. An underpinning fundamental insight is that

this complex challenge requires both interdisciplinary and cross-sectoral collaboration.

Claes Lundström is a Professor in medical visualization and the director of AIDA.

– We saw a need for more knowledge about how to translate AI innovations into actual use in clinical routine, on the healthcare side as well as in technical research. Without more knowledge about each other the engineers will continue to produce solutions they believe are beneficial but in reality, never reach the patients and the healthcare professionals will continue not knowing what to ask for to refine the innovations, Claes explains.

Most of AIDA’s resources are used for projects developing AI-based decision support solutions. These are run by research groups in industry and academia across Sweden, in collaboration with healthcare providers. AIDA also offers a

core environment at CMIV, with technical infrastructure designed to support the development projects. Perhaps even more important is the meeting place aspect of the core environment, where workshops and meet-ups are frequently organized, providing valuable knowledge and exchanges. To give healthcare the right knowledge base to drive the AI development in the most effective direction, AIDA offers both clinical and technical fellowships, where care provider employees or engineers carry out an individual project as continued education.

– The goal is to introduce mechanisms that will continue to build valuable collaborations and innovations even after the AIDA project is concluded, Claes continues.

Developing AI innovations requires large amounts of relevant data and the relevant data is found in healthcare. There is an extensive uncertainty about how to share data in a secure, ethical and



legal way. AIDA has started up a data hub in order to facilitate data sharing in different ways.

– We collect data sets that can be shared for important research and we try to prioritize what the healthcare actually needs help with. If you look at the typical research done in AI right now it is done with data that just happens to be available, not necessarily prioritizing what the healthcare needs help with, Claes says.

Before starting the data collection, it was necessary to work through the legal and ethical questions.

– Several laws are involved here so for us it was important to state how to work with this kind of data. The thorough effort done has resulted in a data policy that is publicly available to guide anyone who work with these questions.

Working with large data sets requires an unusual amount of computer power that is not possible to host for most

research groups. AIDA is now investing in a unique system with 16 GPU processors that can handle large-scale AI computations. The system will be shared between the AIDA researchers across the country and will enable AI model training that is faster and includes larger data volumes than it was possible before.

Around 20 innovation projects are currently running or has been concluded under the AIDA flag. The projects are initiated by both technical and medical researchers from both academy and industry. The knowledge about AI has increased among pathologists and radiologists in Sweden and the departments are more ready to embrace AI as part of their profession now, than a few years back.

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

Computed Tomography

MRI

Digital Microscopy

Ultrasound

Other

Cardiovascular

Neurology

Oncology

Musculoskeletal

Gastrointestinal

Gynecological

Pulmonary

Metabolism

Acquisition

Modeling

AI/Data Analytics

Visualization

PROJECT INFORMATION

Project Name

Analytic Imaging Diagnostic Arena, AIDA

Project Leader

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

Main Project Participants

Caroline Bivik Stadler, Daniel Forsberg, Joel Hedlund, Jonas Unger, Marie Waltersson, Catrin Nejdeby, Gabriel Eilertsen, Darren Treanor, Dennis Carlsson, Sofia Jarkman, Karin Lindman, Mischa Woisetschläger, Jörg Schilcher, Karin Stacke, Martin Lindvall (in addition, several CMIV projects are connected to AIDA)

Grants

Vinnova, Medtech4Health

Key Publications

Hedlund, J.
AIDA data sharing policy. Report No. LiU-2017-01901.

Lindman K, Rose F J, Lindvall M, Lundström C, Treanor D.
Annotations, ontologies and whole slide images – Development of an annotated ontology-driven whole slide image library of normal and abnormal human tissue. *Journal of Pathology Informatics*, 2019 Jul 23;10:22. doi: 10.4103/jpi.jpi_81_18.

Jarkman S, Lindvall M, Hedlund J, Treanor D, Lundstrom C, van der Laak J (2019). Axillary lymph nodes in breast cancer cases doi:10.23698/aida/brln.



Research Projects

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

Clinical Implementation of Synthetic MRI

Conventional MRI is mainly qualitative. The MRI scanner acquires an image with a certain contrast setting, such that there is a signal difference between the various tissues of the human body. Only the difference is important, the signal values in itself are randomly scaled. At CMIV two sequences were developed to actually measure MRI characteristics, providing values to MRI. The first one was in 2007, based on a Fast Spin Echo technique, providing high in-plane resolution, but acquired with relatively thick slices. In recent years, a full 3D version has been developed, which can image the body with isotropic resolution, i.e. the tissue can be visualized from any geometric plane. The scan time for the 3D sequence is about 6 minutes, measuring the most important characteristics for MRI: the R1 relaxation rate ($1/T1$), the R2 relaxation rate ($1/T2$) and proton density (PD).

Based on these physical properties a range of conventional MR images can be recreated, an approach called synthetic MRI. Using a single sequence the conventional contrasts such as T1W, T2W, FLAIR, but even Double IR and Phase-Sensitive IR can be generated. Moreover, being objective data, tissue can be recognized and assessed automatically. This means that a relatively short scan time is sufficient to reproduce a large part of a normal MR examination and additionally, to provide more objective means of patient follow-up. Examples of tissue recognition are brain volume measurement, myelin detection and GD-enhancement detection. These clinical parameters can be used for monitoring development and degeneration of the brain, for example in pediatrics, Multiple Sclerosis, hydrocephalus, cancer and dementia.

A spin-off company, SyntheticMR AB, was created to ensure an installable,

safe product including the necessary regulatory requirements for the European and US market. The current 2D approach has been built in all major vendors and is sold globally as part of the clinical workflow. There is a high demand to move to 3D and that has now become possible.

In the history of MRI, general images were acquired to be interpreted subjectively by radiologists. With the advent of quantitative MRI, scan times will be shorter and the decision support will be more based on numbers and statistics. Automated analysis can make the work of the radiologist both faster and more objective. The technique is available on the major scanner brands, which will decrease the variation between different hospitals. Quantitative MRI is a clear example of excellent cooperation between university, hospital and commercial companies, made possible by CMIV. ■

MRI

Cardiovascular

Neurology

Oncology

Acquisition

Modeling

Visualization

Imaging Biomarker

PROJECT INFORMATION

Project Name

Clinical Implementation of Synthetic MRI

Project Leader

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

Main Project Participants

Ida Blystad, Peter Lundberg, Anders Tisell, Tino Ebbens, Jan Engvall, Ebo de Muinck, Peter Johansson, Catharina Petersen, Johanna Alfredsson

Key Publications

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

Warntjes JBM, Persson A, Berge J, Zech W.

Myelin Detection Using Rapid Quantitative MR Imaging Correlated to Macroscopically Registered Luxol Fast Blue-Stained Brain Specimens. *AJNR Am J Neuroradiol*. 2017 Jun;38(6):1096–1102.

Warntjes JBM, Dahlqvist Leinhard O, West J, Lundberg P.

Rapid Magnetic Resonance Quantification on the brain: Optimization for Clinical Usage. *Magn Reson Med* 2008;60:320–329.

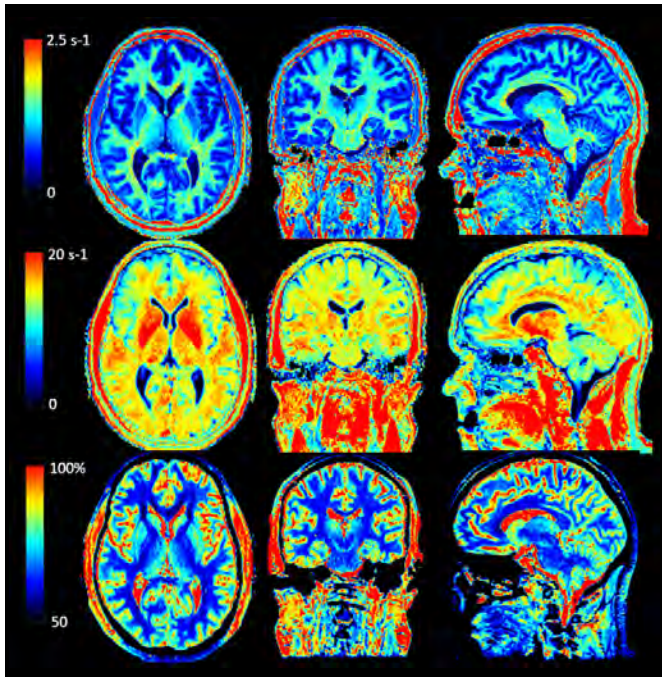


FIGURE 1. Example of quantitative MRI in 3D, showing axial, coronal and sagittal reformats of a single sequence producing R1, R2 and PD maps on an objective scale. The isotropic resolution allows a viewer to scroll through the images from all sides.

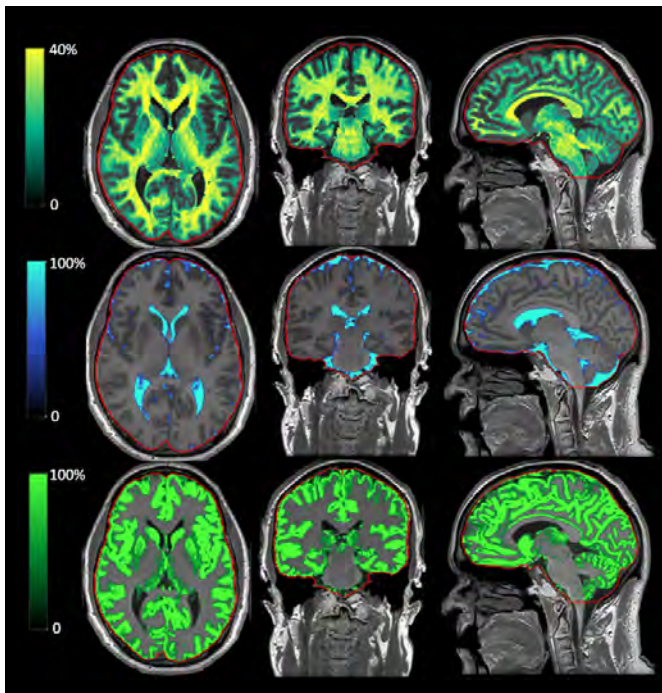


FIGURE 2. Fully automatic brain segmentation of the same data as Figure 1, of myelin, CSF and grey matter. The combination of 3D quantification maps and automatic segmentation in a scan time of only 6 minutes means an incredible amount of patient information in a very short time.

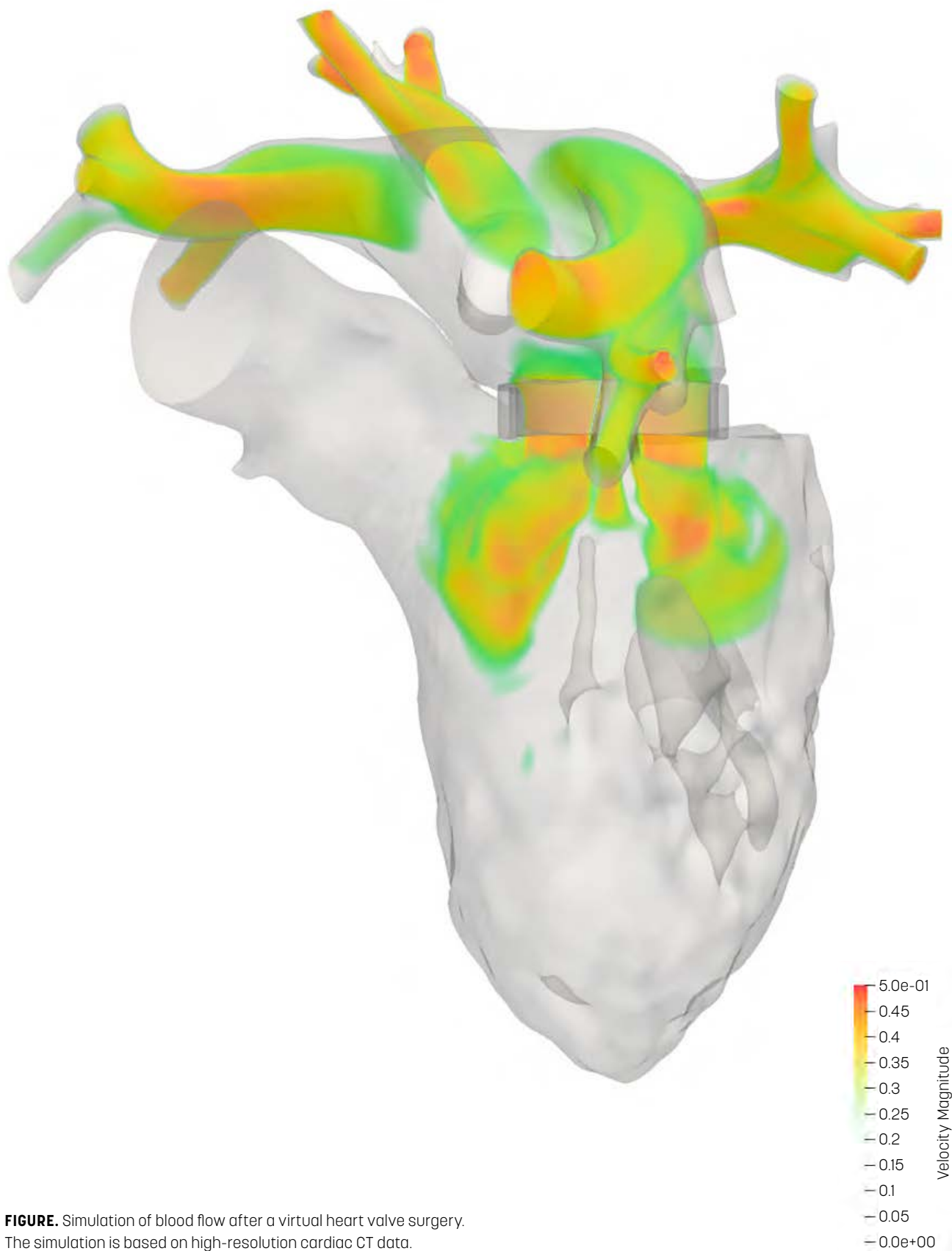


FIGURE. Simulation of blood flow after a virtual heart valve surgery. The simulation is based on high-resolution cardiac CT data.

Medical DigitalTwin

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

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

The platform was formed in early 2019 and has since then connected several partners and created subprojects in many different areas.

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

of physiotherapists and physicians.

For many years CMIV has been involved in cutting edge research on imaging of the cardiovascular system. One of the MeDigiT subprojects is building on this knowledge. Using simulations of heart flow based on CT images, individualized digital twins are tested for diagnosis and treatment evaluation in heart disease. The research aims amongst others for improving valve surgery and risk assessment of blood clot formation in atrial fibrillation. Other parts participating in the project are Siemens and Region Östergötland.

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

An exciting sub-project, which is starting to take shape, aims to create a medical digital twin of a woman (SheDigiT) and a man (HeDigiT). Several partners from the University, the Region and industry have shown interest in this project.

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

Computed Tomography

MRI

Cardiovascular

Musculoskeletal

Modeling

AI/Data analytics

Visualization

Simulation

PROJECT INFORMATION

Project Name

Medical Digital Twin, MeDigiT

Project Leader

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

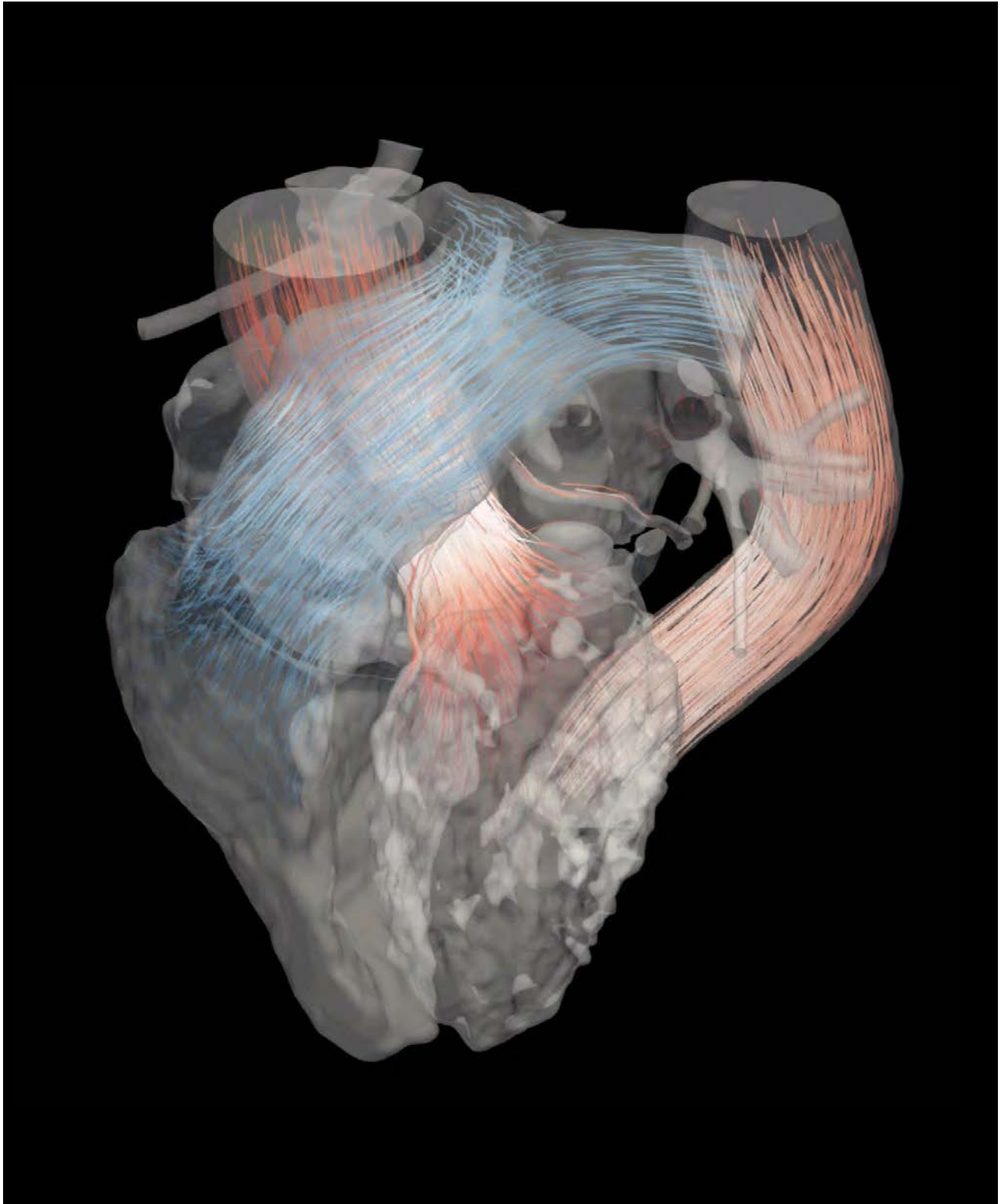
Main Project Participants

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

Grants

Visual Sweden 2019–2020

FIGURE. Simulation of blood flow based on high-resolution cardiac CT data.



4D Flow CT

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

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

Even though many forms of functional imaging data and modelling approaches are currently available a gap persists between modelling and experimental research. This project has bridged the gap by developing and evaluating an approach in which intracardiac flow fields are computed based on patient-specific high-resolution cardiac CT data. The heart is segmented and advanced registration techniques are used to track the heart wall. Using computational techniques usually employed by the automotive or

aerospace industry, detailed intracardiac and vascular blood fields are obtained.

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

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

The simulation-based approach potentially allows for studies of what-if scenarios where different treatment options can be explored. This is challenging, as the heart is complex and adapts to changes in demand and constraints. A model is a simplified version of reality and there has to be a balance in the amount of details included and clinically usability. ■

Computed Tomography

MRI

Cardiovascular

Acquisition

Modeling

Simulation

PROJECT INFORMATION

Project Name

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

Project Leader

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

Main Project Participants

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

Grants

Swedish Heart Lung Foundation, 2019–2021

Key publications

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

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

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

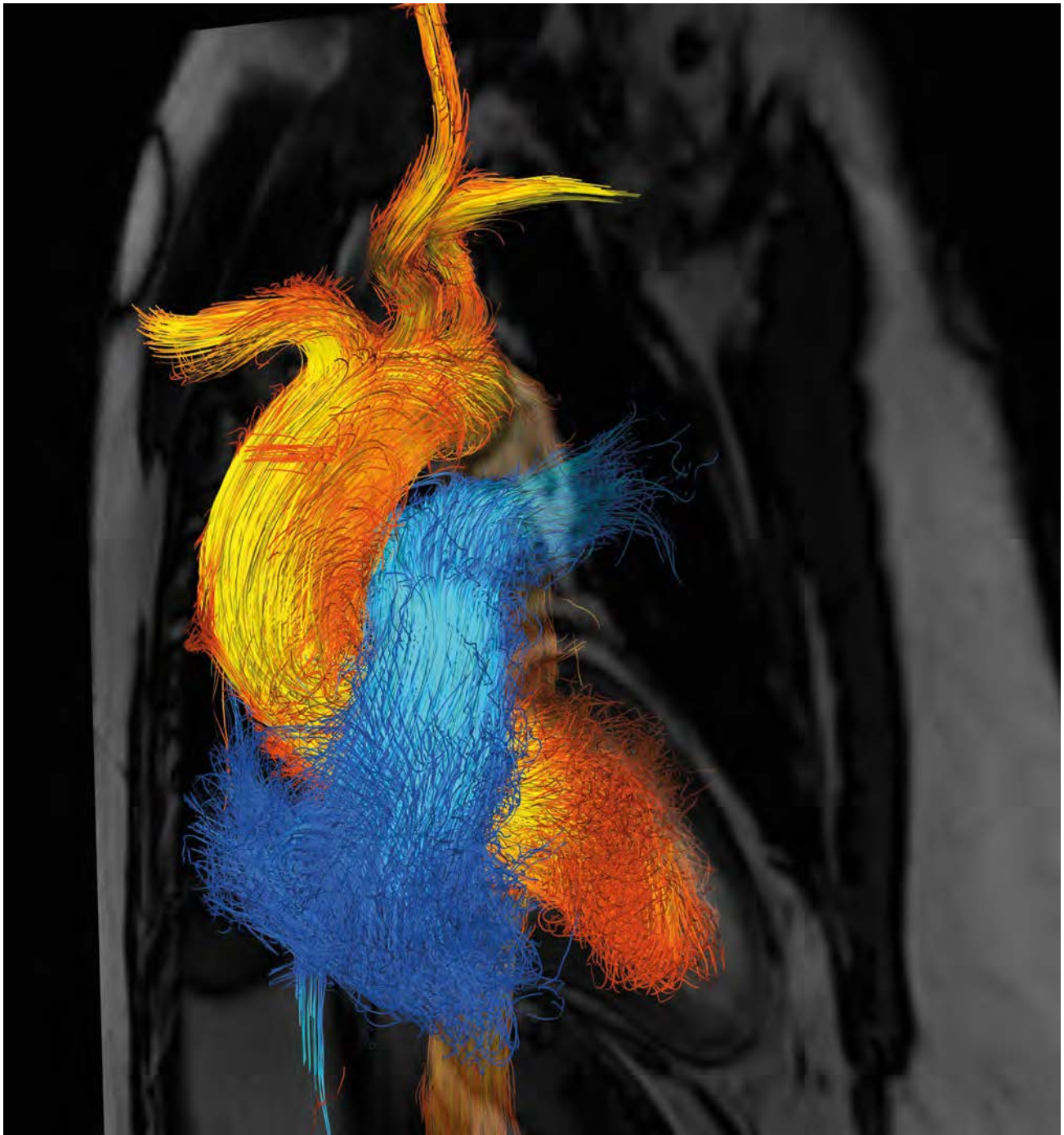


FIGURE. 4D flow visualization of the heart.

Assessment of Cardiovascular Blood Flow

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

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

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

and more accurate detection and improved management of cardiovascular diseases.

The project makes use of a method for flow quantification using MRI which allows for simultaneous measurement of time-resolved, three-dimensional (time + 3D = 4D) blood flow velocity and turbulence intensity. This method, which was pioneered at CMIV, reveals blood flow patterns in the heart and the large vessels. By combining this approach with modelling approaches, more knowledge can be obtained from the data about the cardiovascular system under different conditions.

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

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

MRI

Cardiovascular

Acquisition

Modeling

Simulation

PROJECT INFORMATION

Project Name

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

Project Leader

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

Main Project Participants

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

Grants

Swedish Research Council 2019–2022

Key publications

Viola F, Dyverfeldt P, Carlhäll CJ, Ebbers T, Chiara Bucciarelli-Ducci, Jeroen Bax J, Saul Myerson G. Data Quality and Optimal Background Correction Order of Respiratory-Gated k-Space Segmented Spoiled Gradient Echo (SGRE) and Echo Planar Imaging (EPI) *Journal of Magnetic Resonance Imaging* 51:885–896, 2020.

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

Ha H, Kvitting JP, Dyverfeldt P, Ebbers T. Validation of pressure drop assessment using 4D flow MRI-based turbulence production in various shapes of aortic stenoses, *Magnetic resonance in medicine* 81 (2), 893–906, 2019.

CARMA

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

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

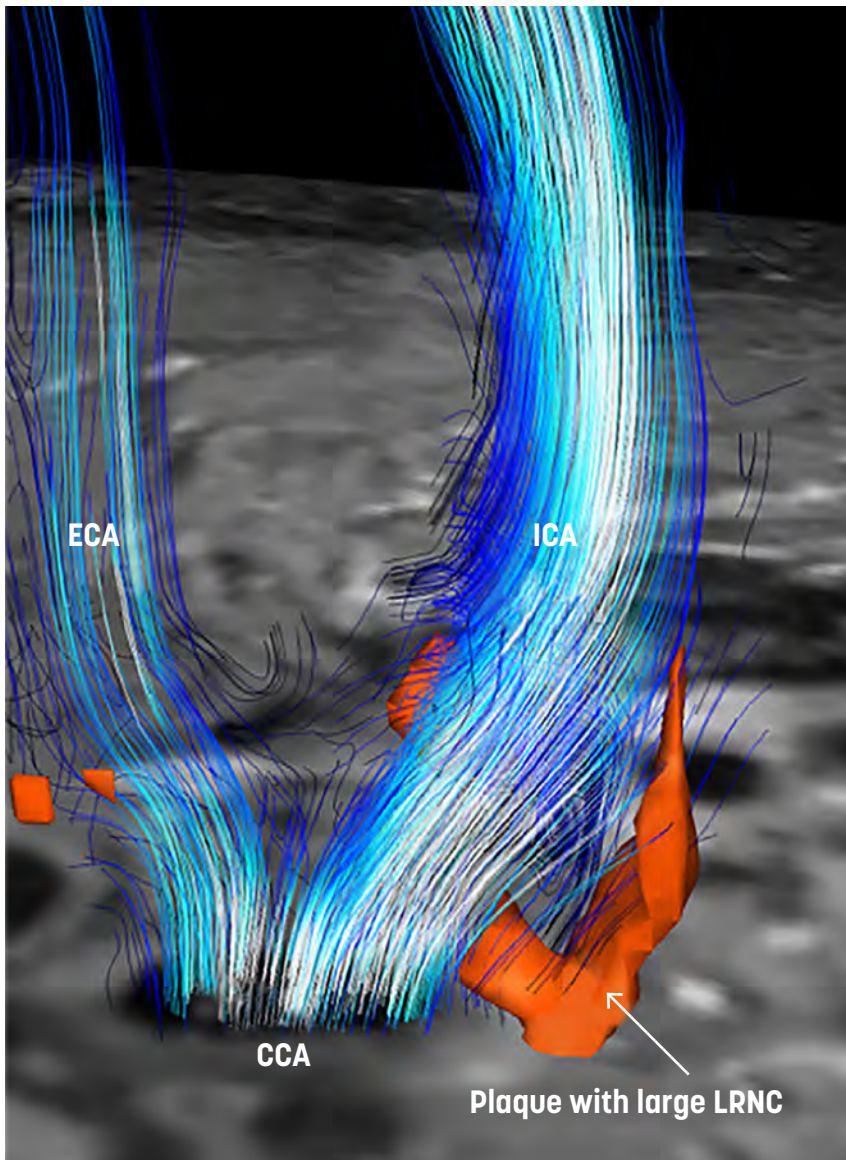
are called atherosclerotic plaques.

Strokes resulting from blood clots that migrate to the brain from plaque in the carotids cause 2.5% of all deaths. Today, plaques that cause more than 70% constriction of the carotid in stroke patients are removed surgically to avoid future strokes. The hypothesis is that the blood clots are formed when the plaque surface ruptures. The composition of the plaque is affecting the rupture risk. Plaque with a large amount of fat and blood are more prone to rupture. However, studies show that only half of the removed plaques have ruptured. Also, removing the plaque is far from a complete safe guard against future stroke. We believe that the blood flow around the plaque also is an important factor for rupture risk. Additionally, if there is stagnant flow, blood clots could

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

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

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



resonance imaging methods with novel image analysis. In this way, we will automatically identify plaque severity based on the extent of fat and blood within the plaque. Similarly, we will provide assessment of the impact of turbulent flow on the vessel wall. The methods will be evaluated in patients with carotid atherosclerotic plaques to optimize and establish the reliability of the technical developments in a clinical setting.

Successful implementation of the project will enable new approaches for risk stratifying carotid plaques clinically and improved cardiovascular risk management. This will not only improve the selection of patients for preventive care and surgery, but also, through improved management, reduce healthcare costs. ■

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

MRI

Cardiovascular

Acquisition

Modeling

PROJECT INFORMATION

Project Name

Carotid Magnetic Resonance Imaging of Atherosclerosis, CARMA

Project Leader

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

Main Project Participants

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

Grants

Swedish Research Council (2018–2021)

Key publications

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

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

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

The Role of Blood Flow in Vascular Disease

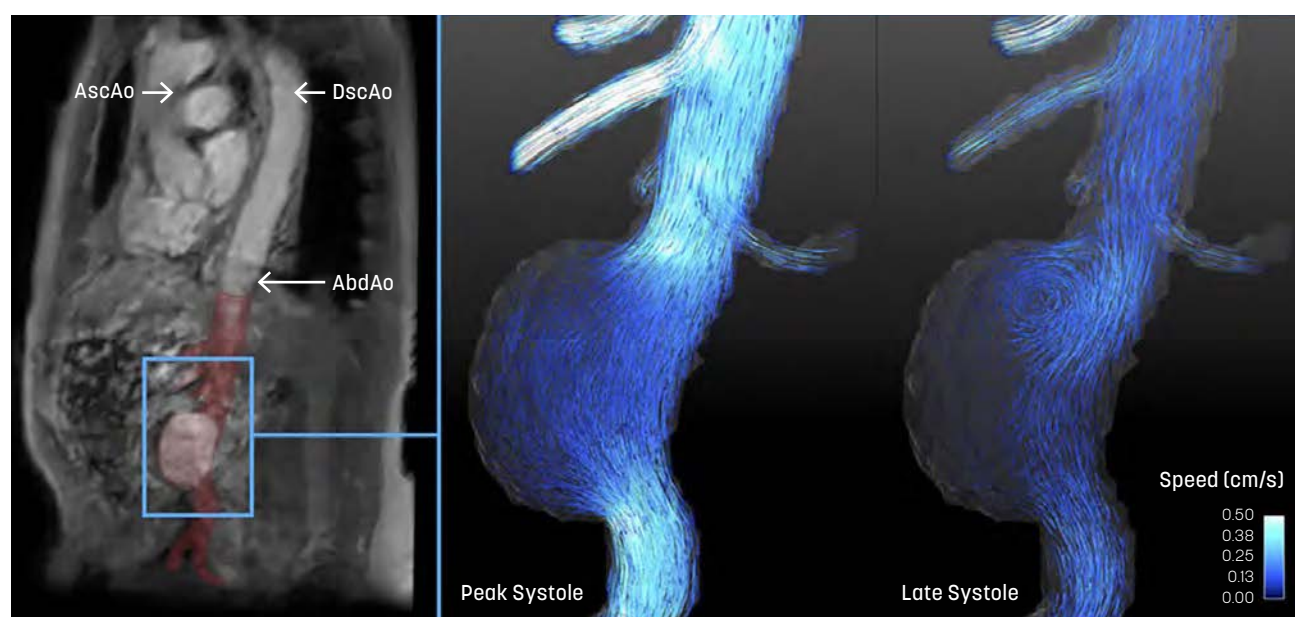


FIGURE. The complex hemodynamics of Abdominal Aortic Aneurysms (AAA) can be investigated using 4D Flow MRI.

Left panel shows an anatomical image in a sagittal orientation, with an AAA delineated in red.

Centre panel shows a streamline visualization of flow in the aneurysmal sac at peak systole.

Right panel shows a streamline visualization of flow in the aneurysmal sac at late systole, where a large vortex has formed at the proximal edge of the sac.

AscAo = Ascending Aorta

DscAo = Descending Aorta

AbdAo = Abdominal Aorta

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

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

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

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

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

MRI

Cardiovascular

Acquisition

AI/Data analytics

Visualization

Imaging Biomarker

PROJECT INFORMATION

Project Name

Non-Invasive Imaging of the Interrelationship between Blood Flow and Vascular disease

Project Leader

Petter Dyverfeldt, Department of Medical and Health Sciences, Division of Radiological Sciences

Main Project Participants

Tino Ebbers, Elin Good, Lena Jonasson, Hanna Lekedal, Marcus Lindenberg, Ebo de Muinck, Eva Swahn, Magnus Ziegler

Grants

Swedish Research Council (2018–2021)

Key publications

Ziegler M, Welander M, Bjarnegård N, Carlhäll CJ, Lindenberg M, Ebbers T, Länne T, Dyverfeldt P. Visualizing and Quantifying Flow Stasis in Abdominal Aortic Aneurysms using 4D Flow MRI. *Magnetic Resonance Imaging* 2019; 57: 103–110.

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

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

Myocardial Perfusion by MRI without Contrast Media

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

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

Arterial Spin Labeling (ASL), is a non-invasive MRI technique where the water protons of the arterial blood are magnetically labeled and used as an endogenous tracer. This technique

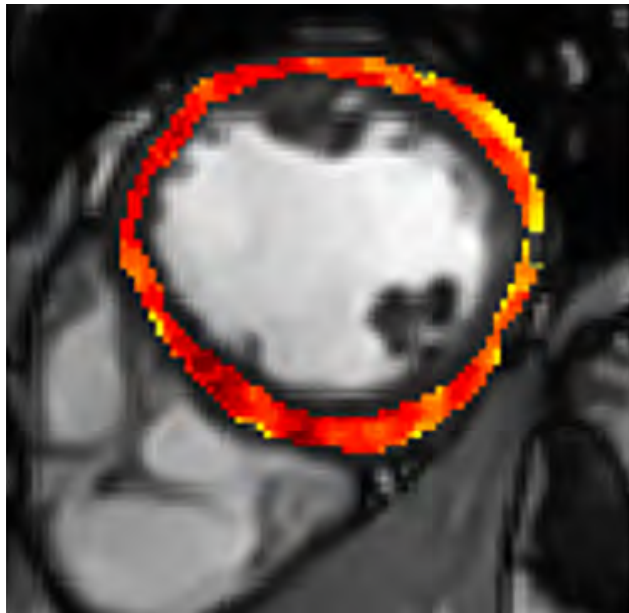
has so far been used for measuring perfusion in the brain. However, performing ASL in the myocardium has several challenges due to movement and extensive blood flow around the myocardium.

After adjusting the ASL sequence into the cardiac context and to the available MRI-scanner, a pilot was performed on ten healthy volunteers. In order to collect images of the heart, the acquisition must be fast. Therefore, comparisons were made between two different acceleration techniques; SENSE and compressed sensing (CS). As the sequence must be reliable at different heart rates, comparisons between imaging in diastole and systole were made. Motion correction techniques were applied to ensure that the image processing is robust.

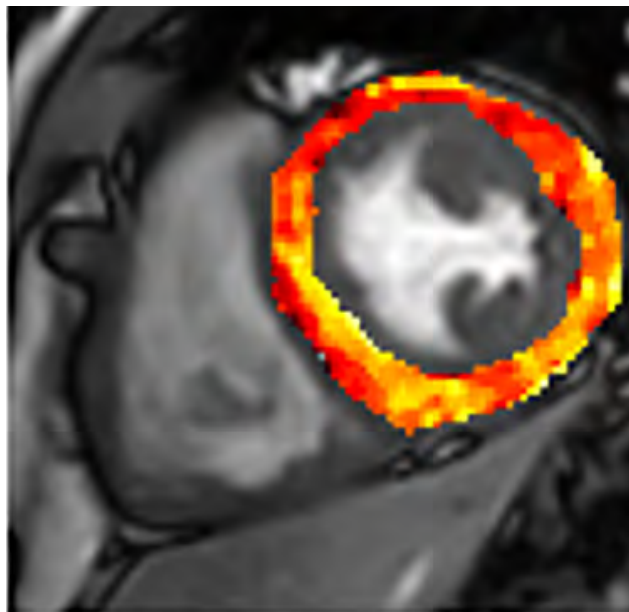
No significant difference was found between the faster compressed sensing

technique and SENSE. By collecting the images during systole, the imaging became less sensitive to heart rate changes. In addition, the noise was significantly reduced as more of the myocardium was included in the image. When an increased heart rate was provoked in one subject image acquisition was shown to be robust, and an expected increased perfusion could be detected.

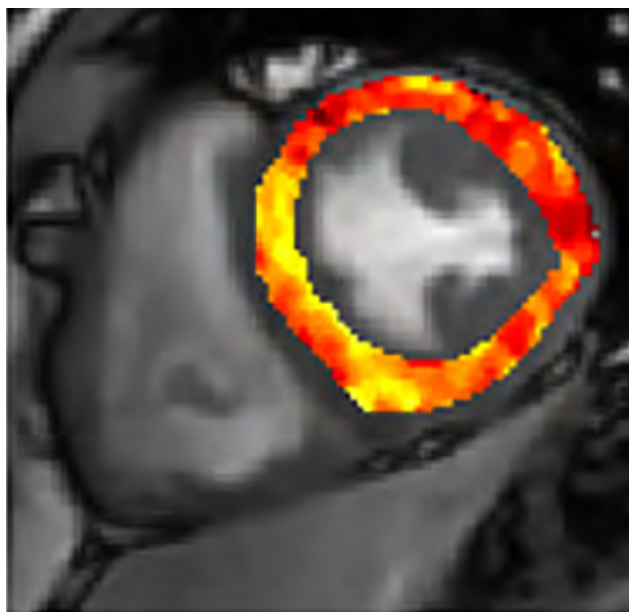
For future studies, patients with ischemic heart disease should be included in the study to investigate if the technology also works in pathological conditions. By optimizing the imaging so that the acquisition can be performed under free breathing, the examination will be further facilitated for the patients. In the long term, perfusion with ASL technology should also be compared with other perfusion techniques. ■



Diastole SENSE



Systole SENSE



Systole CS

MRI

Cardiovascular

Acquisition

PROJECT INFORMATION

Project Name

Myocardial Perfusion by MRI without Contrast Media

Project Leader

Johan Kihlberg, Department of Medical and Health Sciences, Division of Radiological Sciences

Main Project Participants

Markus Henningsson, Carl-Johan Carlhäll

Key publications

Henningsson M, Carlhäll C J, Kihlberg J. Myocardial arterial spin labeling in systole and diastole using flowsensitive alternating inversion recovery (FAIR) with parallel imaging and compressed sensing J Cardiovasc Magn Reson submitted Nov 2019.

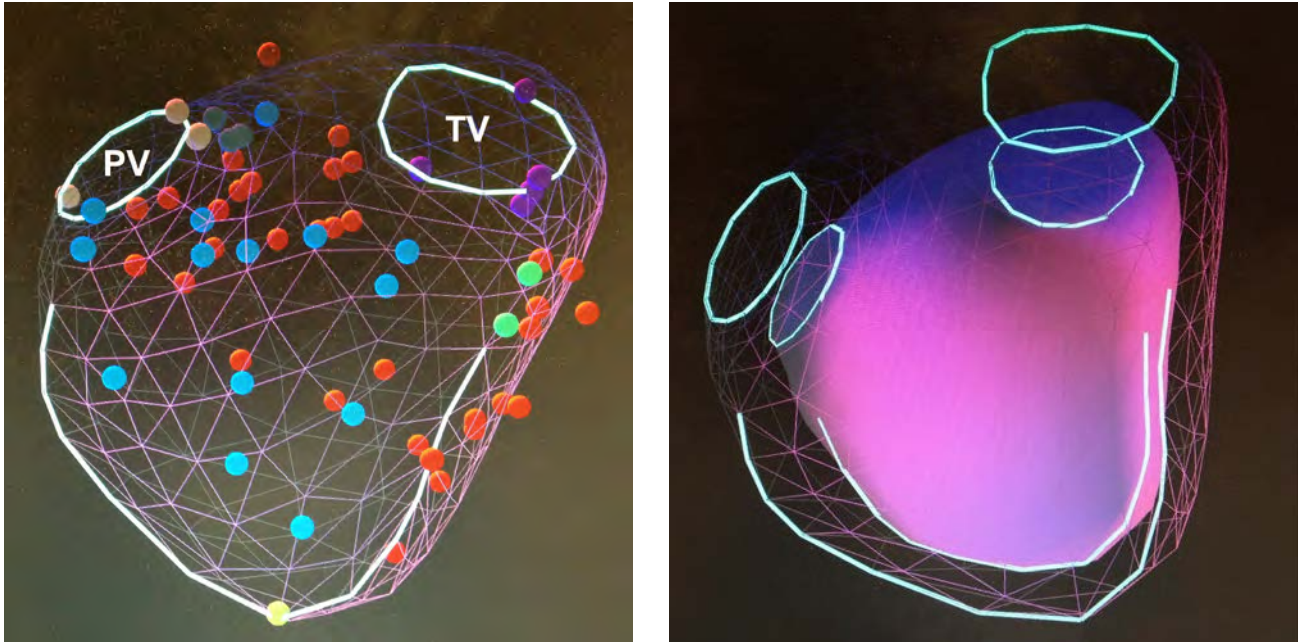


FIGURE 1. The image shows the initial reconstruction and the final result of a knowledge-based reconstruction.

TIMING

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

Adult patients with CHD is now a

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

This project investigates methods to measure and characterize cardiac

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

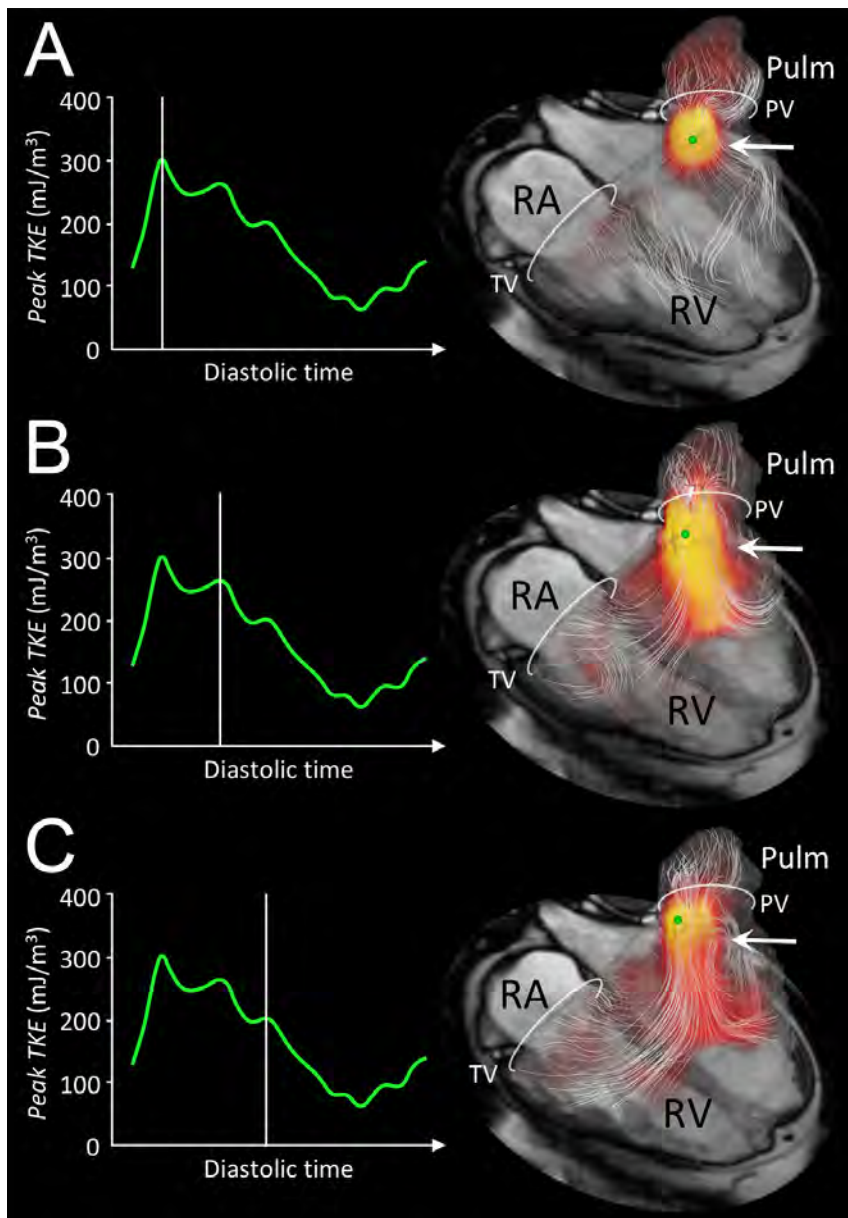


FIGURE 2. Image showing turbulence calculated at three diastolic time frames of the right ventricle used by permission of the publisher Elsevier, *J Magn Reson Imaging*. 2018 Apr;47(4): 1043-1053.

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

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

The project involves the use of ultrasound 3D methods for calculation of volume and function compared to cardiac magnetic resonance (CMR) used as a gold standard. The project

has also provided new measures of intracardiac flow such as turbulence mapping of turbulent kinetic energy. As part of the project a collaboration with the university hospital in Utrecht resulted in an ultrasound study with »Knowledge-based reconstruction« (KBR). KBR uses multiple 2D slices acquired with a clinical 2D ultrasound scanner, stitched together using spatial information from a magnetic positioning system. ■

MRI

Ultrasound

Cardiovascular

Modeling

Visualization

PROJECT INFORMATION

Project Name

Timing of Investigations with MRI in Grown-Ups with Congenital Heart Disease, TIMING

Project Leader

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

Main Project Participants

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

Grants

Swedish Heart-Lung Foundation

Key publications

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

Trzbiatowska-Krzynska A, Swahn E, Wallby L, Nielsen N E, Carlhäll C J, Brudin L, Engvall J.

Afterload dependence of right ventricular myocardial deformation – a comparison between adult patients with atrially corrected Transposition of the Great Arteries and Fallot. *PLoS ONE* 13(9): e0204435.

Trzbiatowska-Krzynska A, Driessen M, Sieswerda GT, Wallby L, Swahn E, Meijboom F. Knowledge-based 3D reconstruction of the right ventricle: comparison with cardiac magnetic resonance in adults with congenital heart disease. *Echo Res Pract*. 2015 Dec 1; 2(4): 109-116 doi: 10.1530/ERP-15-0029.

Cardiac Function after Breast Cancer Treatment

Breast cancer patients who undergo external radiation therapy (RT) may be exposed to unwanted cardiac irradiation. Irradiation of normal tissues can lead to side effects. Acute toxicity appears during or up to six months after radiotherapy is completed and usually disappears without permanent damage. Late complications appear a longer time after the completion of radiotherapy (six months or even later) and are more serious.

Late toxicity includes radiation induced cardiovascular disease that results from injury to the heart and the blood vessels of the myocardium, leading to ischaemia, fibrosis, and depletion of media smooth muscle cells and atherosclerosis.

This project investigates methods for measuring and characterizing cardiac function and tissue components in

patients undergoing radiotherapy and chemotherapy for breast cancer. The research question relates to the development of edema and the reduction of cardiac systolic function induced by the given treatment.

A difficulty in the design of the study is that most patients in need of radiotherapy start with an initial course of chemotherapy, either Herceptin or Herceptin in combination with anthracycline or paclitaxel.

The basic assumption in this study is that patients are characterized in terms of having either left-sided breast cancer, where the heart will receive some unwanted irradiation that could produce side effects in cardiac tissue, or a right-sided lesion where the heart is not included in the field of irradiation. We have planned for a long follow-up period, 2 years, in order to be able to identify whether unintended irradiation

of the left breast induces longterm changes to cardiac function. In total 25 patients have been included in this ongoing study.

This project involves the use of cardiovascular magnetic resonance imaging (CMR) for determining early changes to cardiac systolic function detected by analyzing native T1-values and strain from deformation imaging of the left ventricular myocardium. The CMR measurements use echocardiographic strain analysis as reference.

Monitoring effects of unintended irradiation of cardiac tissue may help detect markers of radiation induced cardiac responses. This may enable early identification of patients at risk that might benefit from preventive measures to reduce cardiovascular complications. ■

MRI

Cardiovascular

Oncology

No Method Development

PROJECT INFORMATION

Project Name

Methods for Measuring Cardiac Function after Radiotherapy and Chemotherapy in Breast Cancer

Project Leader

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

Main Project Participants

Johan Kihlberg, Sofia Kvernby, Anna Flejmer, Alexandru Dasu, Tino Ebbers

Key publications

Kvernby S, Flejmer A, Dasu A, Ebbers T, Engvall J, Kvernby S, Rönnerfalk M, Warntjes M, Carlhäll C J, Nylander E, Engvall J, Tamás É, Ebbers T. T1- and T2-Mapping for Early Detection of Myocardial Changes in Breast Cancer Patients: Longitudinal Assessment during Radiation Therapy. Presented at ACC: Advancing the cardiovascular care of the oncology patient, Washington DC Feb 12–14 2020.

Displacement

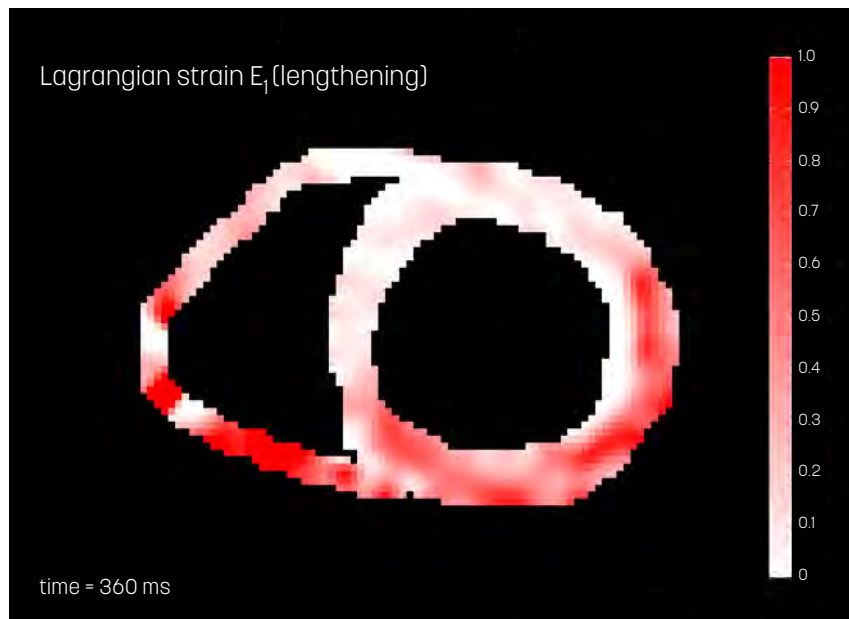
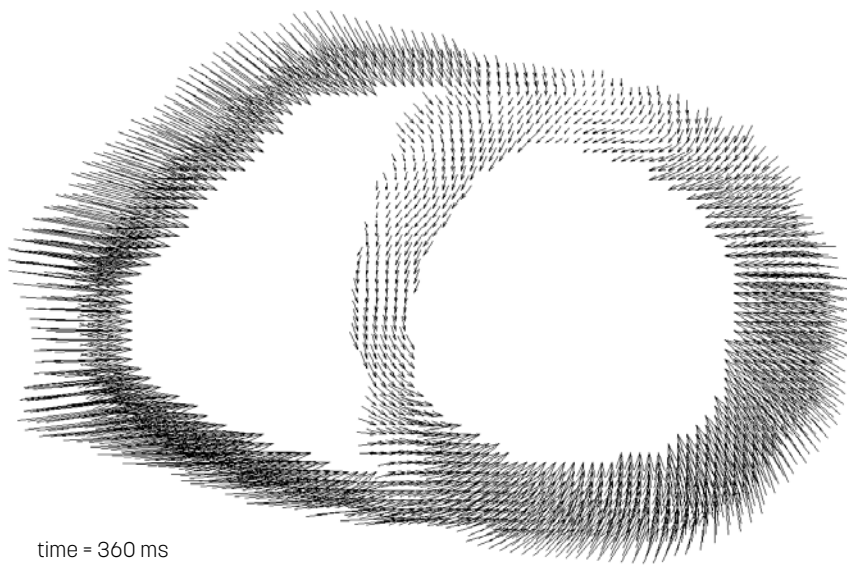


FIGURE. Radial strain (wall thickening) is reduced in the upper left quadrant of the left ventricle. Contracting parts in deep red.

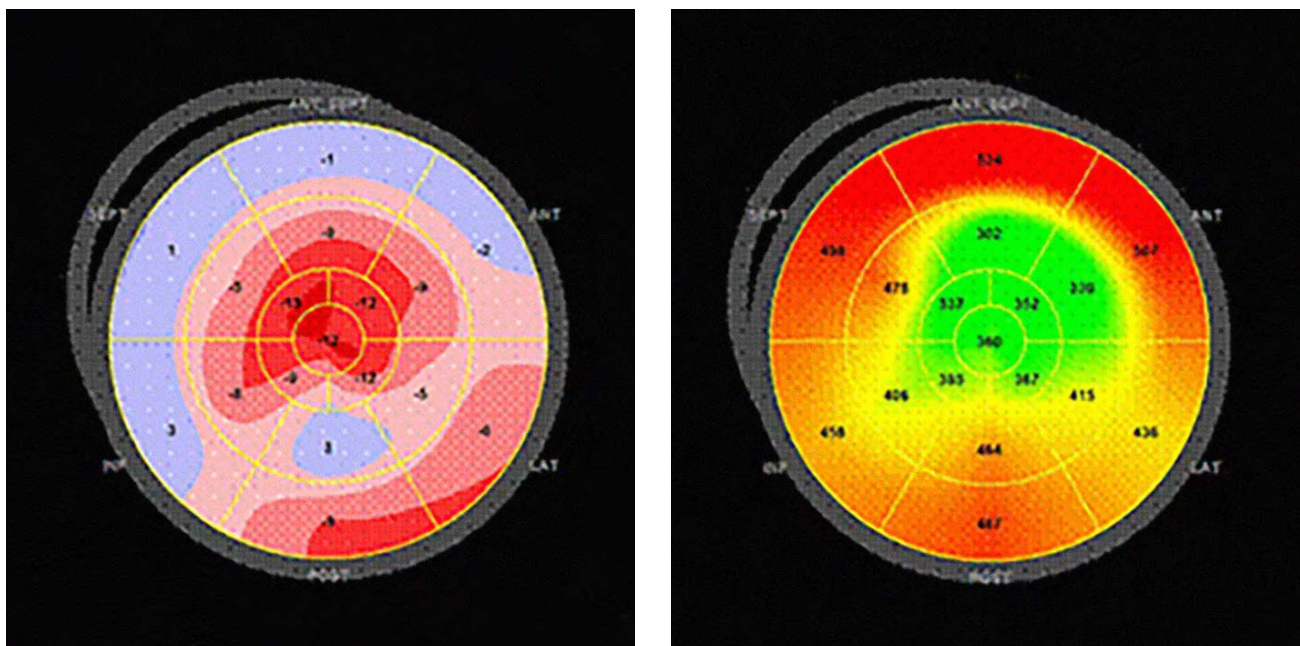


FIGURE. Polar plot representation of the amplitude of peak strain (left), time-to-peak strain (right) and the calculated standard deviation of peak strain, (red box right). The green area of the right polar plot shows normal temporal relationship between segments. The red basal area denotes mechanical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

SCAPIS-Echo

Swedish Cardio Pulmonary bioImage Study (SCAPIS), is a large-scale national population study initiated by The Swedish Heart-Lung Foundation and supported by the Wallenberg Foundation. The study is 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 were examined in the study. Of these 5,000 were examined in Linköping. The participants' lungs and cardiovascular system are examined with computed tomography and ultrasound. All the collected data have been 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 dispersion. Mechanical dispersion has been thought to represent the mechanical effect of electrical dispersion, which in itself represents an electrical instability that could be derived from previous myocardial scarring.

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

Therefore, the purpose of SCAPIS-Echo is to determine global longitudinal strain amplitude and peak systolic dispersion in the Linköping SCAPIS population. 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 cardiovascular risk factors.

Inclusion was completed in 2018, complementary measurements are under way and future cardiovascular events in the cohort will be followed through Swedish disease registries. ■

MRI

Cardiovascular

No Method Development

PROJECT INFORMATION

Project Name

SCAPIS-Echo

Project Leader

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

Main Project Participants

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

Grants

KAW

Swedish Heart-Lung Foundation

Key publications

Bergström G, Berglund G, Blomberg A, Brandberg J, Engström G, Engvall J, Eriksson M, de Faire U, Flinck A, Hansson MG, Hedblad B, Hjelmgren O, Jansson C, Jernberg T, Johnsson Å, Johansson L, Lind L, Löfdahl C G, Mellander O, Östgren C J, Persson A, Sandström A, Schmidt C, Söderberg S, Sundström J, Toren K, Waldenström A, Wedel H, Vikgren J, Fagerberg B, Rosengren A.

The Swedish CARDioPulmonary BioImage Study (SCAPIS): objectives and design. *J Intern Med.* 2015 Dec;278(6):645–59. doi: 10.1111/joim.12384.

Kylhammar D, Hult L, Blomstrand P, Engström G, Johnson J, Östgren C J, Engvall J.

Global longitudinal strain and mechanical dispersion in the general population aged 50–64 years – Results from the echocardiography study of the Swedish Cardiopulmonary bioimage study (Scapis). Presented at the Scientific sessions of the European Society of Cardiology, Paris Sep 2, 2019.

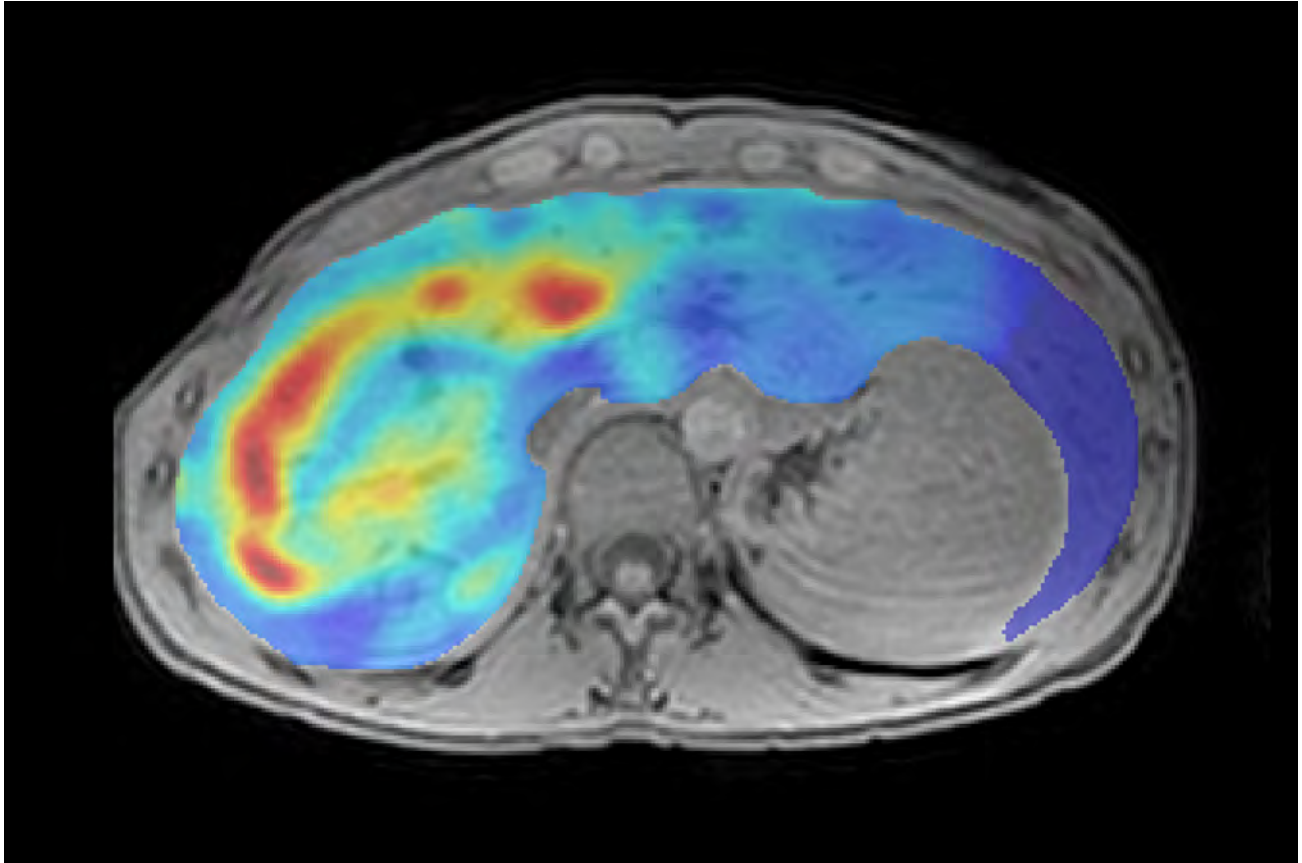


FIGURE. Image showing liver elasticity in a patient with chronic liver disease. Elasticity is a measure of how stiff the liver is and is a measure of fibrosis in the liver.

SCAPIS-Health

Swedish Cardio Pulmonary bioImage Study (SCAPIS), is a large-scale national population study initiated by The Swedish Heart-Lung Foundation and supported by the Wallenberg Foundation. The study is 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 were examined in the study. Of these 5,000 were examined in Linköping. The participants' lungs and cardiovascular system were examined with computed tomography and ultrasound. All the collected data were saved in a knowledge bank, which will be a national resource used for research.

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

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

metabolic disease compared to individual measurements.

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

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

The study subjects was recruited from the SCAPIS cohort. In total 46 individuals with T2DM (as reported in SCAPIS forms) and 46 matched control subjects without T2DM were recruited. Data analysis is ongoing and the plan is that the first HEALTH paper will be published during 2020. ■

MRI

Cardiovascular

Acquisition

AI/Data analytics

Imaging Biomarker

PROJECT INFORMATION

Project Name

SCAPIS-Health

Project Leader

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

Main Project Participants

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Grants

KAW
Swedish Heart-Lung Foundation
Swedish Research Council

Key publications

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

SCAPIS – Microcirculation

The Swedish CARDioPulmonary BioImage Study (SCAPIS) was initiated as a major joint national effort to reduce mortality and morbidity from cardiovascular disease (CVD), chronic obstructive pulmonary disease and related metabolic disorders, all of which are important issues for public health. The main goal was to characterize a Swedish cohort of 30,000 men and women aged 50–64 years to obtain novel information that is relevant in today's environment. The population was

studied in terms of phenotype, environmental and socio-economic influences to identify and treat individuals with cardiopulmonary and metabolic diseases and to optimize the ability to investigate disease mechanisms. SCAPIS capitalizes on the latest developments in imaging that enable direct investigation of subclinical disease in multiple organs and vascular beds. The study was completed at Linköping University in the summer of 2018.

At Linköping University Hospital, we have several add-on investigations

targeting the 5 000 SCAPIS participants included from the region in addition to data collected according to the core study protocol.

In this local add-on project at Linköping University we will use data on the microcirculatory function in the skin. The data is based on advanced laser doppler flowmetry, diffuse reflectance spectroscopy, echocardiography, and determination of pulse wave velocity. The goal is to identify new pathophysiological pathways of atherosclerosis. We will use SCAPIS imaging data from

Computed Tomography

Ultrasound

Cardiovascular

Pulmonary

No Method Development

PROJECT INFORMATION

Project Name

SCAPIS – Microcirculation

Project Leader

Carl Johan Östgren, Department of Medical and Health Sciences, Division of Community Medicine

Main Project Participants

Jan Engvall, Eva Swahn, Anders Persson, Fredrik Nyström, Carl Johan Carlhäll, Lena Jonasson

Grants

Swedish Heart-Lung Foundation

Key publications

Bergström G, Berglund G, Blomberg A, Brandberg J, Engström G, Engvall J, Eriksson M, de Faire U, Flinck A, Hansson MG, Hedblad B, Hjelmgren O, Janson C, Jernberg T, Johnsson Å, Johansson L, Lind L, Löfdahl C G, Melander O, Östgren C J, Persson A, Persson M, Sandström A, Schmidt C, Söderberg S, Sundström J, Torén K, Waldenström A, Wedel H, Vikgren J, Fagerberg B, Rosengren A.

The Swedish CArdioPulmonary BioImage Study: objectives and design. *J Intern Med.* 2015;278 (6):645–59.

Ekström MP, Blomberg A, Bergström G, Brandberg J, Caidahl K, Engström G, Engvall J, Eriksson M, Gränsbo K, Hansen T, Jernberg T, Nilsson L, Nilsson U, Olin AC, Persson L, Rosengren A, Sandelin M, Sköld M, Sundström J, Swahn E, Söderberg S, Tanash HA, Torén K, Östgren CJ, Lindberg E. The association of body mass index, weight gain and central obesity with activity-related breathlessness: the Swedish Cardiopulmonary Bioimage Study. *Thorax.* 2019 Oct;74(10):958–964. doi: 10.1136/thoraxjnl-2019-213349.

Sundström J, Lind L, Lampa E, Angerås O, Bachus E, Bergström G, Carlberg B, Engström G, Engvall JE, Eriksson M, Gigante B, Hagström E, Hjelmgren O, Jansson JH, Jernberg T, Mannila M, Nyström FH, Oldgren J, Persson M, Sandström A, Swahn E, Söderberg S, Torén K, Östgren CJ, Rosengren A. Weight gain and blood pressure. *J Hypertens.* 2020 Mar;38(3):387–394. doi: 10.1097/HJH.0000000000002298.

the coronary and carotid arteries and monitor future cardiovascular events in the cohort to verify our findings.

The results emerging from the current project have the potential to push the boundaries of cardiovascular disease diagnosis, prognosis, and therapy.

The specific aims of the microcirculation project are to clarify the biological pathways of atherosclerosis by linking data from technologies characterizing the function of the micro- and macrovascular bed with direct imaging of the atherosclerotic process in coronary

and carotid arteries. Furthermore, we will validate the clinical relevance of pathways discovered by evaluating the future nonfatal or fatal cardiovascular events in the cohort.

The present project will make it possible to proceed to the next step of exploiting the SCAPIS resource, i.e., analyses of data characterizing the micro- and macrovascular bed to delineate the pathophysiology of atherosclerosis and cardiovascular disease and to improve risk prediction of myocardial infarction and stroke. ■

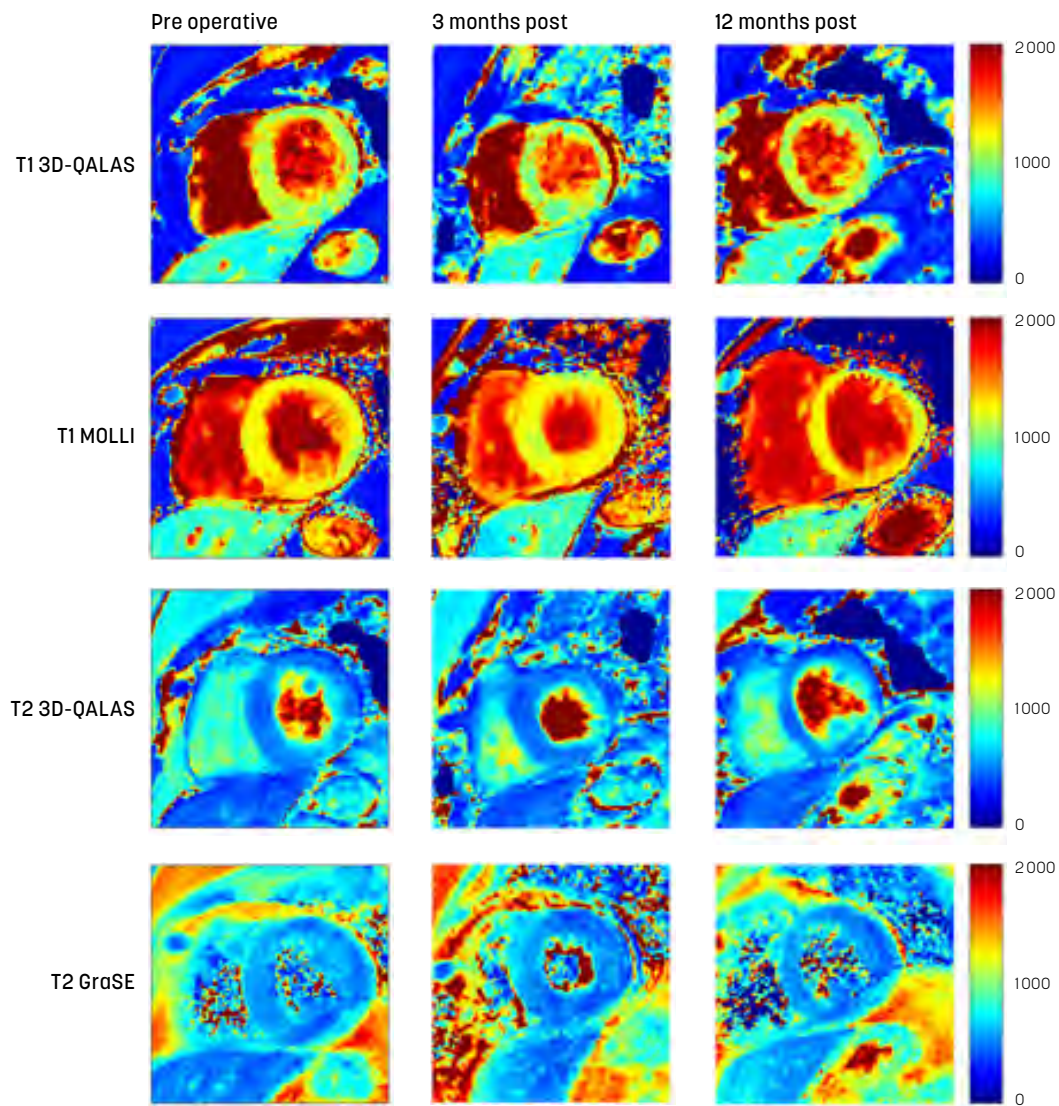


FIGURE. Illustration of mid-ventricular maps with 3D-QALAS, MOLLI, and GraSE in a patient with severe aortic stenosis. The T1 and T2 relaxation times maps are acquired at three different timepoints: before, 3 and 12 months after surgery.

Diffuse Myocardial Fibrosis

Approximately 1800 aortic valve implantations are performed every year in Sweden, the majority due to aortic valve stenosis. Symptoms and/or impairment of left ventricular function are indications for surgery. However, symptoms and ventricular dysfunction occur late in the natural history of aortic valve stenosis. Irreversible impairment of left ventricular function (LVF) is believed to be related to diffuse myocardial fibrosis, which develops during disease progression as the heart compensates and develops hypertrophy. Regional fibrosis is known to cause impaired LVF after myocardial infarction, but data are scarce on how diffuse fibrosis affects cardiac performance and aerobic exercise capacity.

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

and aerobic exercise capacity.

The preliminary results showed that our novel automated assessment support for diastolic function proved to be consistent for the analysis of a larger group of patients with aortic stenosis pre- and postoperatively. The algorithm is freely available for researchers and clinicians on-line (<https://liu.se/en/research/left-ventricular-diastolic-function-decision-support>).

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

This study has a unique design, where we adapt and develop new technology (both for research purposes and clinical use) within echocardiography, cardiopulmonary exercise testing and cmr. We also perform myocardial biopsy in the same patients, making it possible to gain new insights into the functional consequences of fibrosis, the effects of valve surgery, and ultimately, optimize pre- and post-operative treatment for patients with aortic stenosis. ■

MRI

Cardiovascular

No Method Development

PROJECT INFORMATION

Project Name

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

Project Leader

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

Main Project Participants

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

Grants

Swedish Heart-Lung Foundation

Key publications

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

Kvernby S, Rönnerfalk M, Warntjes M, Carlhall CJ, Nylander E, Engvall J, Tamás É, Ebbers T. Longitudinal changes in myocardial T1 and T2 relaxation times related to diffuse myocardial fibrosis in aortic stenosis; before and after aortic valve replacement. *J Magn Reson Imaging*. 2018 Feb 23. doi: 10.1002/jmri.25980.

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

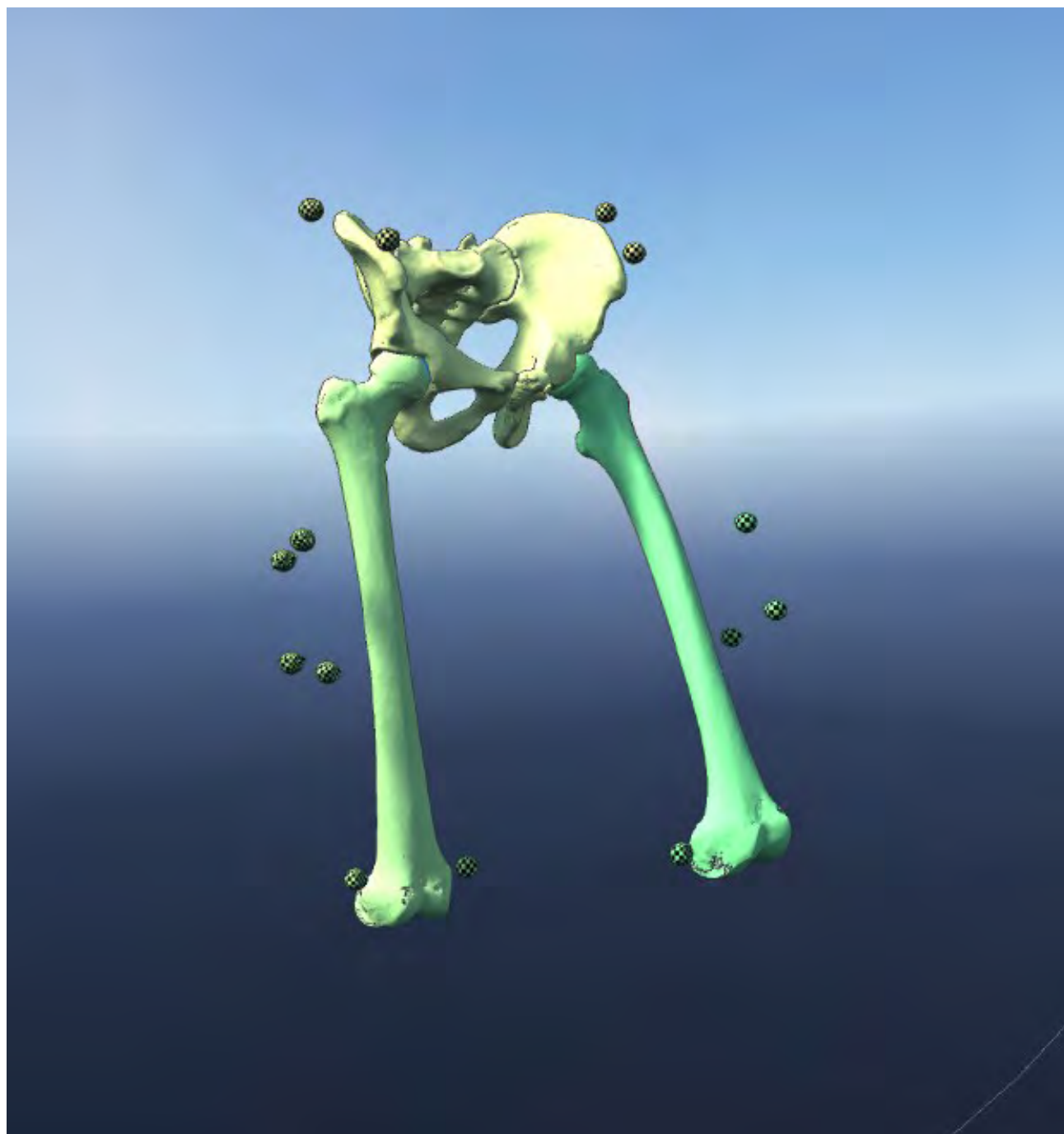


FIGURE. Motion analysis combining patient specific low-dose CT images with traditional motion capture techniques.

PROJECT INFORMATION

Project Name

CT Mocap – Visualizing Musculoskeletal Functional Disorders

Project Leader

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

Main Project Participants

Ludvig Vavruch, Marcus Malmqvist, Abtin Daghigi, Stefan Lindholm

Grants

Vinnova

CT Mocap

CT-mocap is a new method for visualizing the musculoskeletal functional disorders. It is based on the integration of information from a conventional low-dose CT with high quality motion analysis (motion capture). The method allows a patient specific study of skeleton and joints (including the soft tissues seen on CT) during activity.

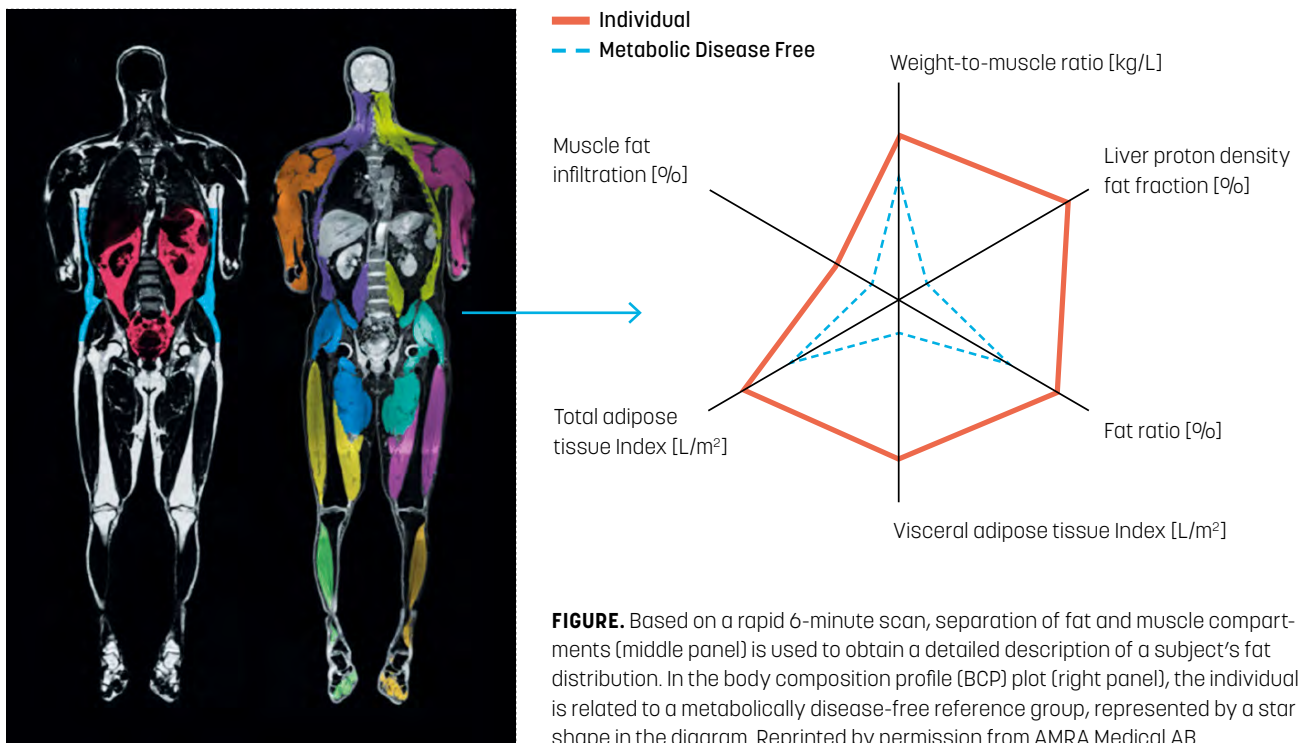
We utilize the CT that is part of the clinical routine (eg before surgery) and then allow the individual to undergo physical examination, as well as perform functional tests in provocative situations. The patient is examined with markers attached to the body's segments (pelvis, femur, lower leg, etc.). The method was developed in the Vinnova funded project PRECIS. New and innovative software has been developed in a collaboration between Sectra, Qualisys and Region Östergöt-

land following an original idea presented by the main applicant.

In order to establish this method in a clinical setting, the software must be further developed to describe the motions and loads of different joint systems in a biomechanically correct way. CT-mocap involves three-dimensional visualization which sets new eligibility requirements on the presentation.

Two biomechanical problem areas must be addressed. The first applies to how joint centers are calculated and the second to the accuracy of the motion analysis, which is influenced by the movement of the markers towards the skeleton (soft tissue artefacts). We have ethical approval for five different applications for our clinical method; femuroacetabular impingement, neuromuscular and idiopathic scoliosis, anterior cruciate ligament injury and femuropatellar knee problems. ■

MRI-Based Body Composition Analysis



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

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

To be able to measure fat accumulation in different parts of the abdomen an image analysis method was combined with knowledge in MR physics. The measurement technique has been refined and can now be used for measurements of fat infiltration in the muscles as well as for muscle volumes, not only in more detail but also for larger parts of the body.

MRI is not in itself a quantitative

method. In the project a postprocessing technique has been developed, which calibrates the images against the fat signal to produce a quantitative result. This technique was patented and placed in the spin-off company AMRA.

AMRA allows the use of an industrial production process that would otherwise not be possible in a research environment. The research group is now in the process of analyzing 100,000 whole body scans.

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

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

MRI

Musculoskeletal

Acquisition

Modeling

AI/Data analytics

Imaging Biomarkers

PROJECT INFORMATION

Project Name

MRI-based Body Composition Analysis

Project Leader

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

Main Project Participants

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

Grants

Medtech4Health, AIDA, 2018–2019

Key publications

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

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

Linge J et al.
On the Definition of Sarcopenia in the Presence of Aging and Obesity – Initial Results from UK Biobank. *The Journals of Gerontology: Series A.* (2019).

Health Effects of Exercise on Postmeno- pausal Women



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

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

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

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

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

In November 2016 we included and randomized the 65:th woman and by March 2017 all women had gone through the 15 weeks of intervention or being in the control group. The results of the 15 weeks study have been analyzed as also the results from blood analyses on blood lipids and oxidative stress. A test-retest investigation has been performed with a number of MRI examinations performed twice.

The study has been prolonged including all measurements after 24 months. During spring 2019 we have investigated the final women who have been long-term compliant to regular exercise and presently compare with women who have been sedentary or less physically active.

The 15-week resistance-training program decreased the frequency of moderate and severe hot flushes among postmenopausal women and could be an effective and safe treatment option to alleviate vasomotor symptoms. ■

MRI

Musculoskeletal

Gynecological

Metabolism

No Method Development

PROJECT INFORMATION

Project Name

Health effects of resistance training on postmenopausal women

Project Leader

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

Main Project Participants

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

Grants

Swedish Research Council

Key publications

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.

Berin E, Hammar ML, Lindblom H, Lindh-Åstrand L, Spetz Holm AC. Resistance training for hot flushes in postmenopausal women: A randomised controlled trial. *Maturitas* 2019;126:55-60.

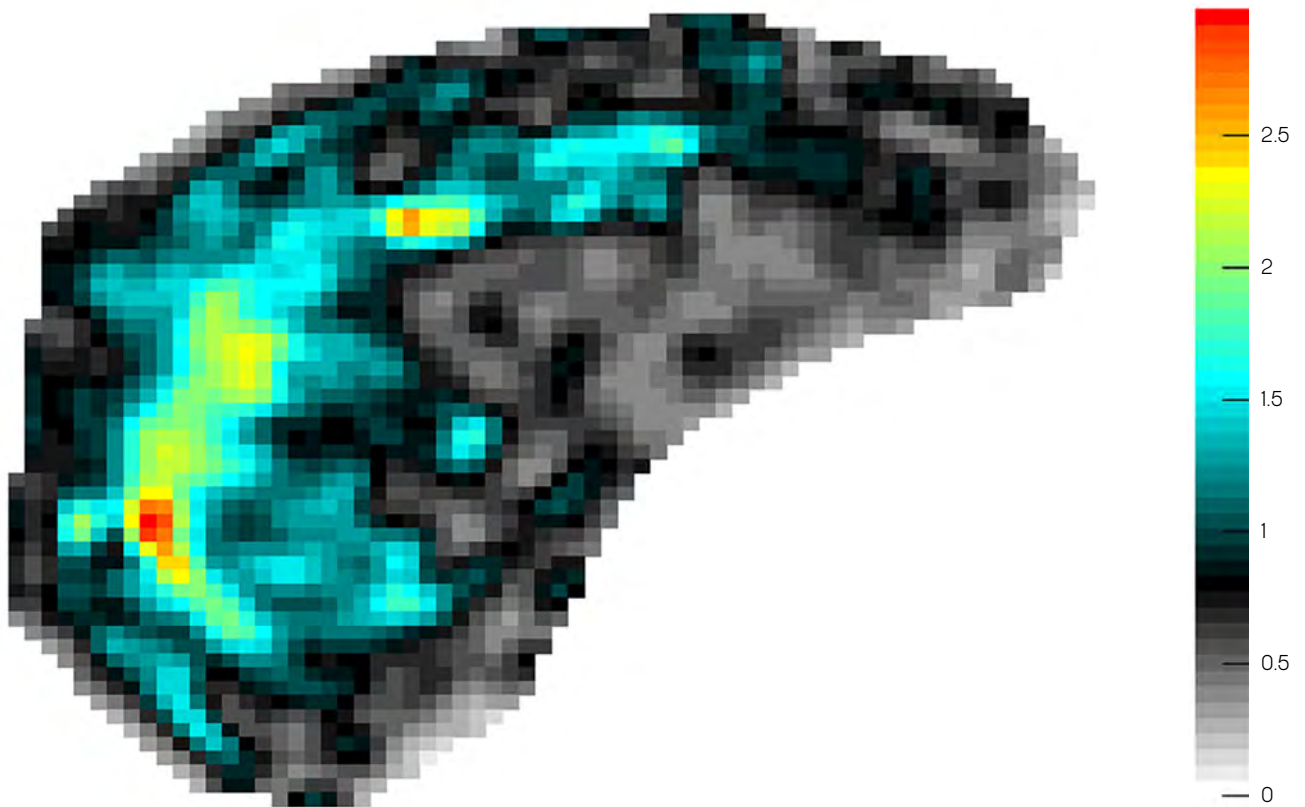


FIGURE. In Magnetic Resonance Elastography, a device placed on the right side of the upper abdomen emits low frequency vibrations during the MR examination. The speed at which the waves travel depend on the mechanical properties of the liver, which makes it possible to measure the elasticity of the liver. The image above shows a map of elasticity measurements. The image on the next page is a standard anatomical MR image through the upper abdomen.

MRI

Other

Cardiovascular

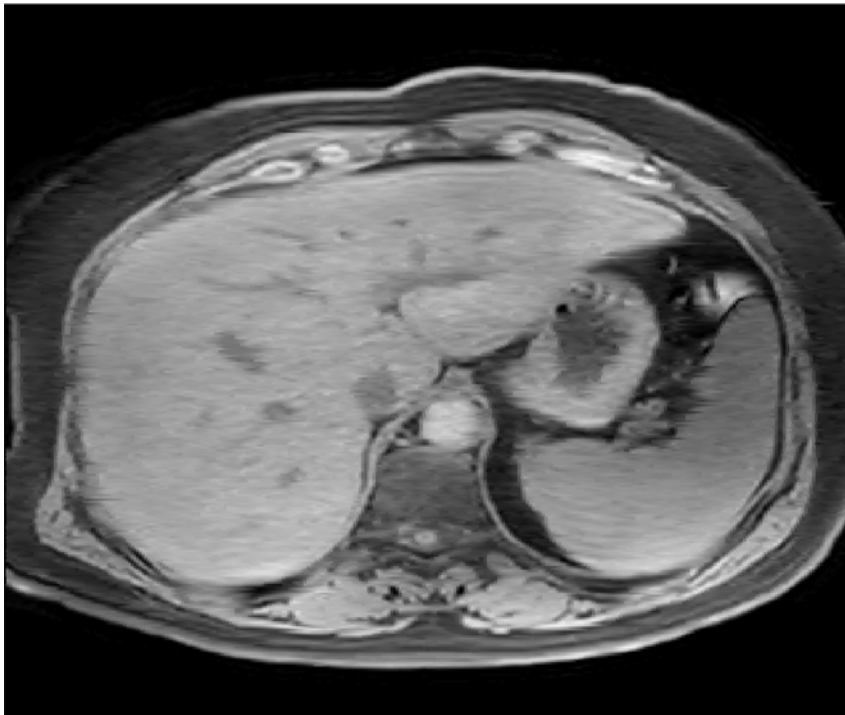
Gastrointestinal

Metabolism

Acquisition

Visualization

Imaging Biomarkers



PROJECT INFORMATION

Project Name

Evaluate Prevalence and Severity of Non-Alcoholic Fatty Liver Disease in Primary Care, EPSONIP

Project Leader

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

Main Project Participants

Stergios Kechagias, Peter Lundberg, Nils Dahlström, Fredrik Iredahl

EPSONIP

In EPSONIP the latest magnetic resonance (MR) imaging techniques are used to investigate 400 patients with diabetes type 2.

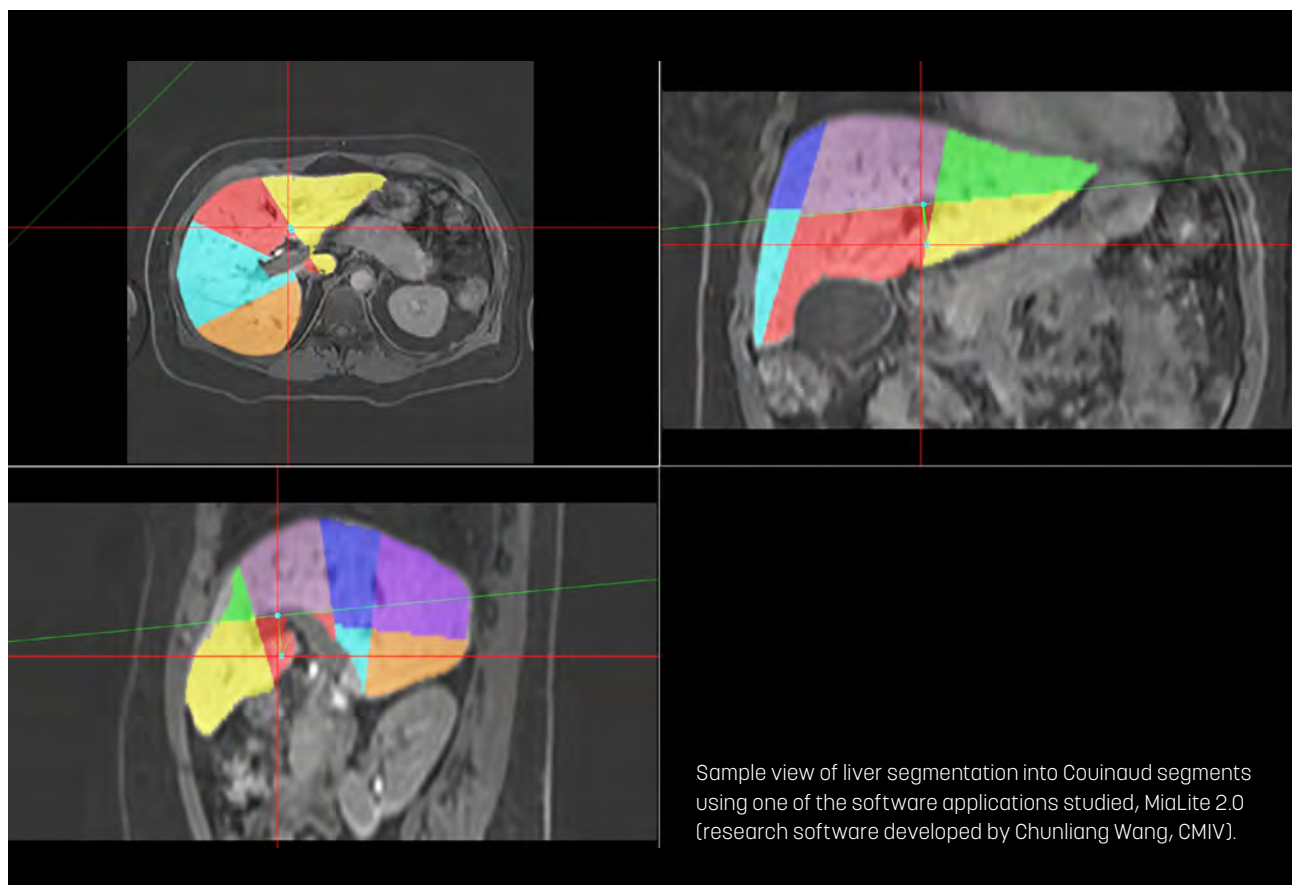
The patients are identified in primary care ensuring a representative selection of typical Swedish diabetes patients. The MR technique can measure body composition and map fat content in different adipose tissue throughout the body, such as intra-abdominal and gluteal. Moreover, we can with great detail measure fat content within several internal organs, such as the liver.

Fatty liver is the most common liver disease worldwide. One in five have fatty liver with a risk of developing diabetes, cardiovascular disease and severe liver disease. Fatty liver is the fastest growing indication for liver

transplantation in Sweden. There is a strong link between diabetes and fatty liver but it is not known how many diabetes patients that are affected. Even though fatty liver is very common, only a minority develop severe liver disease. The main goal of this project is to learn to identify patients with risk of developing severe liver disease.

Fatty liver is closely related to the metabolic syndrome and share several risk factors for developing cardiovascular disease. This project will investigate fat infiltration in the heart as well as measurement of cardiac function using MR imaging. Through EPSONIP we will gain a unique insight into the relationship between fat distribution and development of liver and cardiovascular disease in diabetic patient. ■

Semiautomatic Liver Volume Determination and Segmentation



PROJECT INFORMATION

Project Name

Semiautomatic Liver Volume Determination and Segmentation

Project Leader

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

Main Project Participants

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

A common trait of diffuse liver diseases is that they may lead to the formation of fibrosis, inflammation and ultimately, cirrhosis. Since the liver can regenerate and thus compensate for some damage, liver diseases are often not discovered until at a late stage when there is a loss of liver function. At this stage liver transplantation may be the only available treatment. Patients with malignant liver tumors are often surgically treated by removing the part(s) of the liver with tumors. Measuring the expected liver volume that remains after resection has become standard procedure. To improve treatment planning, adding an evaluation of liver function to the liver volume measurements is desired.

Magnetic resonance imaging (MRI) offers a noninvasive method to monitor liver function using liver specific contrast agents. In developing system biology models for describing liver function, it is important to estimate the total liver volume and preferably also liver segment volumes. Although tools for liver segmentation using datasets from computed tomography have become easily available, useful applications aimed at MRI datasets are lacking. A sub-project within the Liver Function Evaluation project was formed to evaluate available software to measure 3D volumes of late hepatobiliary phase datasets from examinations of patients with diffuse liver disease.

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

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

Another objective is to provide the total liver measurements needed for modeling the individual liver function estimates in quantitative MRI studies and also to introduce the means for segment-based liver function modeling.

In 2016 the in-house application was extended to include segmentation of the liver into the classical Couinaud segments, producing 3D masks defining the shape and volume of each segment. This feature is currently not readily available for MRI datasets in clinical segmentation or surgery planning applications, which rely on CT studies. The measurement of liver segmental volumes will permit segmental liver function assessment in our other liver projects. In 2018, the project began further exploration and testing of new algorithms for automatic segmentation. ■

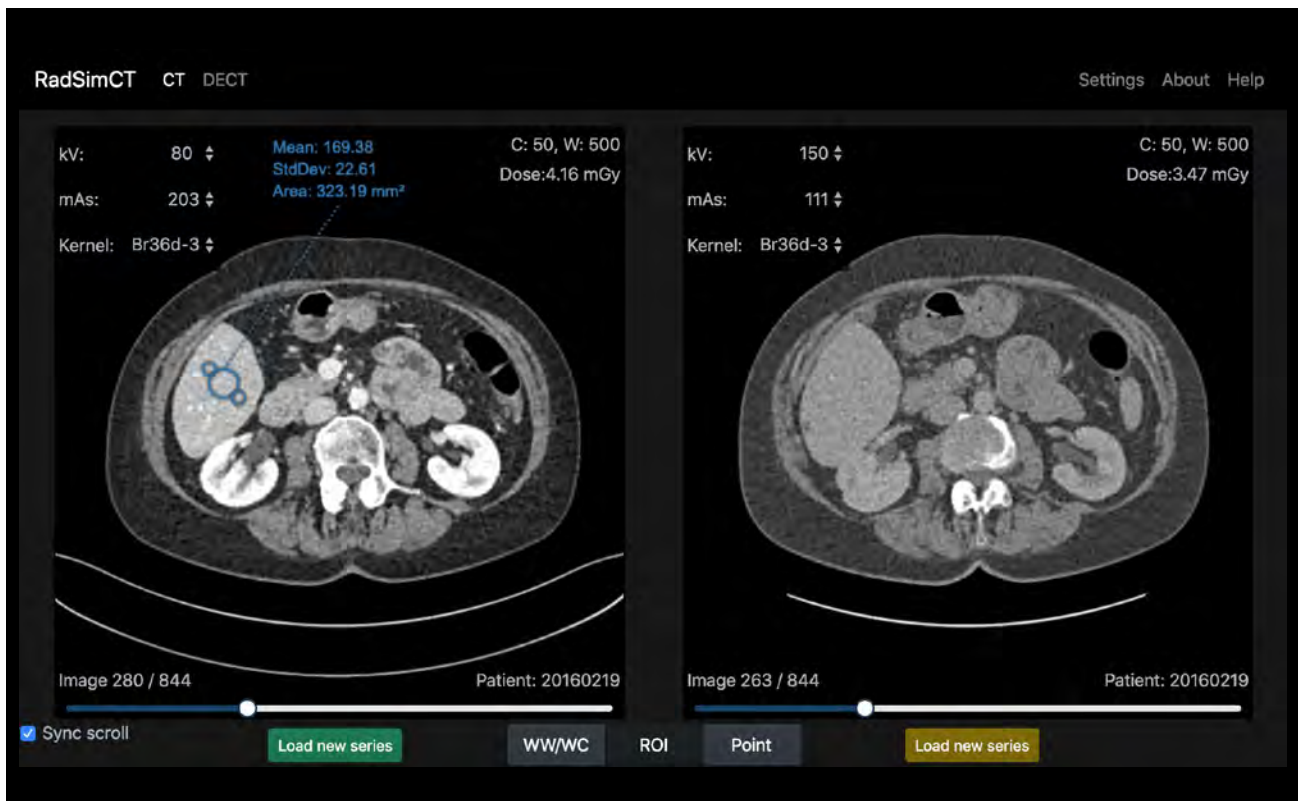
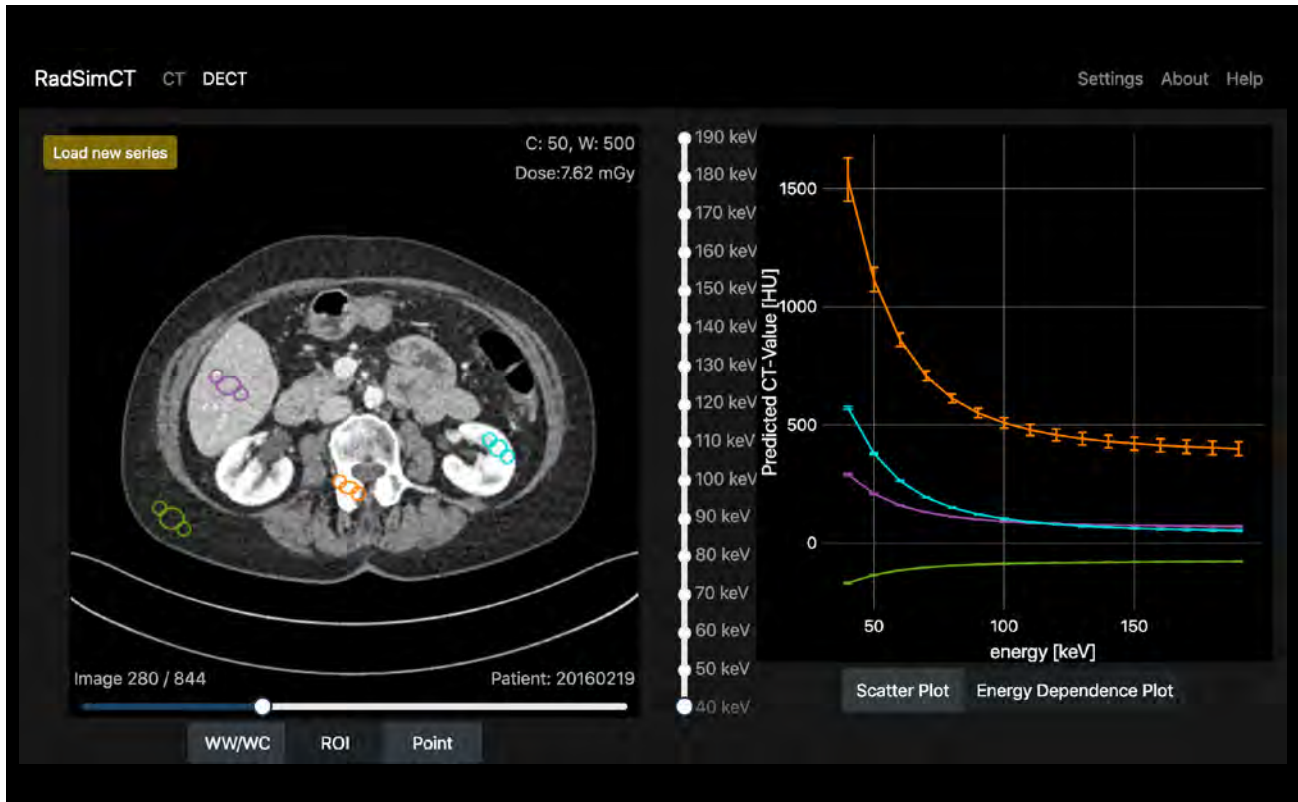


FIGURE. The images show examples from the RadSimCT module.

PROJECT INFORMATION

Project Name

RadSimCT: Simulation Based Training Program for CT Protocol, Iterative Reconstruction and Dual Energy

Project Leader

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

Main Project Participants

Alexandr Malusek, Nils Dahlström, Angie Liu, Filip Landgren, Peter Vorel

Grants

Radiological Society of North America, RSNA

Key publications

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

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

Computer Tomography simulator as a e-learning tool to promote low dose examinations. European Congress in Radiology Vienna 2019.

RadSimCT

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

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

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

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

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

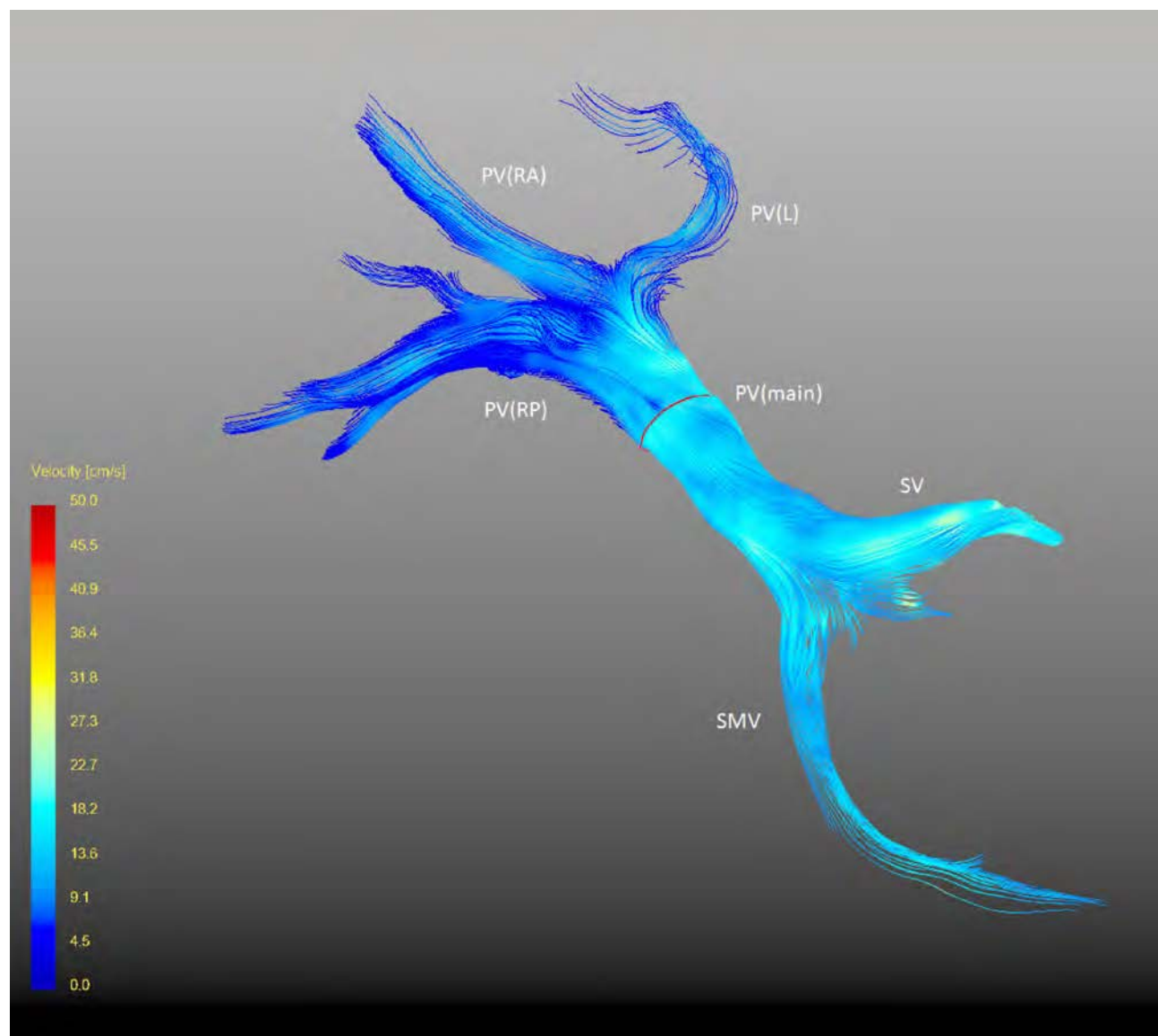


FIGURE. MR-measurements of blood flow in the portal system at 3 T using 4D-flow MRI streamlines visualization. The Portal Vein transports blood from the gastrointestinal tract, the spleen and the pancreas and consists of the Main Portal Vein, here denoted PV(main), which inside the liver divides into the following major branches: PV(RA): Right Anterior branch, PV(RP): Right Posterior branch and PV(L): Left branch. The two major tributaries to the Main Portal Vein are the Superior Mesenteric Vein (SMV) and the Splenic Vein (SV), seen in the lower right corner. Colour signifies the local blood velocity, here showing a lowering of the velocity as the blood travels from the SMV and SV into the liver.

Assessment of Hepatic Function

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

One of the aims of the project is to allow early detection of liver inflammation and fibrosis as proxies for chronic liver disease. Another aim is to be able to understand the consequences of fibrosis and fat storage on up-stream events including portal hypertension.

Portal hypertension is clinically highly significant and early signs are therefore of importance. Quantitative measurement of hepatic blood flow would be useful in the understanding of disease progression in the cirrhotic

liver since the development of liver fibrosis and lipid accumulation constrict the blood flow to the liver.

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

MRI

Gastrointestinal

Acquisition

Imaging Biomarkers

PROJECT INFORMATION

Project Name

Comprehensive Assessment of Hepatic Function in Health and Disease, HEALeD, Techniques for early Disease Detection and Tissue Characterization

Project Leader

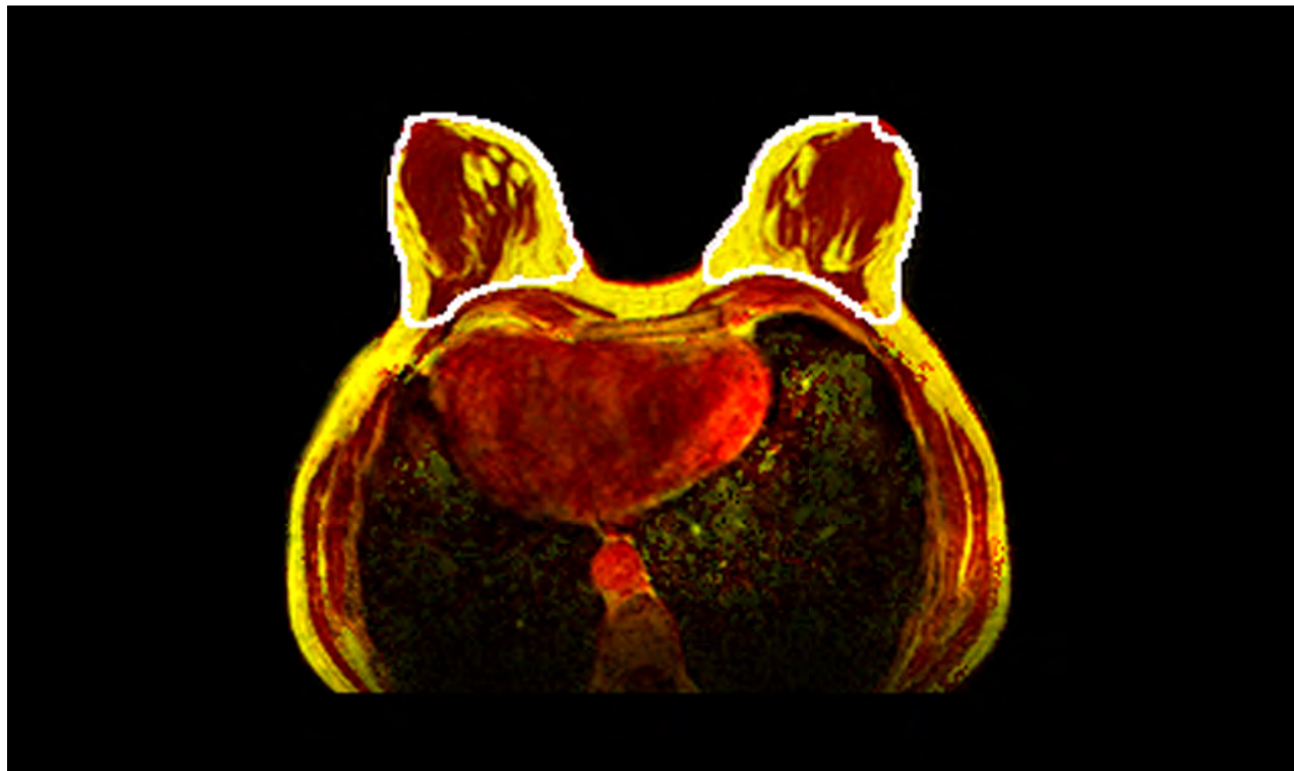
Peter Lundberg, Department of Medical and Health Sciences, Division of Radiological Sciences

Main Project Participants

Stergios Kechagias, Mattias Ekstedt, Nils Dahlström, Markus Karlsson, Bengt Norén, Jens Tellman, Christian Simonsson, Frederik Testud

Grants

Swedish Research Council
2015–2018/2019



MR Mammography

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

Dense breast tissue contains higher amounts of stroma, including collagen, and less fat tissue. Conflicting results regarding a difference in the amounts of epithelial cells have been reported,

although it varies only between 1–6% and the proliferation of these cells is also very low. Hence, the underlying biological mechanism(s) of a higher breast cancer risk of dense breast tissue is to date unexplored.

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

larly use anti-inflammatory drugs.

Despite the wide use of mammography as a general screening tool for breast cancer, this method has a painfully high false-negative rate (about 10–25%).

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

MRI

Oncology

Metabolism

Acquisition

Modeling

Imaging Biomarkers

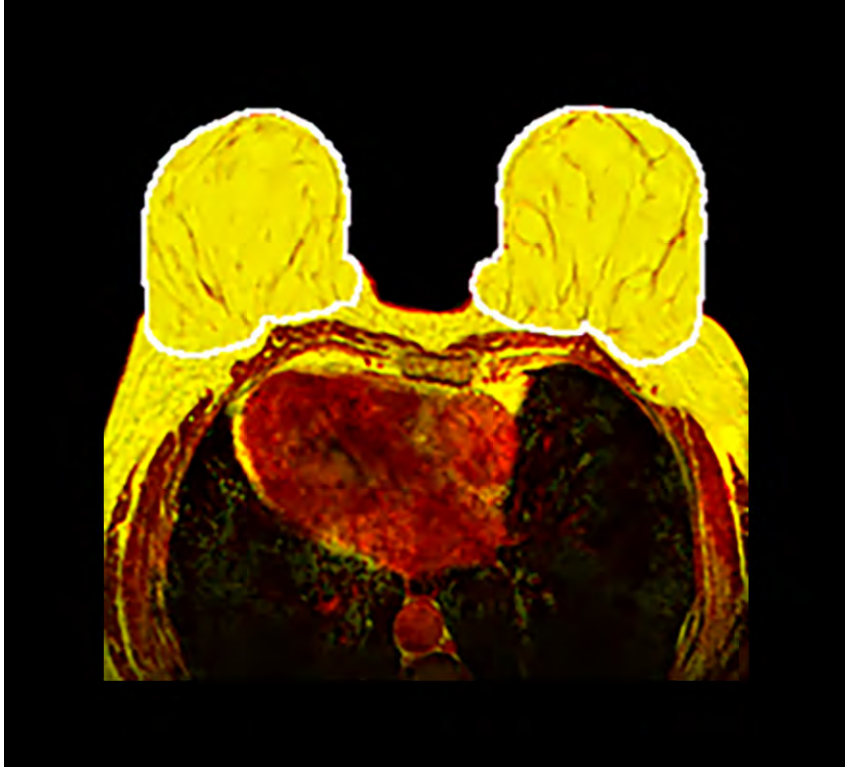


FIGURE. MR-quantification of lean tissue fraction in postmenopausal women attending the regular mammography screening program. The images are representative for dense (left page) and non-dens (above) breasts.

interesting tool for clinical research on breast cancer risk factors.

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

The aims of BREASA are to further validate a comprehensive MR proto-

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

PROJECT INFORMATION

Project Name

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

Project Leader

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

Main Project Participants

Magnus Borga, Charlotta Dabrosin, Olof Dahlqvist Leinhard, Thobias Romu, Mikael Forsgren, Johan Kihlberg, Pantelis Gialias, Anna Rzepecka

Grants

LiU-Cancer
The Swedish Cancer Society

Key Publications

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

PROJECT INFORMATION

Project Name

Liver Function Evaluation

Project Leader

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

Main Project Participants

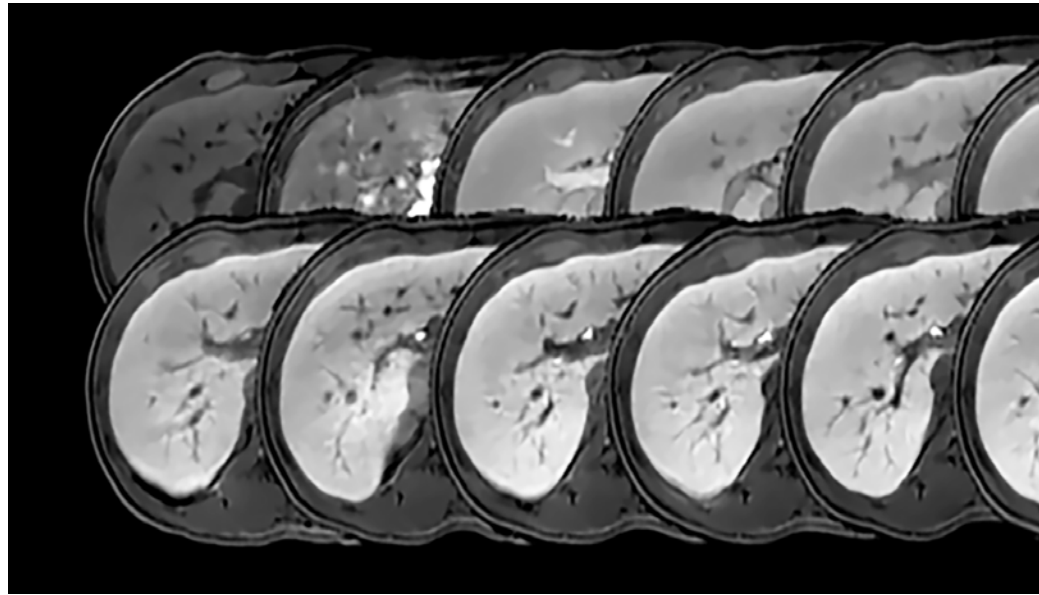
Stergios Kechagias, Mattias Ekstedt, Per Sandström, Olof Dahlqvist Leinhard, Nils Dahlström, Mikael Forsgren, Markus Karlsson, Thobias Romu, Patrik Nasr, Johan Kihlberg, Anna Lindhoff Larsson, Gunnar Cedersund, Bengt Norén, Torkel Brismar, Martin Henriksson, Lars-Åke Levin, Wolf Bartholomä

Grants

Swedish Research Council
2015–2018/2019

POPULAR SCIENTIFIC SUMMARY

Peter Lundberg



Liver Function Evaluation

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

Many malignant liver diseases are diagnosed when they are in an advanced stage and the liver may be seriously damaged. At that time, surgery or liver transplantation is often

the only curable treatment option. In order for the patient to survive a liver tumor operation, a healthy piece of the liver has to be left in the body. The liver is then growing during 4–5 weeks to regain almost full size and function. The first week after the surgery is a critical time since the small sized liver has to manage the job of a full liver.

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

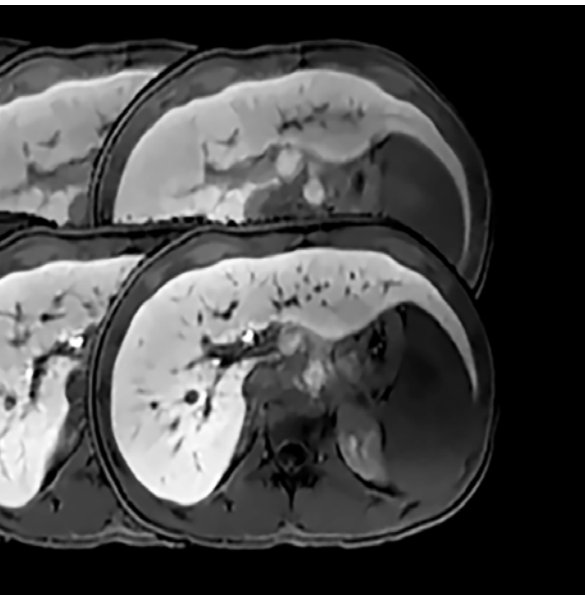


FIGURE. MR images of the liver before and at several time points after injection of contrast agent. The liver becomes brighter as more contrast agent is accumulated.

size and function in the liver residue more patients could be surgical candidates.

With the help of MR it is possible to measure several parameters in the liver without invasive procedures. The MR also enables a better overview of the liver status as a whole compared to biopsies, as they only show status at the location where the sample is taken. If the biopsy is extracted from the wrong area there is a risk that important information is overlooked.

The magnetic resonance technology may, among other things, be used to measure the amount of fat in the liver, measure the uptake of a contrast agent to get an idea of how well the liver works and measure levels of many

different elements, including iron and phosphorus compounds. In this project multimodal methods for analyzing the liver is developed.

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

MRI

Digital Microscopy

Musculoskeletal

Gastrointestinal

Metabolism

Acquisition

Modeling

AI/Data analytics

Simulation

Imaging Biomarkers

Key publications

Karlsson M, Ekstedt M, Dahlström N, Norén B, Forsgren MF, Ignatova S, Dahlqvist Leinhard O, Kechagias S, Lundberg P (2019).

Liver $R2^*$ is affected by both iron and fat: A dual biopsy-validated study of chronic liver disease. *J Magn Reson Imaging*. 2019 Jan 13. doi: 10.1002/jmri.26601.

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

Using a 3% Proton Density Fat Fraction as a Cut-Off Value Increases Sensitivity of Detection of Hepatic Steatosis, Based on Results From Histopathology Analysis. *Gastroenterology*. 2017 Jul;153(1):53–55. e7. doi: 10.1053/j.gastro.2017.03.005. Epub 2017 Mar 9.

Homeyer A, Nasr P, Engel C, Kechagias S, Lundberg P, Ekstedt M, Kost H, Weiss N, Palmer T, Hahn HK, Treanor D, Lundström C (2017).

Automated quantification of steatosis: agreement with stereological point counting. *Diagn Pathol*. 2017 Nov 13;12(1):80. doi: 10.1186/s13000-017-0671-y.

Detection and Neurological Effects of Manganese



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

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

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

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

functions, increased tremor and an increased frequency of neuropsychiatric symptoms among groups of manganese exposed workers at significantly lower exposure levels than 1 mg/m³.

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

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

MRI

Neurology

Acquisition

Imaging Biomarkers

PROJECT INFORMATION

Project Name

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

Project Leader

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

Main Project Participants

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

Grants

FORTE

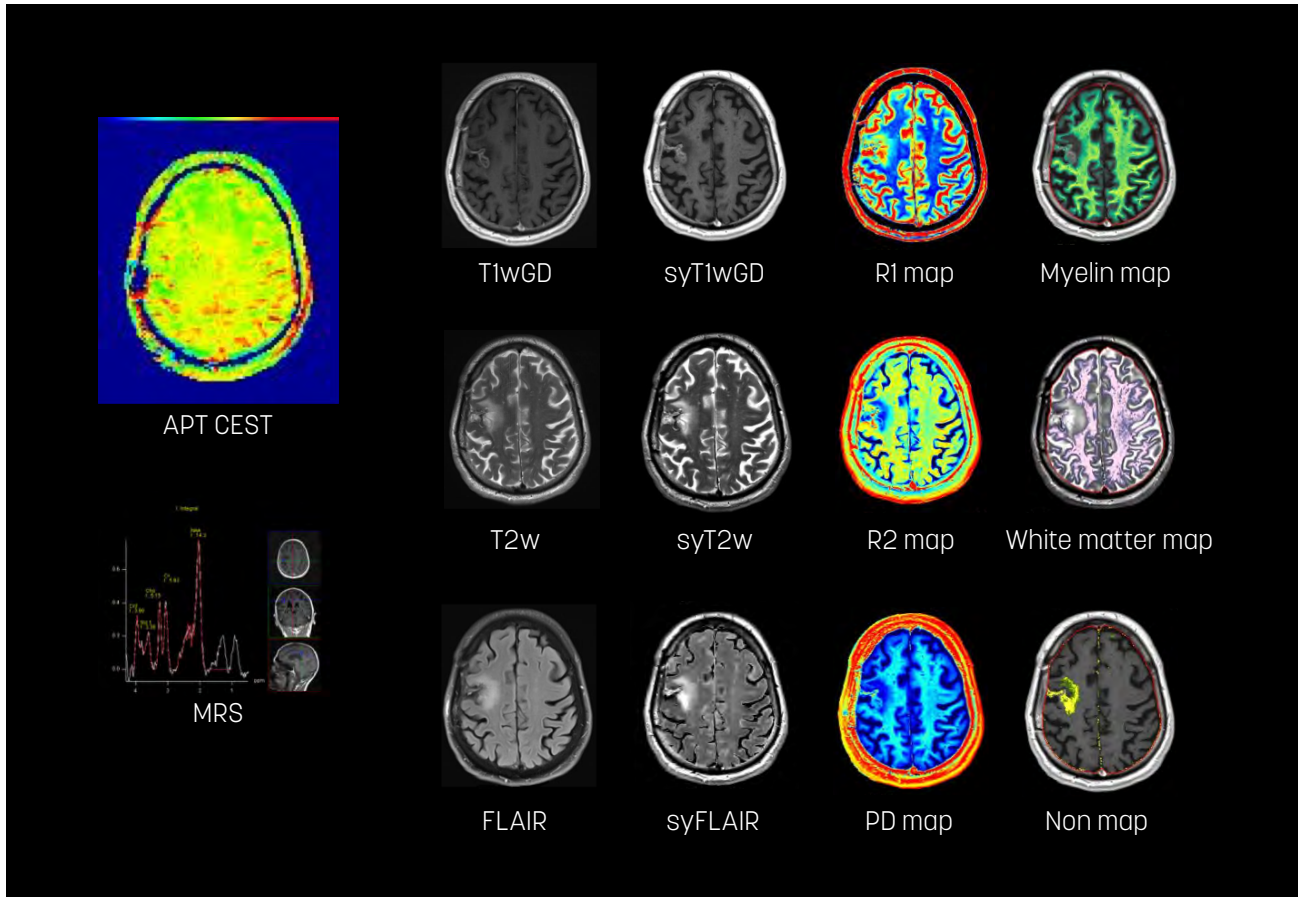


FIGURE. Multi-parametric quantitative MR-data of glioma patient with ongoing pseudoprogression.

Investigating Neurological Disease Using APT-CEST

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

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

from tumor progression is essential.

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

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

MRI

Neurology

Oncology

Acquisition

Imaging Biomarkers

PROJECT INFORMATION

Project Name

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

Project Leader

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

Main Project Participants

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

Grants

Strategic Cancer Research

Key publications

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

Blystad I, Warntjes JBM, Smedby Ö, Lundberg P, Larsson E-M, Tisell A (2017). Quantitative MRI for Analysis of Peritumoral Edema in Malignant Gliomas, PLoS ONE, 2017 May 23;12(5):e0177135. doi: 10.1371/journal.pone.0177135. eCollection 2017. PMID: 28542553.

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

SouthEast Sweden Neuro inflammation Cohort

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

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

There are an increasing number of immunomodulatory treatments available for inflammatory active MS, but guidelines on how these potent thera-

pies should be used are often lacking as are data on long-term outcome and side-effects of these drugs.

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

MS brain lesions cannot be detected by conventional non-quantitative MR. This advocate a shift from conventional MRI to the use of more advanced MR-methods including quantitative MRI methods (qMRI) like magnetic resonance spectroscopy (MRS). qMRI can be used for volume determination of grey and white matter, cerebrospinal fluid (CSF) and automatic lesion measurements in MS. Such accurate measures are critical when determining the overall atrophy of the brain.

More specifically, qMRI can be used to create myelin concentrations maps that may be useful in determining the level of disease progression, at a regional or global level.

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

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

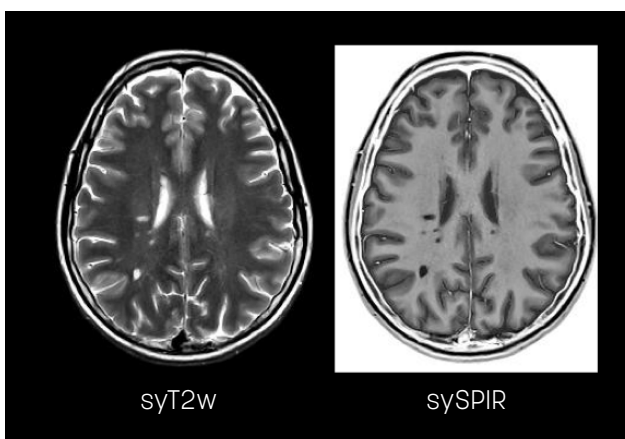
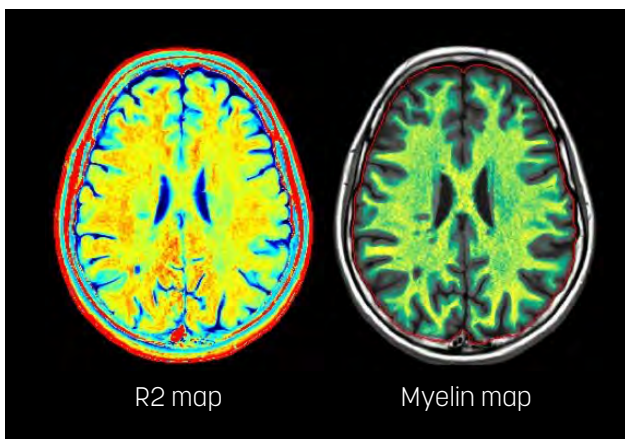
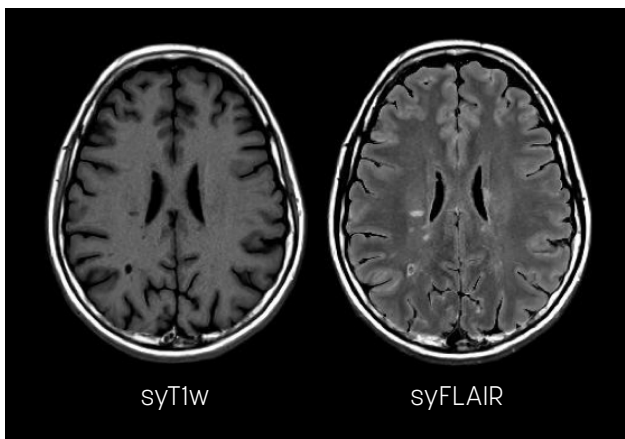
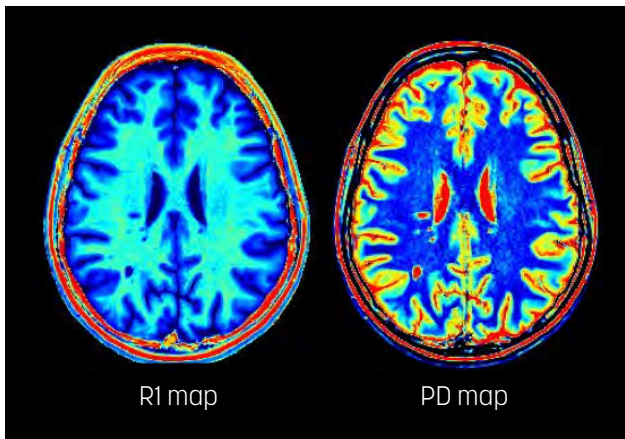


FIGURE. Quantitative maps and synthetic MR-images of MS-patient. All images generated from one 6 min scan.

MRI

Neurology

Acquisition

Imaging Biomarkers

PROJECT INFORMATION

Project Name

SouthEast Sweden Neuroinflammation Cohort (SESNIC)

Project Leader

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

Main Project Participants

Johan Mellergård, Peter Lundberg, Jan Ernerudh, Ida Blystad, Charlotta Dahle, Magnus Vrethem, Angie Liu, Jonas Lind, Maria Kristoffersen Wiberg, Irene Håkansson, Kristina Söderberg

Grants

Swedish Research Council

Key publications

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

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

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

Localization of Seizure Onset Zone in Epilepsy

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

Epilepsy is a disorder with uncontrolled electric activity in the cortex of the brain. In most people with epilepsy, the seizures are controlled by medication. About 30 % of the patients continue to have seizures despite medication with one or more antiepileptic drugs. The disease is then defined as medically refractory and some of these patients are evaluated for epilepsy surgery. Epilepsy surgery is a treatment option that can cure patients with epilepsy. In most cases, a small part of the brain is re-

sected. Before this operation, it is very important to define the area where the seizures starts, called the seizure onset zone. There are many different methods such as MRI (structural lesion), EEG (electrical activity), PET (metabolism) and SPECT (blood flow) used to localize this zone. Sometimes invasive methods like intracranial EEG must be used.

Combined EEG-fMRI allow mapping of BOLD (blood oxygen level dependent) signal changes correlated to epileptiform discharges in the EEG. The electrical discharges in the cortex that is typical for epilepsy correlates to localized changes in oxygen consumption and blood flow, which alters the BOLD-signal (the hemodynamic response function). The EEG defines the time for epileptiform discharges and fMRI is recorded continuously. Studies in other centers have concluded that this method can accurately localize the seizure onset zone. It is difficult to record EEG of good quality in the MR scanner because of artifacts induced by the magnetic and electromagnetic

fields. Special equipment is necessary to be successful in recording a good quality EEG in the MR scanner. CMIV and The Department of Clinical Neurophysiology at the University Hospital in Linköping has the equipment for recording of EEG in the MR scanner.

EEG is recorded using an MR safe EEG cap with 64 electrodes during 30 minutes of fMRI scanning. Offline analysis of EEG is performed to identify epileptiform discharges and timing of these events. fMRI data is analyzed with different hemodynamic response functions in relation to the events in EEG. This gives maps with the strongest BOLD changes.

20 adult patients with medically refractory focal epilepsy who are evaluated for epilepsy surgery are included in the study. The collection of data started in September 2019 and so far, four healthy persons and four patients with epilepsy have been examined. In two of the patients, we recorded epileptiform activity in the EEG and BOLD responses can be analyzed. ■

PROJECT INFORMATION

Project Name

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

Project Leader

Hans Lindehammar, Department of Clinical Neurophysiology, Region Östergötland

Main Project Participants

Helena Gauffin, Mats Svantesson, Robin Kämpe, Paul Hamilton

Grants

Margarethahemmet

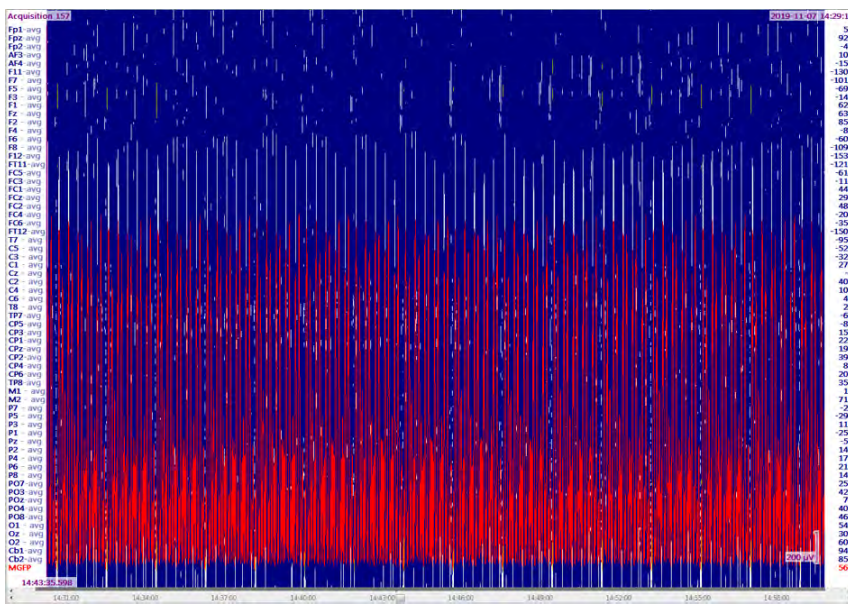


FIGURE 1. EEG recorded in the MR scanner during scanning.

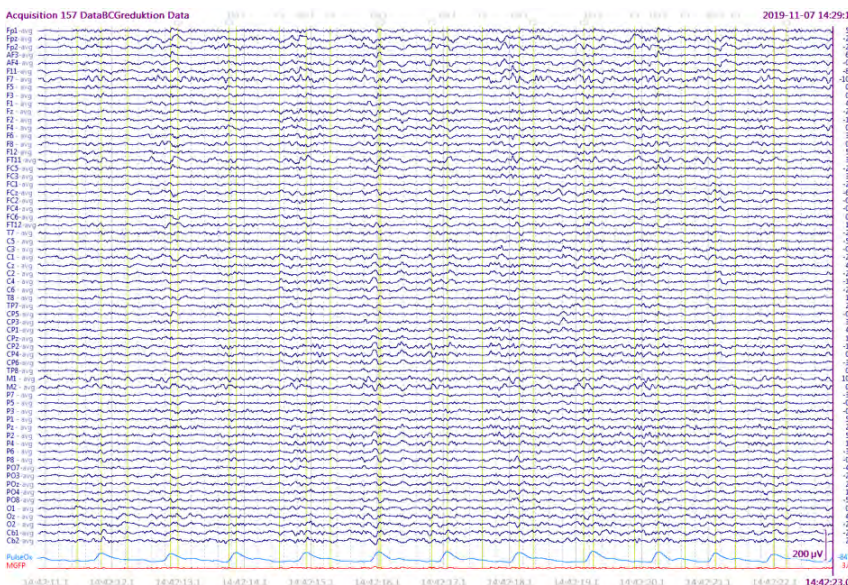


FIGURE 2. EEG recorded in the MR scanner during scanning after "cleaning" of artifacts.



FIGURE 1. The Default Mode Network during resting state fMRI scan.

Meditation at Mild Cognitive Impairment

The earliest stage of memory loss in Alzheimer's disease (AD) is termed mild cognitive impairment (MCI), which also encompasses patients with normal age-related cognitive decline. Physicians are currently lacking accurate biomarkers, non-invasive diagnostic methods, and preventative measures for MCI patients, which are essential to impede subsequent neuron loss and patient decline.

Studies employing fMRI techniques have shown that the anatomical regions of neuron loss and plaque deposition in AD overlap with a constellation of regions collectively referred to as the

default mode network (DMN). DMN exhibits synchronous activity during thought processing. Regions of the DMN are activated during specific cognitive processes such as autobiographical memory, self-reflective thought, rumination, envisioning future events, daydreaming, and considering the thoughts and perspectives of others. This intriguing network has been called the psychological "seat of self" and is an important component in the cognitive identification of self. Thereby, neurodegeneration in these regions sheds light on AD clinical symptoms described as a "loss of self", clearly designating this network as a focal point for diagnostics

and therapeutic intervention.

In healthy individuals, DMN activity has been anti-correlated with task-positive networks (TPNs). In other words, when a healthy individual engages in a specific task, DMN activity, such as rumination and daydreaming, should be reduced. Rather, while performing a task in fMRI, MCI patients exhibit hyperactivity within regions of the DMN.

As research strengthens the link between pathology and psychology, interest has been directed toward non-pharmacological means of altering hyperactive patterns of behavior within the DMN. Meta-analyses examining the specific neurocorrelates of meditation

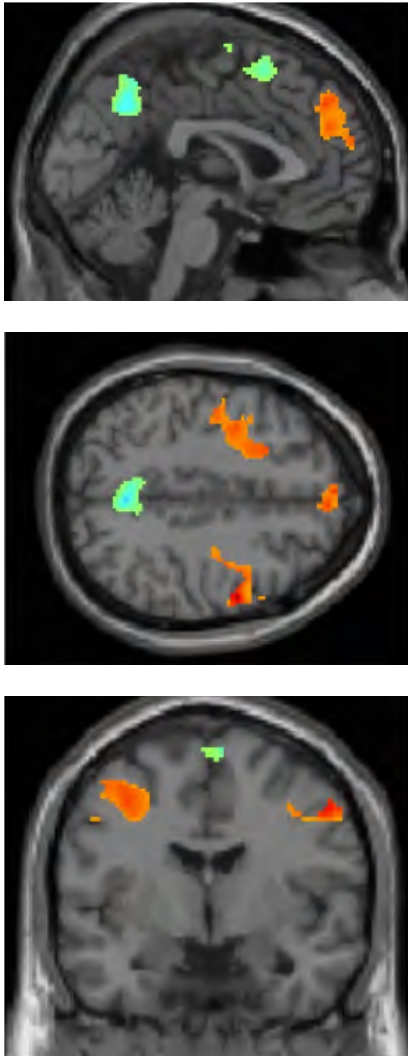


FIGURE 2. Green and red activations and deactivations respectively showing the increase in DMN activation of the posterior cingulate cortex during meditation on breath versus resting state fMRI.

have shown reductions in DMN activity to be a primary outcome of practice. By employing real-time fMRI feedback, individuals have been trained to use meditation to reduce DMN activations. This ability to reduce DMN activity through the conscious training of attention, directly reduces hyperactive neuron firing in these regions, restoring DMN activity to normal levels.

To date the project has conducted a pilot study with a group of elderly patients with MCI and their nearest caretakers. All participants attended an eight-week mindfulness course including home assignments and recorded meditation exercises. Parti-

cipants underwent MRI scans both before and after the course so that structural and functional changes could be investigated in addition to a number of questionnaires on memory, cognition, and quality of life resulting from meditative training. Analysis of the results is ongoing.

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 while providing a new perspective on the value of the present moment. ■

MRI

Neurology

Acquisition

Modeling

PROJECT INFORMATION

Project Name

Mindfulness Meditation Practice for Elderly Patients with Mild Cognitive Impairment (MCI)

Project Leader

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

Main Project Participants

Maria Engström, Birgitta Andersson, Maria Nordell, Inger S. Rehn, Elisabet Classon, Katarina Nägga, Jan Marcusson

Grants

FORSS
Azhiemersfonden
Stiftelsen för Gamla Tjänarinnor

Key publications

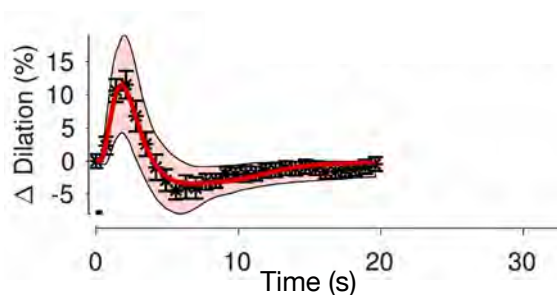
Simon R, Pihlsgård J, Berglind U, Söderfeldt B, Engström M. Mantra meditation suppression of default mode beyond an active task: a pilot study. *Journal of Cognitive Enhancement* 2017.

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

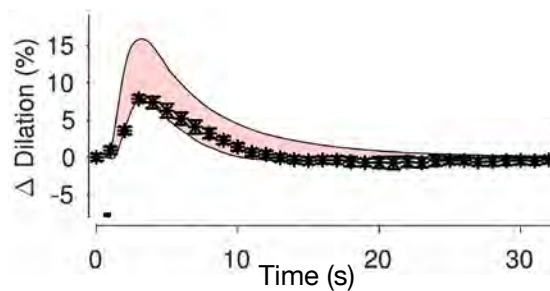
Engström M, Pihlsgård J, Lundberg P, Söderfeldt B. Functional magnetic resonance imaging of hippocampal activity during silent mantra meditation. *Journal of Alternative and Complimentary Medicine*, 2010;16:1253–1258.

Image-Based Biomarkers of Brain Disorders

CURRENT STATUS



A. Model validation & data explanation



B. Prediction of new data

AIMS FOR THE FUTURE



C. Explanation of fMRI data

D. Disease biomarkers

FIGURE. Project description. The current status of the project is that we have developed a mathematical model that mechanistically explain experimental data (A) and predict new data that was not used for model training (B). Modelling and images: Sebastian Sten, submitted manuscript. Experimental data on changes in blood vessel diameter in response to optogenetic stimuli from Uhlirova et al. (Elife, 2016). Future aims are to explain fMRI data (C) and to define model-based imaging biomarkers (D). Images from Georgiopoulos et al. (NeuroImage Clinical, 2019).

With functional magnetic resonance imaging (fMRI) we can visualise brain areas that are activated by certain tasks or sensory stimuli. Despite the wide use of fMRI in both research and clinic, the biological mechanisms behind the visualised brain activation are largely unknown. This means that we have only little knowledge about the relation between activated neuronal cells and the subsequent changes in blood oxygenation that underlie the blood oxygen level dependent (BOLD) response in fMRI.

This lack of knowledge can be overcome by mathematical modelling and systems biology, where different hypotheses describing e.g., excitatory and inhibitory neurotransmitters are translated to mathematical equations (= models). These models are tested against experimental data: if a model cannot explain data the hypothesis is rejected, if a model can explain data it is further investigated and tested against new data. In this way, we can deepen our knowledge about the mechanisms behind the BOLD response in fMRI, and we can also predict and simulate new fMRI data.

We have shown that a mechanistic model based on the influence of neurotransmitters on the brain's blood flow can both explain and predict fMRI data. Importantly, we have rejected the previous hypothesis of brain metabolism being the driving force behind fMRI. In addition, the BOLD response can be both positive and negative with respect to baseline. Positive signals are

strongly correlated to neuronal activity, but less is known about the negative signals. We have shown that neural inhibition can explain these negative signals, thus proving a more complete explanation of fMRI data.

Our modelling approach can advantageously be used to study pharmacological effects. We have shown that working memory activation in certain brain areas are influenced by the inhibitory GABA-modulator diazepam. At diazepam administration, the BOLD response changes from positive to negative and this can be explained by enhanced GABA effect on the calcium influx in neuronal cells.

Research during 2019 has been focused on explaining the interactions between excitatory pyramidal cells and inhibitory interneurons, as well as explaining the effects of an anesthetic agent. In addition, we have modelled mechanisms that regulate the brain's blood flow and blood volume in different blood vessels, and in this way we are able to explain multiple data-sets from different experimental conditions.

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

MRI

Neurology

Modeling

AI/Data analytics

Simulation

Imaging Biomarkers

PROJECT INFORMATION

Project Name

Image-Based Biomarkers of Brain Disorders

Project Leader

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

Main Project Participants

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

Grants

Swedish Research Council 2019–2022
Swedish Brain Foundation 2018–2020

Key publications

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

Lundengård K, Cedersund G, Sten S, Leong F, Smedberg A, Elinder F, Engström M. Mechanistic mathematical modelling tests hypotheses for the neurovascular coupling in fMRI. *PLoS Computational Biology*, DOI:10.1371/journal.pcbi.1004971, 2016.

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

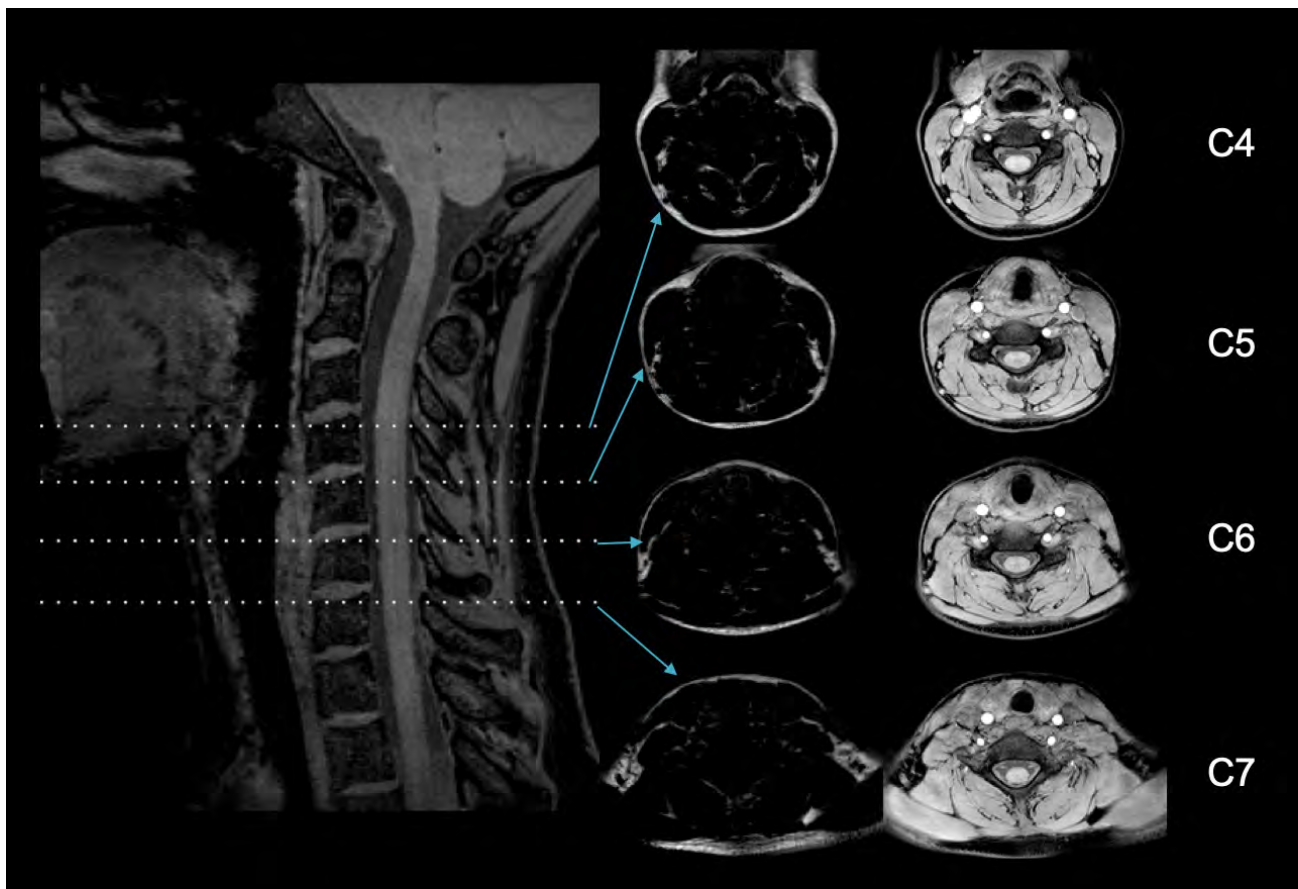


FIGURE. A sagittal section and four axial section (at cervical levels C4, C5, C6 and C7) of a fat and water separated volume over the neck. The volumetric resolution is $0.75 \times 0.75 \times 0.75$ in order to see all the small muscles in the neck.

Whiplash Associated Disorders

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

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

The participants is a sub-group (n=30) of individuals recruited from an ongoing randomized controlled study (RCT). Measurements in this experimental prospective study will be made at baseline (before intervention)

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

MRI

Neurology

Imaging Biomarkers

PROJECT INFORMATION

Project Name

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

Project Leader

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

Main Project Participants

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

Grants

Swedish Research Council
Vinnova

Pain Mechanisms in Widespread Pain

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

mechanisms is mainly lacking.

In the first part of this project we investigated the function (connectivity) of some of the networks in the brain with functional magnetic resonance imaging (fMRI) i.e. the default mode network (DMN) and the salience network (SN). An important result was that the connectivity within the DMN was decreased and connectivity within the SN was increased for CWP. The anterior insula is part of the SN and plays a key role in switching between internally and externally oriented tasks. Thus, the insula has a

reflective role and can switch between monitoring subjective feelings such as emotions and paying attention to external events.

In a second on-going part of the project the brain networks are investigated in fibromyalgia patients and healthy controls. In addition, clinical characteristics (e.g. pain intensity, psychological distress, quality of life etc.), fitness level, pain sensitivity and biochemical alterations in blood, muscles and fat tissues are investigated.

An important research question is if there exist associations between pe-

MRI

Neurology

Musculoskeletal

Acquisition

Imaging Biomarkers

PROJECT INFORMATION

Project Name

Pain Mechanisms in Chronic Widespread Pain Including Fibromyalgia

Project Leader

Björn Gerdle, Department of Medical and Health Sciences, Division of Community Medicine

Main Project Participants

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

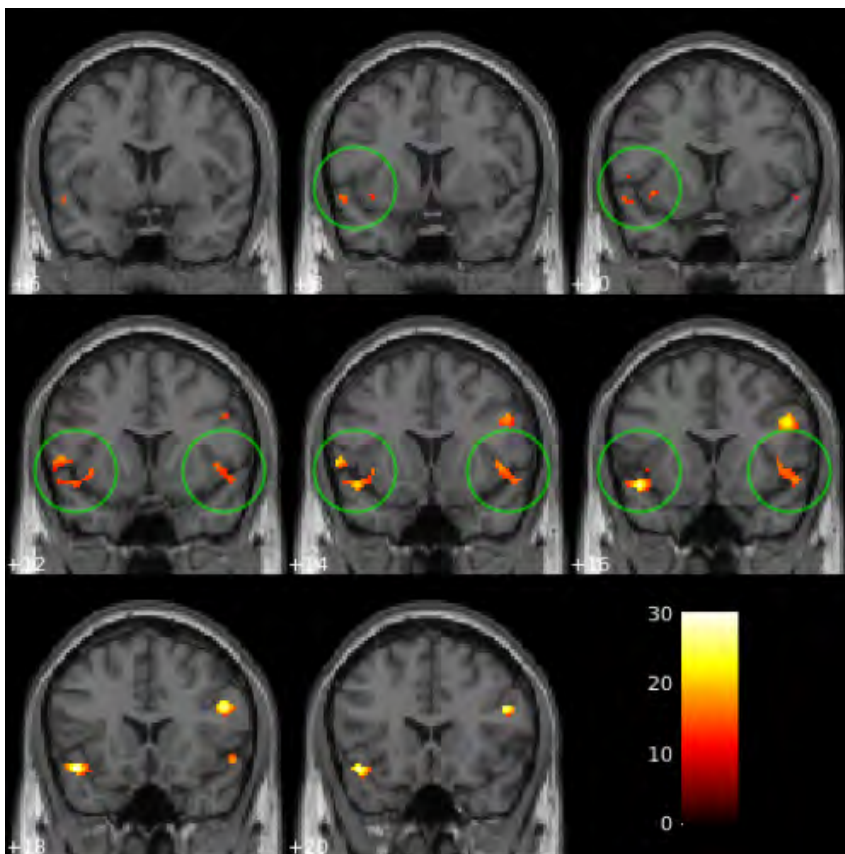
Grants

Swedish Research Council FORSS

Key publications

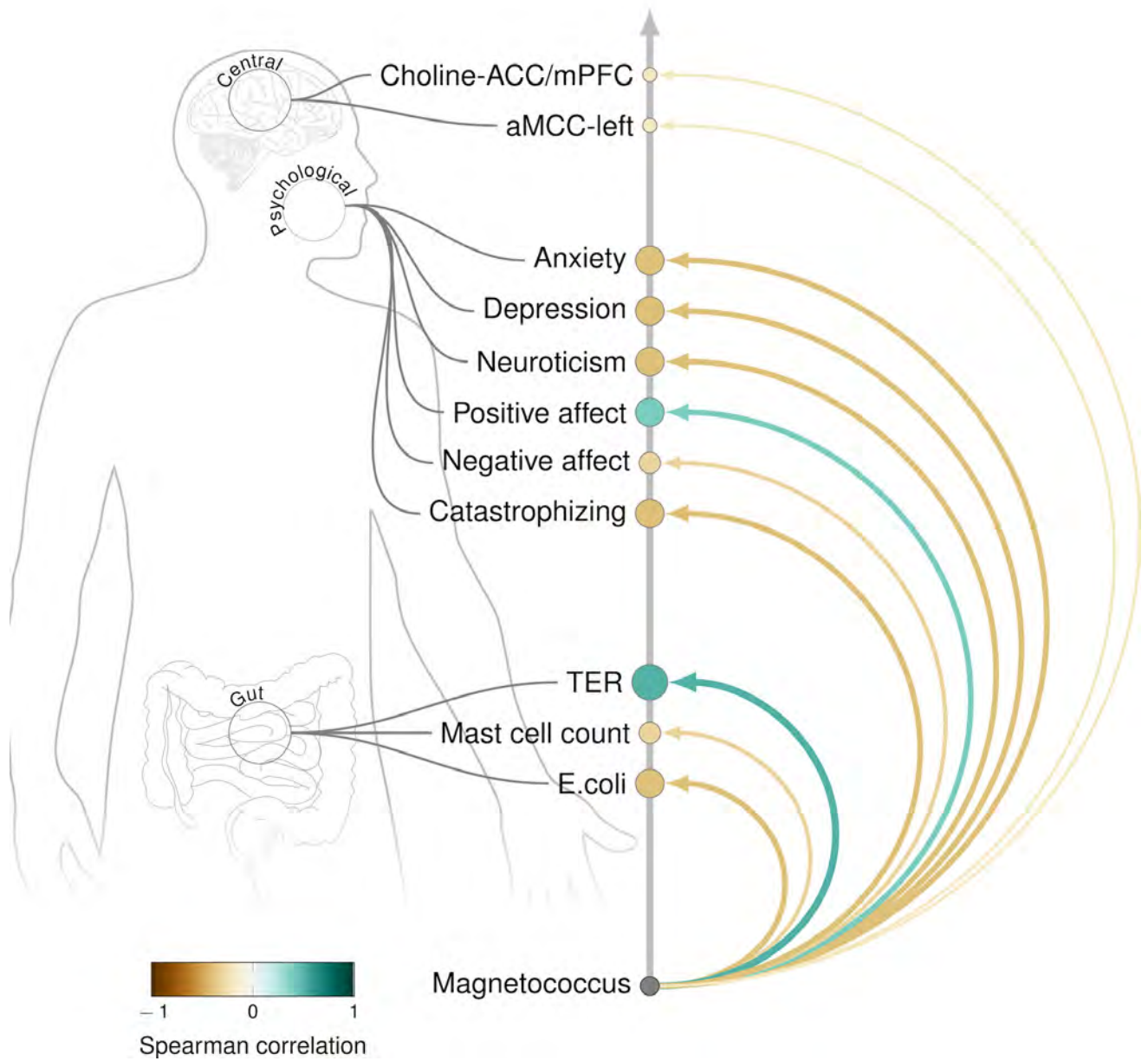
van Ettinger-Veenstra H, Lundberg P, Alföldi P, Södermark M, Graven-Nielsen T, Sjörs A, Engström M, Gerdle B.

Chronic Widespread Pain patients show disrupted cortical connectivity in Default Mode and Salience Networks, modulated by pain sensitivity. *J Pain Res* 2019;12 1743–1755.



ripheral biochemical tissue alterations and alterations in the brain of patients with fibromyalgia. The first results show that the anterior insula shows stronger coupling with an attentional network in fibromyalgia patients who report a higher level of pain. Altered insular coupling may have impaired reflection on internal subjective input versus externally-oriented attention. The results will be clinically important both with respect to assessment and when designing and choosing interventions for these patients. ■

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



Brain-Gut Interactions in IBS

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

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

To date research has identified several components, both in the gut and the

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

In this ongoing study, we are investigating multiple factors along the gut-brain axis in the same sample and within the same time period, both in patients with well-established IBS and healthy controls. We investigate gut related colonic mucosal function, gut microbiota and brain functional connectivity, magnetic resonance spectroscopy for the detection of neurotransmitter density in the brain, and brain structure. Soon we will start an intervention study to follow brain-gut related measures over a longer period of time. ■

MRI

Neurology

Gastrointestinal

No Method Development

PROJECT INFORMATION

Project Name

Brain-Gut Interactions in IBS

Project Leader

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

Main Project Participants

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

Grants

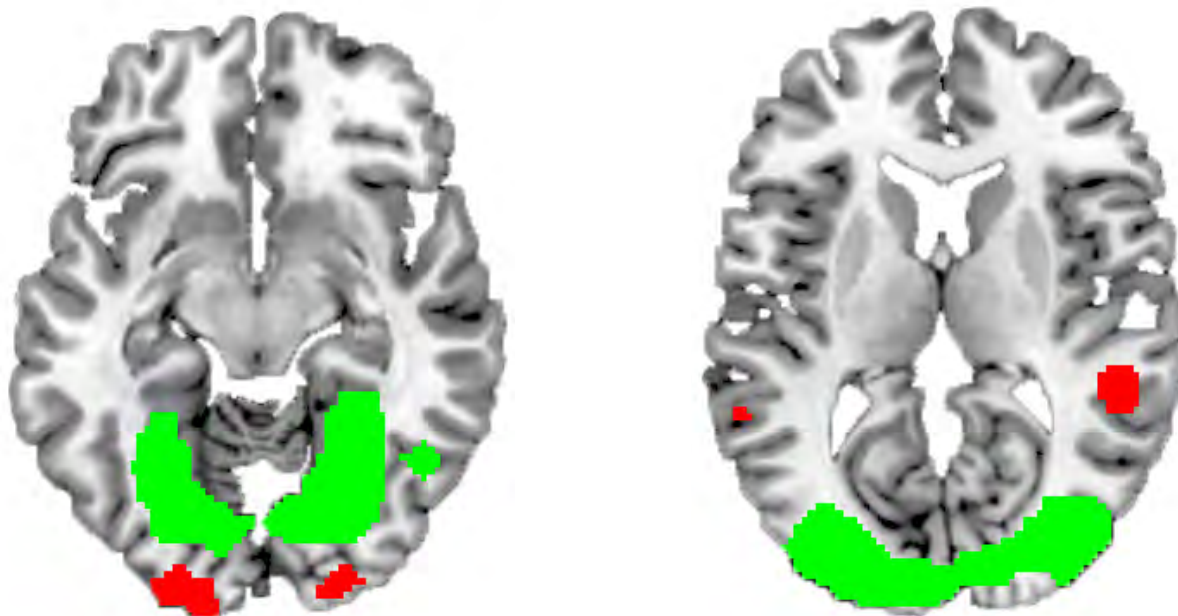
AFA, Region Östergötland

Key publications

Icenhour A, Tapper S, Bednarska O, Witt ST, Tisell A, Lundberg P, Elsenbruch S, Walter S. Elucidating the putative link between prefrontal neurotransmission, functional connectivity, and affective symptoms in irritable bowel syndrome. *Sci Rep.* 2019 Sep 19;9(1):13 590.

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

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



Working Memory in Visual Noise

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

an important phenomenon to study.

In the present study we are investigating the effect of poor visual resolution on working memory for sign language. Working memory was investigated using the n-back task in which participants were instructed to match presented signs with signs presented 1, 2 or 3 steps back in a sequence of signs (this is referred to as working memory load). The study includes data from 16 deaf early signers (DES) and 22 hearing non-signers (HHNS), who performed a working memory task based on high- and low-resolution signs during functional

Magnetic Resonance Imaging (fMRI).

The results show that there is no difference between deaf and hearing individuals in how well they performed the n-back task. However, performance was poorer for both groups when stimuli were degraded compared to when they were clear. Performance was also poorer when the working memory load was high. We also found a significant interaction between visual resolution and working memory load such that the effect of stimulus degradation was greater when load was greater. However, this effect was equal for both groups.

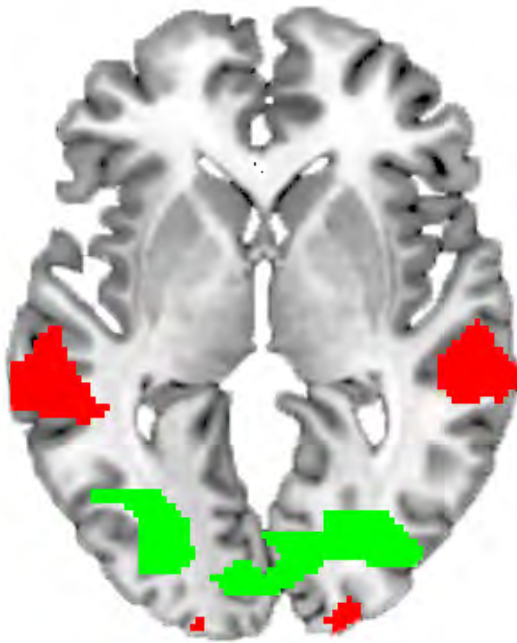


FIGURE. Significant activation pertaining to effects of resolution. Red indicates clear > degraded. Green indicates degraded > clear. (Reproduced from Andin et al., 2019, SNL).

These behavioral results generalize the effect of stimulus degradation from speech to sign language. Whole brain fMRI analysis showed increasing activation of the fronto-parietal working memory network as load increased. Working memory processing of clear compared to degraded stimuli led to greater activation of the ventral visual stream (red in figure) and the opposite contrast led to greater activation of the dorsal visual stream (green in figure). Further, non-signers compared to signers showed greater activation in the dorsal visual stream while signers compared to non-signers showed more

activation in the superior temporal lobe. This pattern of results shows that working memory for signs is sensitive to both load and visual resolution irrespective of sign language knowledge. In particular, it suggests that working memory for degraded or less well represented signs (in non-signers) is less reliant on identification in the ventral stream and more reliant on localization in the dorsal stream. Results also confirm previous findings of differences between deaf signers and hearing individuals in the engagement of superior temporal cortex during a visual cognitive task. ■

MRI

Neurology

No Method Development

PROJECT INFORMATION

Project Name

Working Memory in Visual Noise

Project Leader

Mary Rudner, Department of Behavioral Science and Learning, Division of Disability Research

Main Project Participants

Josefine Andin, Emil Holmer

Grants

Swedish Research Council (2016–2020)

Key publications

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

Andin J, Holmer E, Rudner M (2019). Reducing the visual resolution of lexical signs increases working memory load. 11th Annual Meeting of the Society for the Neurobiology of Language, August 20–22, Helsinki, Finland.

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

Brain Correlates to Affective Processing

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

We use magnetic resonance imaging to investigate how the two clinical groups respond to different types of stress (social stress, exposure to emotionally charged images) and light touch to investigate whether there are psycho-biological differences with regard to neural correlates

compared to healthy controls.

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

Participants engaged in a social interaction task which involved judging other players and also being judged by others. Together with brain correlates to social judgment, the goal of the study was to address how participants

experienced social interactions. We therefore gave a balanced amount of positive and negative feedback, and after the game we asked a few questions that addressed the quality of the experienced interaction.

Healthy participants activate the salience network when they feel judged by others, during online social interaction, independently on the quality of the judgment. The salience network activates to direct our cognitive resources towards relevant stimuli in the environment. We conclude that this activation is involved in properly attributing salience to self-relevant social stimuli, a function that is disrupted

PROJECT INFORMATION

Project Name

Brain correlates to Affective Processing in Typical Individuals and Clinical Groups

Project Leader

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

Main Project Participants

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

Grants

The Swedish Medical Research Council

Key publications

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

Perini I, Gustafsson PA, Hamilton JP, Kampe R, Mayo LM, Heilig M, Zetterqvist M. Brain-based Classification of Negative Social Bias in Adolescents with Nonsuicidal Self-injury: Findings From Simulated Online Social Interaction. *EClinicalMedicine*, 2019, 13:81–90.

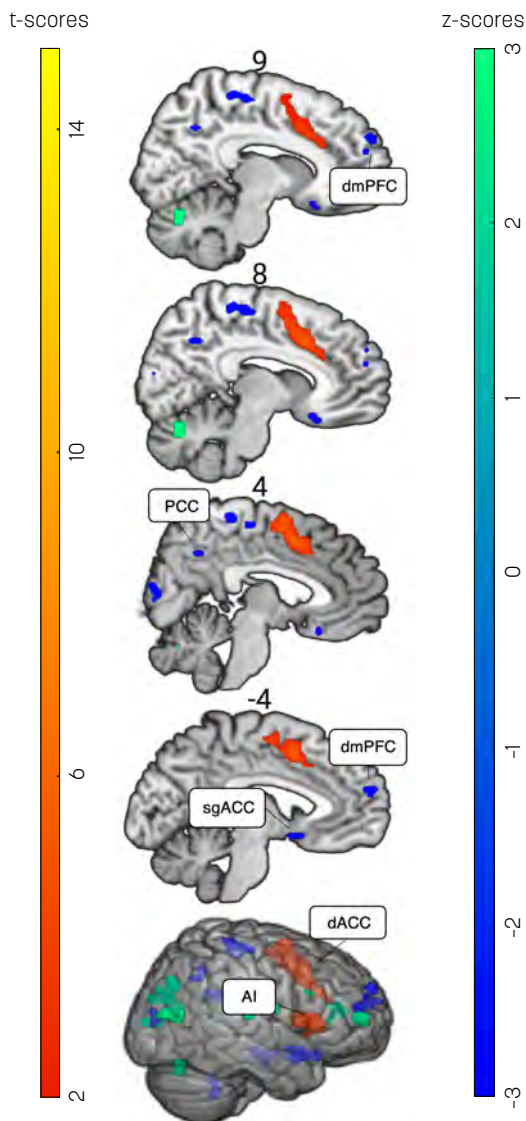


FIGURE. Multi-voxel pattern analysis results. GLM-based results showing common activity in both groups for the effect of “self” vs “other” during the anticipation interval (red-yellow).

Weight vector map showing brain regions which contributed to the discrimination between groups during the anticipation interval (blue-green).

in several disease states. The salience network finding was replicated in the following study which included female adolescents with NSSI and controls.

Although the salience network was equally active for self-relevant processing in both NSSI and controls, we identified significant behavioral and brain differences between the groups. Individuals with NSSI showed a negative bias in reading the social interaction: they felt more disliked than controls and when their picture received a negative feedback they felt worse than controls.

Using multi voxel pattern analysis, we identified brain regions that signi-

ficantly classified between groups during anticipation of social judgment. These regions, including subgenual anterior cingulate cortex (sgACC) and default mode network nodes are regions involved in self-reflection and emotion processing (Figure). Classification scores correlated significantly to sensitiveness to negative feedback from others in the patients but not in the controls. These findings suggest that individuals with NSSI interpret social interactions more negatively than controls and that altered activity during anticipation of social judgment might result in the observed negative bias. The analysis in the ASD groups is still ongoing. ■

Effects of rTMS Targeting the Insula on Alcohol Use

The objective of this study was to investigate the effects of repetitive transcranial magnetic stimulation (rTMS) targeting the insula on alcohol use and neural responses in alcohol-dependent patients. Craving and an impaired ability to stop alcohol use despite adverse consequences are key features of alcohol addiction. Functional brain imaging studies have shown that insula activity in response to drug cues is positively correlated with cravings. 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. Anatomically, 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 rTMS, a non-invasive tool for neuromodulation, to reduce craving and cue reactivity in addic-

tion has been suggested by small pilot studies in alcohol, cocaine and opiate users. In these studies, rTMS has typically been applied to the dorsolateral prefrontal cortex (DLPFC), a superficial structure.

The present study uses a different coil, designed to allow “deep rTMS”, to examine whether stimulation of the insula offers a novel alcoholism treatment.

The study population consisted of treatment seeking alcohol dependent subjects who have first completed standard alcohol withdrawal treatment if needed. Participants underwent an MRI scan to collect resting state and

PROJECT INFORMATION

Project Name

Effects of Repetitive Transcranial Magnetic Stimulation (rTMS) Targeting the Insula on Alcohol Use and Neural Responses in Alcohol-Dependent Patients

Project Leader

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

Main Project Participants

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

Grants

The Swedish Medical Research Council
EU Horizon 2020

Key Publication

Perini I, Kämpe R, Arlestig T et al. Repetitive transcranial magnetic stimulation targeting the insular cortex for reduction of heavy drinking in treatment-seeking alcohol-dependent subjects: a randomized controlled trial. *Neuropsychopharmacol.* 2019, Nov 11. <https://doi.org/10.1038/s41386-019-0565-7>

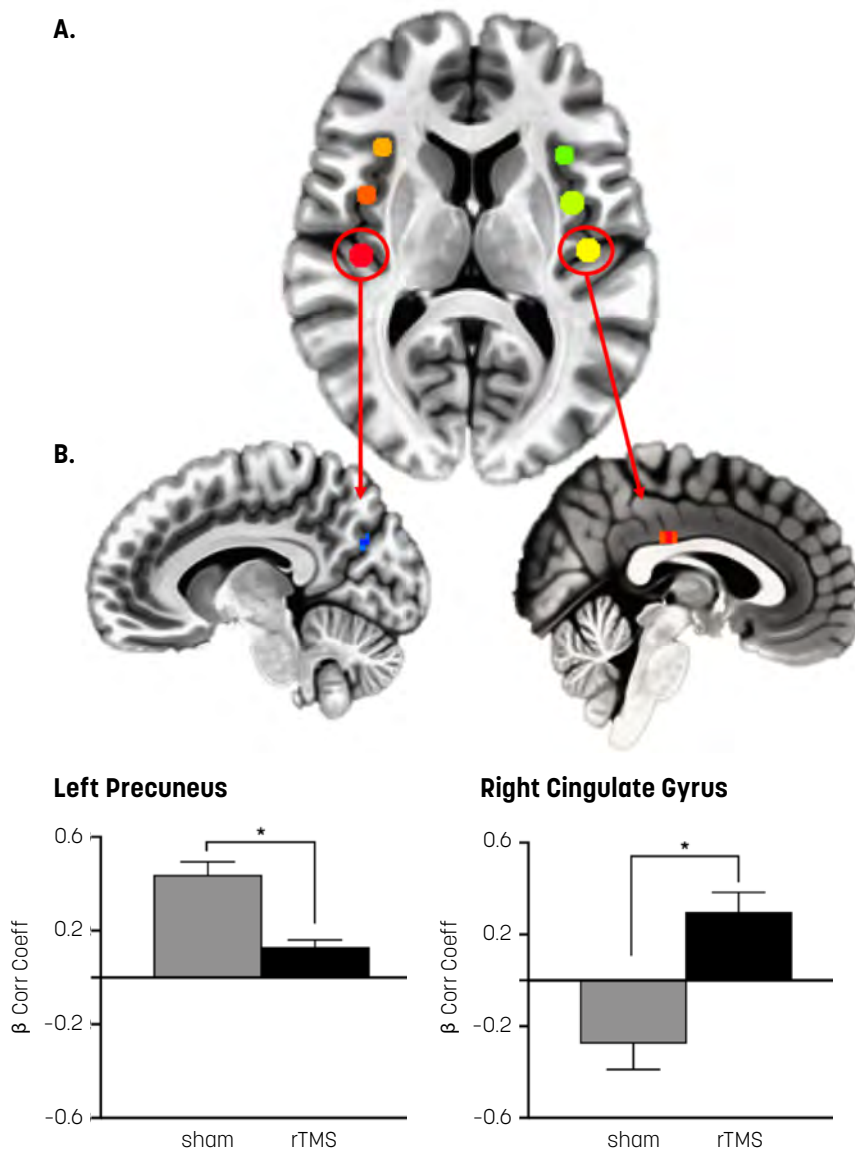


FIGURE. Resting-state connectivity analysis at follow-up.

A. Insula seed locations identified by maximizing the bilateral connectivity of each seed location. **B.** Brain regions showing significantly different correlation scores in rTMS and sham groups between right PI seed regions and left precuneus and left PI seed and right posterior cingulate.

structural data, and then received one of two treatments: active (10Hz) rTMS or sham stimulation, both targeting the insula bilaterally. The treatment procedure was double-blinded, meaning that both participants and study personnel were unaware of the randomization of the treatment. Outcome measures included alcohol craving and consumption during treatment and follow-up phases. In addition, brain responses to alcohol related cues and reward were analyzed and compared between stimulation types.

A marked overall decrease in craving and drinking measures was observed during treatment, but did not differ be-

tween rTMS or sham stimulation. Both groups equally increased their alcohol use following completion of treatment and through the 12-week follow-up. Analysis using seeds in the insula identified differences in resting-state connectivity between active and sham groups at completion of treatment, potentially indicating an ability of treatment to modify insula function (Figure). However, while each task robustly replicated brain responses established in the literature, no effects of rTMS were found. Collectively, this study does not support efficacy of rTMS targeting the insula in alcohol addiction. ■

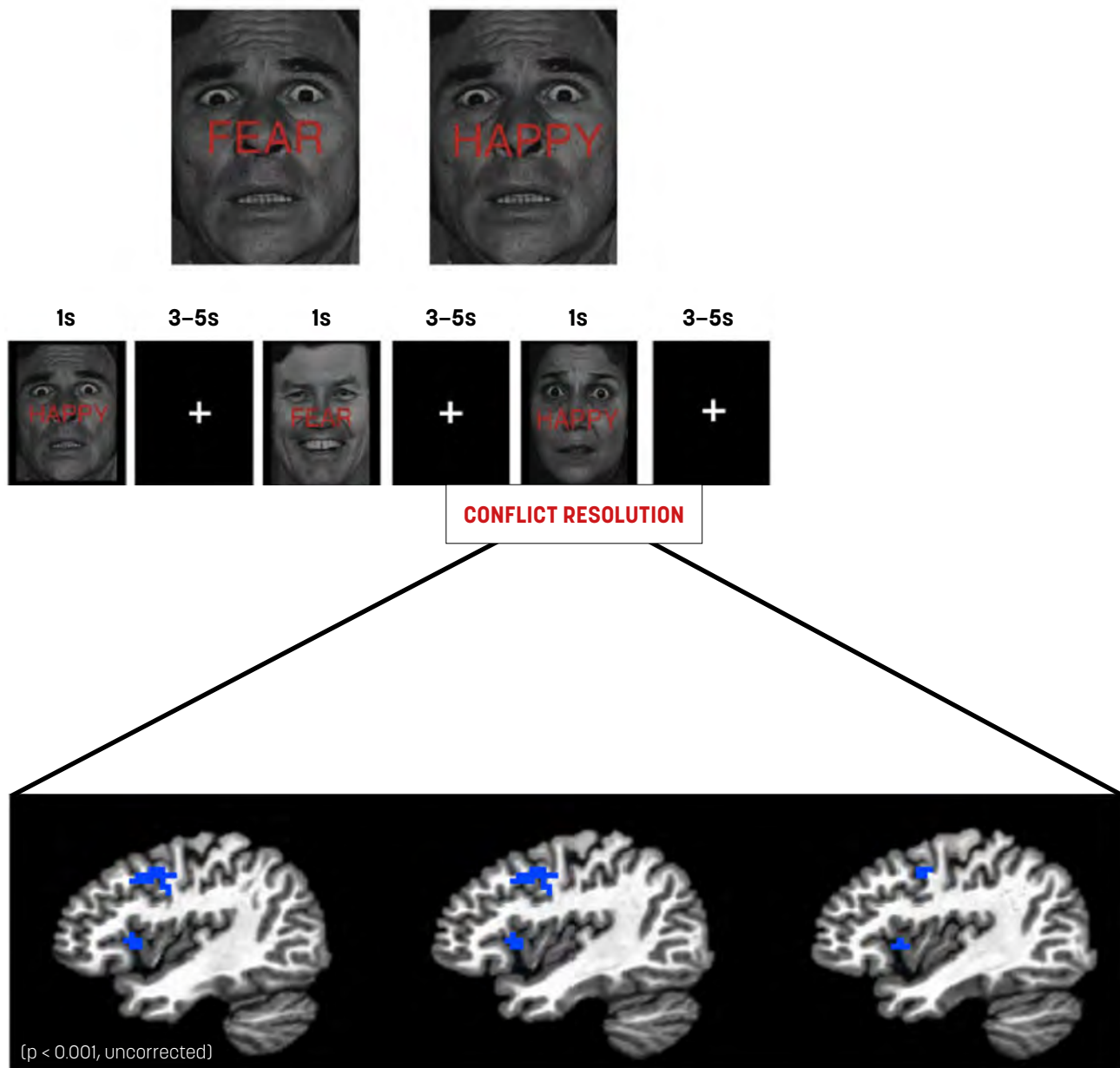


FIGURE. The emotion conflict task. Participants are instructed to identify the underlying facial emotion (fearful or happy) while ignoring an overlying emotional distractor. This task has been used to successfully discern between brain mechanisms involved in two components of emotional regulation.

Affective Processing when Exposed to Early Life Trauma

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

The specific aim regarding the MRI-data collection of this project is to investigate experimentally whether the regulation of affect and stress responses differs in individuals who have experienced early trauma, compared to controls. In order to address these aims the following paradigms are tested in the Magnetic Resonance Imaging (MRI) scanner:

Matching of images

Emotionally negative pictures 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.

Matching alcohol & non-alcohol images

Alcohol related and non-alcohol related

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

Emotion conflict task

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

The study is currently ongoing. Data collection is planned to be completed by spring 2020. ■

MRI

Neurology

No Method Development

PROJECT INFORMATION

Project Name

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

Project Leader

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

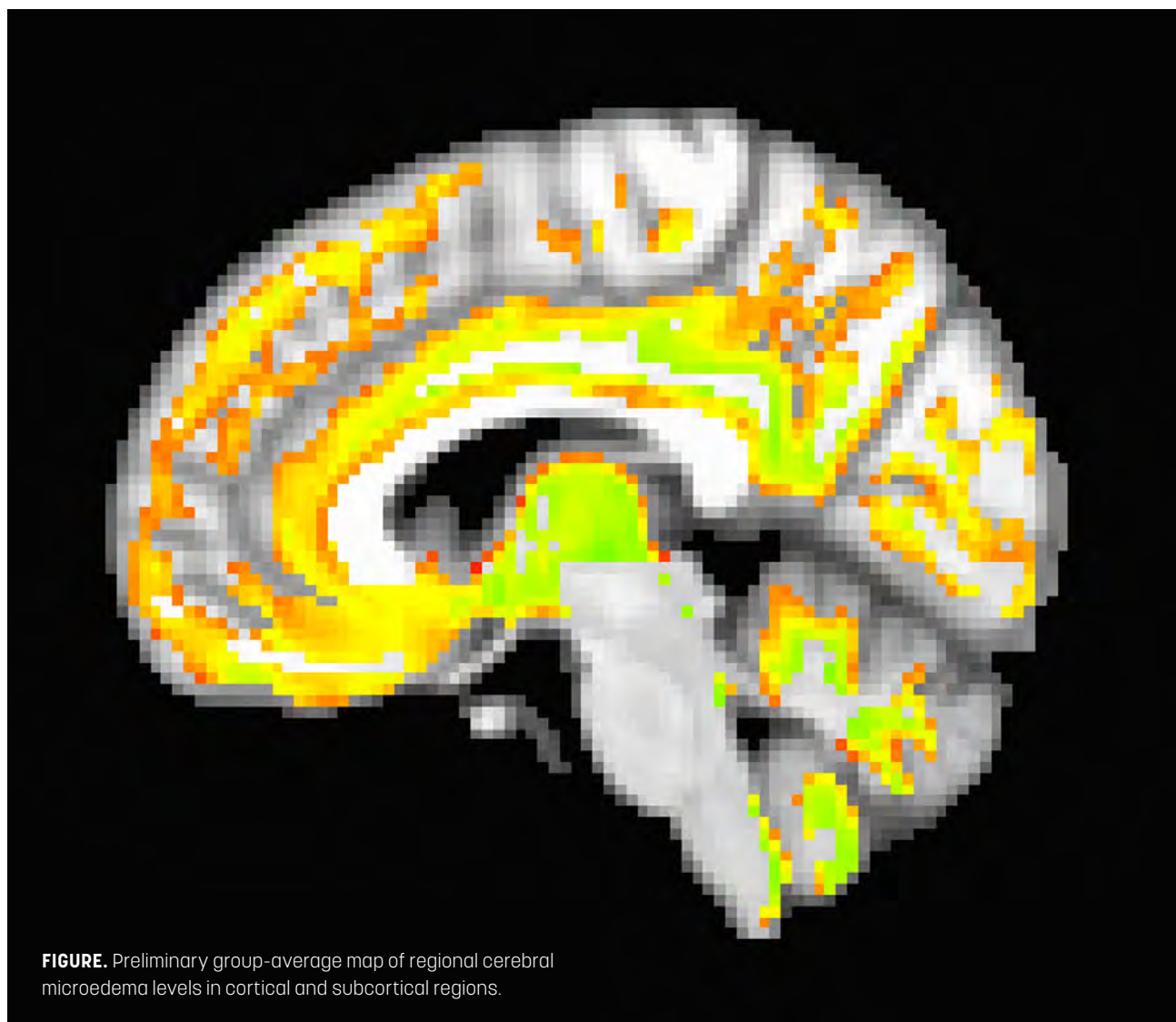
Main Project Participants

Åsa Kastblom, Paul Hamilton, Robin Kämpe, Irene Perini

Grants

The Swedish Medical Research Council

Modulating Inflammation in the CNS in Major Depression



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

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

The primary objective of our study is to evaluate the efficacy of tocilizumab – an anti-inflammatory drug that inhibits the effects an inflammatory cytokine implicated in MDD – in reducing measures of inflammation in the central nervous system.

Individuals diagnosed with MDD will be asked to enroll in a double-blind, placebo-controlled treatment study in which half of participants will receive tocilizumab and the other half will receive a matched placebo. Before and after the treatment or placebo, cerebrospinal fluid (CSF), and magnetic resonance imaging (MRI) data will be collected. From the CSF, we will determine whether anti-inflammatory treatment reduces levels of chemical signaling of inflammation in the brain.

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

Recent genome-wide association studies on very large samples of depressed and non-depressed persons have identified ~100 genome-wide-significant single-nucleotide polymorphisms associated with depression. These effects can be summed into a single polygenic risk score (PRS) for depression. In an independent replication cohort, persons with high PRS (top tenth percentile) were found to be two times more likely to have a history of depression than persons with a low PRS (bottom tenth percentile). A group of particular interest to us are the patient group who develop MDD in the absence of genetic factors. We believe that metabolic imbalance and distress could account for the development of MDD in these low-genetic-risk individuals. One marker of metabolic imbalance is fatty liver. Using the whole-body imaging sequence available at CMIV, we have scanned both depressed and healthy persons and, in collaboration with Magnus Borga and Anette Karlsson, will estimate liver fat levels from these data. We predict that depressed individuals without genetic risk will exceed groups with genetic disposition in liver fat levels. ■

MRI

Neurology

No Method Development

PROJECT INFORMATION

Project Name

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

Project Leader

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

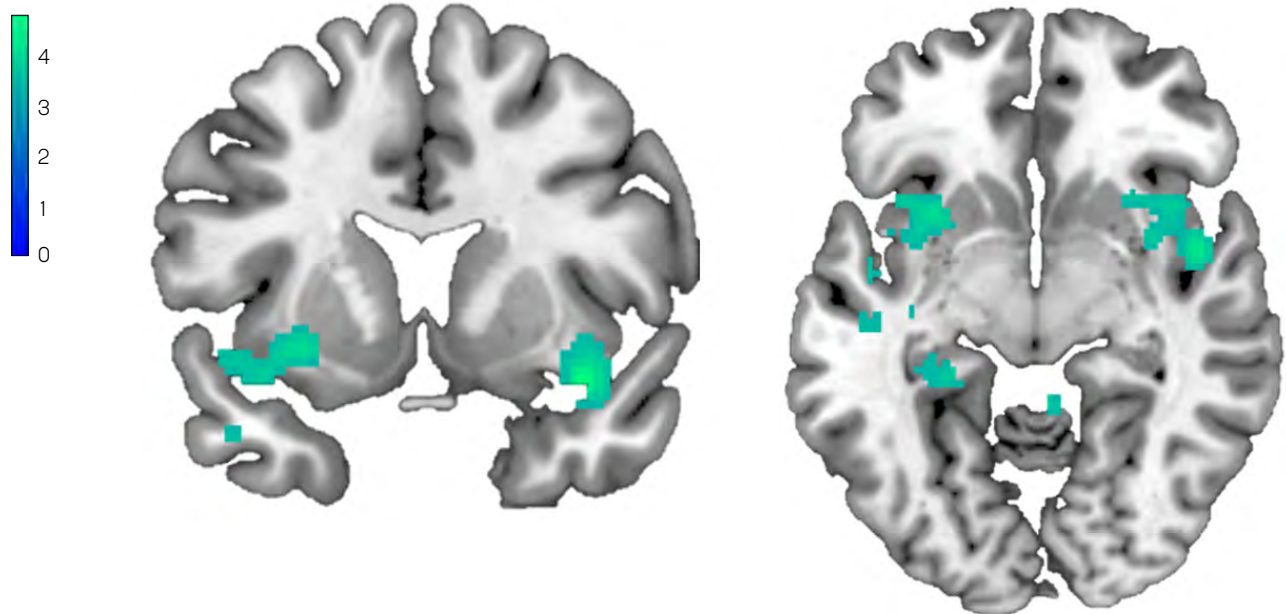
Main Project Participants

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

Grants

The Swedish Medical Research Council

A. Self, HC > ADHD



B. Other, ADHD > HC

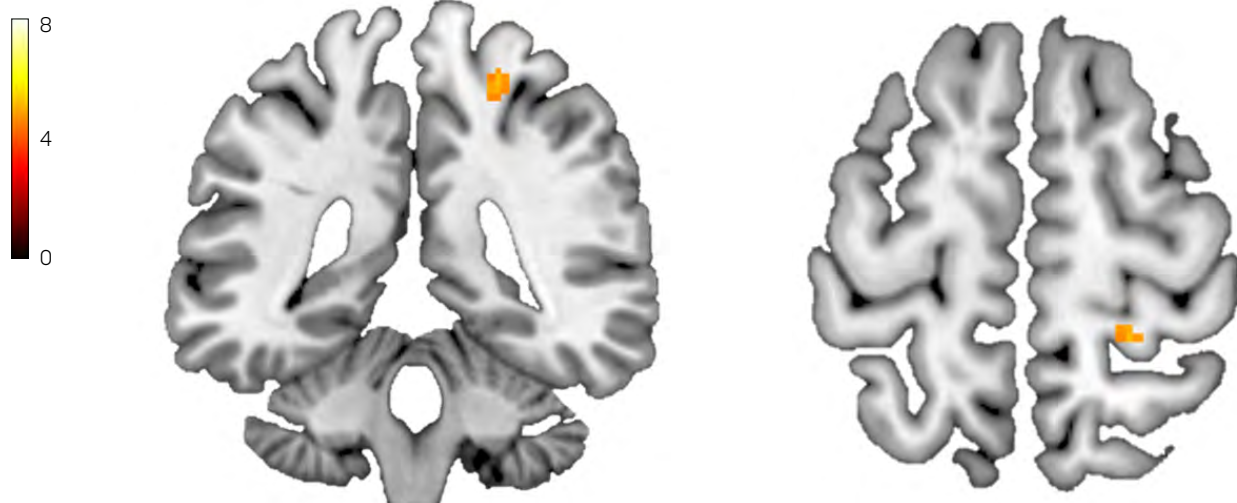


FIGURE. Brain activation in ADHD patients compared to healthy controls (HC) when stroking their own arm (A) or being stroked by someone else (B).

Distinction of Touch in Psychiatry

Somatosensation, the sense of touch, and interoception, the perception of sensations from inside the body, are necessary for the establishment of the bodily self. To develop a functional bodily self, humans need to identify the boundaries of their body and differentiate "self" from "others". Disturbed tactile self-other-distinction might affect the establishment of the bodily -the minimal -self, and even of the higher -order, i.e. the reflective self. Such dysfunctional self-processes constitute a core symptom in many psychiatric disorders, e.g. in autism, schizophrenia and bipolar disorder.

In this study the participants are asked to stroke their own arm or will be stroked on the arm by the experimenter, while we collect functional imaging brain data. In healthy participants, we were able to show how the neural responses to self-touch differ from social touch by someone else: while other-touch is associated with activations in areas involved in somatosensation and social cognition, self-touch is associated with widespread deactivations.

We want to compare these processing patterns of healthy controls (HC) with participants who have a psychiatric diagnosis. The first group studied were individuals with attention deficit hyperactivity disorder (ADHD). These individuals are often hypersensitive to touch and other sensory stimulation. Comparing ADHD individuals with controls (HC), we found an enhanced differentiation between other-touch and self-touch, a stronger deactivation during self-touch in bilateral insula and an increased activation in response to touch by others in right somatosensory cortex. This suggests an even stronger differentiation between self-produced and non-self-produced sensations.

Other populations for which we are currently collecting data are people with anorexia nervosa and autism.

This project lays the groundwork for the development of novel interventions for treating the symptom domain of the bodily self, which is affected in many psychiatric disorders, and substantially enhances our understanding of the sense of self. ■

MRI

Neurology

No Method Development

PROJECT INFORMATION

Project Name

Distinction of Self-Touch and other-Touch in Psychiatry

Project Leader

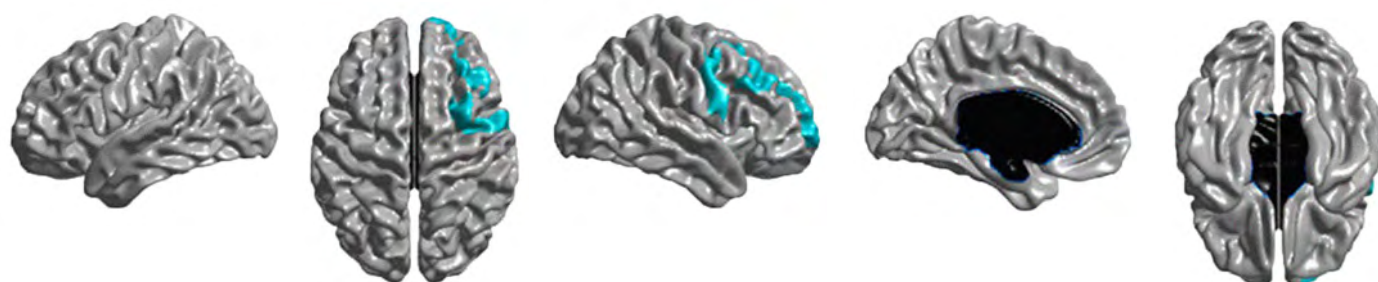
Håkan Olausson, Department of Clinical and Experimental Research, Center for Social and Affective Neuroscience

Main Project Participants

Rebecca Böhme

Key publications

Boehme R, Hauser S, Gerling G J, Heilig M, Olausson H (2019). Distinction of self-produced touch and social touch at cortical and spinal cord levels. *Proceedings of the National Academy of Sciences*, 116(6), 2290–2299.



Cognition after Bilateral Salpingo- Oophorectomy

Women with bilateral salpingo-oophorectomy (removal of the ovaries; BSO) prior to the age of 50 have higher incidence of all causes of death including, Alzheimer's dementia (AD). Women with the breast cancer gene mutations, BRCA1 and 2 are routinely counseled to have a BSO prior to the age of 50 to reduce the risk of ovarian cancer. Since one effect of BSO is to remove the body's major source of 17-B-estradiol (E2, one of three naturally occurring estrogens), these data suggest that early life

withdrawal of E2 may be detrimental for cognition. This study aims to elucidate brain and cognitive changes out to 10 years post-BSO.

This project focus on the long term effects on cognition and brain of the most common treatment for women with BRCA mutations, BSO and more broadly, how breast cancer survivorship affects the brain. The objectives are to determine the domains in which cognition and memory change (neuropsychological testing) and the effects of E2 withdrawal on brain re-

gions involved with memory (imaging). Moreover, the interaction between, and impact on brain changes and cognition of E2 withdrawal, inflammation markers, and Apolipoprotein E (APOE) (via hormone assay, immunological testing, and genotyping) will be studied as well as women's qualitative sense of surgery, quality of life, and memory (interview).

Results of this study will contribute to our understanding about important cognitive and brain outcomes of an increasingly common elective surgery for women with BRCA mutations, as well as

MRI

Neurology

Gynecological

No Method Development

PROJECT INFORMATION

Project Name

CABSOE – Cognition after Bilateral Salpingo-Oophorectomy

Project Leader

Gillian Einstein, Department of Thematic Studies, Division of Gender Studies

Main Project Participants

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

Grants

The Swedish Cancer Society 2016–2019

Key publications

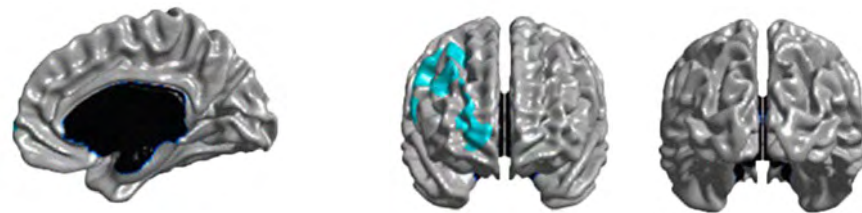
Almey A, Gervais N, Duchesne A, Reuben R, Gravelsins L, Baker-Sullivan E, Witt ST, Rydmark Kersley Å, Classon E, Lykke N, Shildrick M, Åsberg C, Theodorsson E, Ernerudh J, Åvall Lundqvist E, Kjölhede P, Grady C, Einstein G, (2018).

The effect of bilateral salpingo-oophorectomy prior to spontaneous menopause on cortical thickness and measures of attention and working memory: preliminary findings. Poster at Society for Neuroscience, San Diego, CA. Nov 3–7.

Almey A, Gervais N, Duchesne A, Reuben R, Gravelsins L, Baker-Sullivan E, Witt S T, Rydmark Kersley Å, Classon E, Lykke N, Shildrick M, Åsberg C, Theodorsson E, Ernerudh J, Åvall Lundqvist E, Kjölhede P, Grady C, Rajah N, Einstein G, (2018).

The effect of bilateral salpingo-oophorectomy prior to spontaneous menopause on cortical thickness and measures of attention and working memory: preliminary findings. Poster presented at the International Neuroinformatics Coordinating Facility (ICNF) conference, Montreal, QC. Aug 9–10.

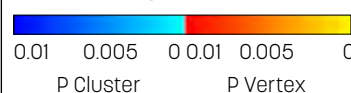
Witt S T, Rydmark Kersley Å, Classon E, Lykke N, Shildrick M, Åsberg C, Grady C, Theodorsson E, Ernerudh J, Åvall Lundqvist E, Kjölhede P, Einstein G, (2018). Bilateral salpingo-oophorectomy prior to natural menopause is associated with Alzheimer’s disease-like reductions in gray and white matter. Poster at Joint Annual Meeting International Society for Magnetic Resonance Imaging in Medicine & European Society for Magnetic Resonance Imaging in Medicine 3762.90., Paris, France. June 16–21.

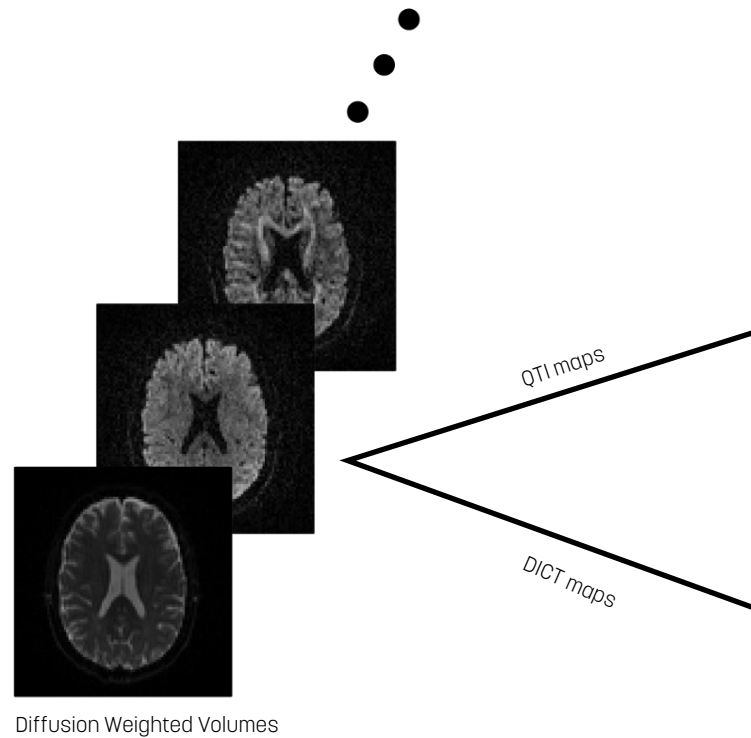


estrogen’s role in young women’s cognition and memory. It will also provide important information on survivorship of women with BSO – information particularly important for those who carry the AD risk factor variant of the APOE gene. Only with this knowledge will women be able to make fully informed decisions about BSO. This research may also lead to clinical trials of non-hormonal treatments and encourage invention of better ovarian imaging methods. ■

FIGURE. Blue indicates clusters that differ significantly between groups after correction ($p < 0.01$). Two clusters in the right frontal cortex are thinner in BSO to AMC, these clusters include the right frontal pole, the right middle frontal gyrus and the right precentral gyrus.

RFT corrected p-val, AMC > BSO





Advanced Diffusion MRI

As part of the projects “Unraveling intravoxel tissue composition via diffusion MRI” and “Intelligence based iMprovement of Personalized treatment And Clinical workflow support (IMPACT), we aim to unravel the intravoxel microstructure of the human brain using advanced diffusion MRI acquisition and analysis schemes, and apply the results to assess brain tumors.

Diffusion MRI allows non-invasive characterization of the tissue microstructure by probing the random

motion of water molecules. Clinically, this technique has gained interest due to its inherent sensitivity to changes in the local structure, which improves our capabilities in diagnosing diseases such as ischemic stroke. The technique also allows the computation of new biomarkers, which can be related, for example, to tumor cellularity.

To this day, the most commonly adopted protocol involves the acquisition of diffusion sensitized images using a pair of gradient pulses applied in different magnitudes and directions. The protocol also includes the compu-

tation of quantities such as the apparent diffusion coefficient and diffusion tensor from which certain features can be mapped. Contradictory results on the use of these maps and indices in the context of analyzing tumorous tissue have been reported in the literature. This suggests that more complex models are needed to study disease-induced changes in the brain microstructure.

With the introduction of advanced acquisition schemes, it has been possible to use such sophisticated models to analyze the data and also obtain new and different types of

MRI

Neurology

Oncology

Acquisition

Modeling

AI/Data analytics

Imaging Biomarker

PROJECT INFORMATION

Project Name

Elucidating Intravoxel Structure of Neural Tissue with Advanced Diffusion MRI

Project Leader

Evren Özarslan, Department of Biomedical Engineering, Division of Biomedical Engineering

Main Project Participants

Ida Blystad, Deneb Boito, Anders Eklund, Magnus Herberthson, Carl-Fredrik Westin, Cem Yolcu

Grants

Vinnova

Key publications

Herberthson M, Yolcu C, Knutsson H, Westin CF, Özarslan E. Orientationally-averaged diffusion-attenuated magnetic resonance signal for locally-anisotropic diffusion. *Sci Rep*, 2019; 9:4899.

Westin C-F, Knutsson H, Pasternak O, Szczepankiewicz F, Özarslan E, van Westen D, Mattisson C, Bogren M, O'Donnell L, Kubicki M, Topgaard D, Nilsson M. Q-space trajectory imaging for multi-dimensional diffusion MRI of the human brain. *NeuroImage*, 2016; 135:345–362.

Yolcu C, Memiç M, Şimşek K, Westin CF, Özarslan E.

NMR signal for particles diffusing under potentials: From path integrals and numerical methods to a model of diffusion anisotropy. *Phys Rev E*, 2016; 93:052602.

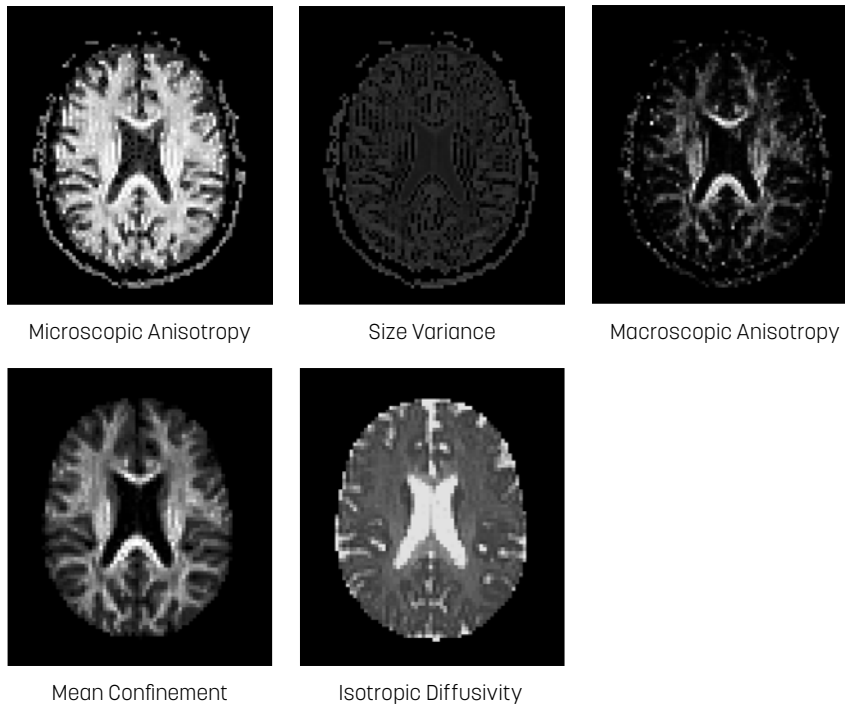


image contrasts that could potentially lead to better diagnosis and monitoring of brain tumors. During this project, we will acquire data from patients presenting brain tumors using advanced diffusion MRI sequences at CMIV. We will analyze the data using, for example, the q-space trajectory imaging (QTI) framework, and the diffusion imaging with confinement tensor (DICT) model. The figure shows examples of maps and parameters that can be obtained by applying these two approaches on data acquired using advanced diffusion MRI. ■

FIGURE. Left: Selected images from a collection of diffusion weighted brain volumes acquired via advanced diffusion MRI (Szczepankiewicz et al., *Data Brief*, 25,104208, 2019). Right: Examples of maps obtained using QTI and DICT analyses.

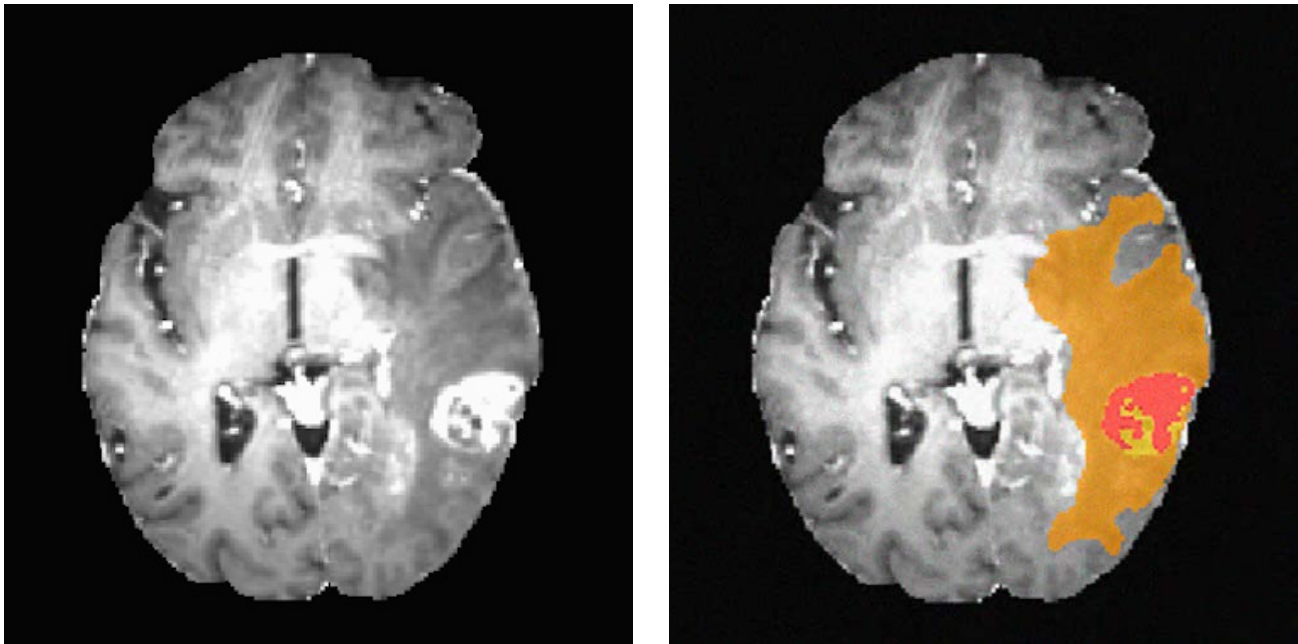


FIGURE. Left: A T1-weighted image (after injection of gadolinium contrast) from the open BraTS dataset. Right: An automatic deep learning based segmentation of the brain tumor into different parts.

Automatic Brain Tumor Segmentation

Brain tumors affect the quality of life for approximately 260,000 subjects globally. To improve outcome and quality of life it is important that tumors can be detected and treated at an early stage.

Magnetic resonance imaging (MRI) enables non-invasive imaging without any ionizing radiation. Structural MRI e.g. T1-weighted (with and without gadolinium contrast) and T2-weighted anatomical images is often used for detecting and segmenting brain tumors. Prior to treatment (surgery, radiation or chemotherapy), it is important to know the number of tumors or metastases, how large they are and where the border is. After treatment, it is vital to know if there is any tumor residue.

Manual segmentation of a tumor is, however, a time consuming and error prone task, which can take 30–120 minutes for a single subject. In this project we will therefore develop auto-

matic segmentation of brain tumors, using deep learning techniques where a computer is trained by showing many manual segmentations performed by an expert. Fast automatic segmentation will save time for neuro radiologists, and the treatment can be improved through better localization of the tumor border. This can in turn lead to a higher quality of life for the brain tumor patients.

We have so far used an open dataset (BraTS) of 200 brain tumor patients to train a computer to perform automatic tumor segmentation, see Figure, which takes about 20 seconds. In future work we will scan brain tumor patients at CMIV, using structural MRI as well as two additional MRI sequences (quantitative MRI and advanced diffusion MRI). Our hypothesis is that the additional MRI sequences will provide more information about the tumor, and therefore make the segmentation more exact. ■

MRI

Neurology

Oncology

Acquisition

Modeling

AI/Data analytics

PROJECT INFORMATION

Project Name

Automatic Brain Tumor Segmentation Using Multi-Modal MRI

Project Leader

Anders Eklund, Department of Biomedical Engineering, Division of Biomedical Engineering

Main Project Participants

Ida Blystad, Evren Özarslan, David Abramian, Marco Cirillo, Xuan Gu, Deneb Boito

Grants

Vinnova
Medtech4Health, AIDA

Key publications

Gu X, Eklund A.
Evaluation of six phase encoding based susceptibility distortion correction methods for diffusion MRI, *Frontiers in Neuroinformatics*, 2019.

Abramian D, Eklund A.
Refacing: reconstructing anonymized facial features using GANs, *IEEE International Symposium on Biomedical Imaging*, 2019.

Gu X, Knutsson H, Nilsson M, Eklund A.
Generating diffusion MRI scalar maps from T1-weighted images using generative adversarial networks, *Scandinavian Conference on Image Analysis*, 2019.

CT

Oncology

Acquisition

Modeling

AI/Data analytics

POPULAR SCIENTIFIC SUMMARY

Åsa Carlsson Tedgren

PROJECT INFORMATION

Project Name

Tissue Classification Using Dual Energy CT and Iterative Reconstruction

Project Leader

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

Main Project Participants

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

GrantsThe Swedish Cancer Society 2019–2021
Swedish Research Council 2017–2020**Key publications**

Malusek A, Magnusson M, Sandborg M, Alm Carlsson G.

A model-based iterative reconstruction algorithm DIRA using patient-specific tissue classification via DECT for improved quantitative CT in dose planning. *Medical Physics* 44, pp 2345–2357, 2017.Magnusson M, Björnfoth M, Carlsson Tedgren Å, Alm Carlsson G, Sandborg M, Malusek A. DIRA-3D – a Model-based Dual-Energy Iterative Algorithm for Quantitative 3D Helical CT. *Biomed. Phys. Eng. Express* 5 065005, 2019.González Sánchez J, Magnusson M, Sandborg M, Carlsson Tedgren Å, Malusek A. Segmentation of bones for radiation therapy from medical dual-energy computed tomography volumes using the 3D U-Net. Accepted for publication in *Physica Medica: European Journal of Medical Physics*, 2019.

Classification Using DECT and Iterative Reconstruction

Today's computed tomography (CT) images are affected by inaccuracies and artifacts caused by the use of polyenergetic photon beams. Despite an active research in this field, even the most advanced image reconstruction algorithms still do not provide quantitatively accurate CT numbers. We have developed a dual-energy iterative image reconstruction algorithm (DIRA) which improves the accuracy of CT numbers by modeling the material composition of the imaged object. For instance, image pixels of a patient are classified into bone and soft tissue.

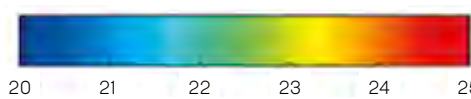
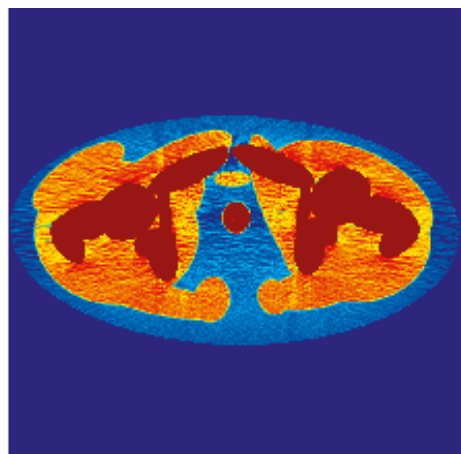
Bone pixels carry information about percentages of compact bone, red and yellow bone marrow. Soft tissue pixels carry information about percentages of water, protein and lipid. The estimated material composition can be used for improved medical diagnosis and treatment. As an example, DIRA can be used for the determination of calcium content in the prostate gland. Such information is useful for radiation treatment planning in brachytherapy with low-energy photons. A high calcium content in the prostate changes the spatial distribution of absorbed dose since the dose strongly depends on

tissue's atomic number, Z . DIRA is also useful in proton radiation therapy since the position of the dose maximum is sensitive to the material composition of the patient tissues.

To verify the method, we applied DIRA on simulated projections of a mathematical pelvic phantom. The projections were calculated for tube voltages of 80 and 140kV, photon noise was included, and the geometry was the same as for the CT-scanner at CMIV. DIRA notably suppressed the beam-hardening artifact, see Figure 1. Figure 2 shows the same phantom decomposed to the lipid, protein and water base material triplet. Knowledge of these mass fractions allows the estimation of the elemental composition of the phantom which are of interest in radiotherapy planning.

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

80kV recon [1/m], iter=0



80kV recon [1/m], iter=8

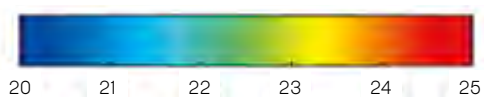
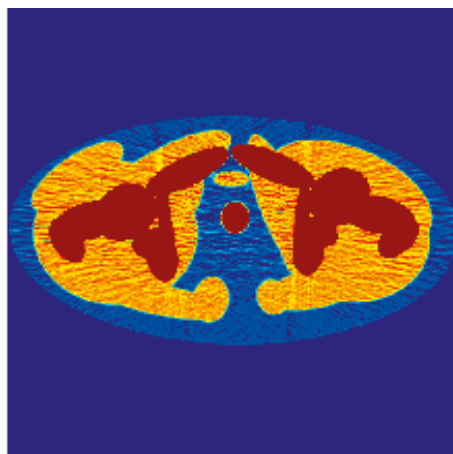
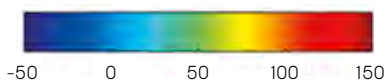
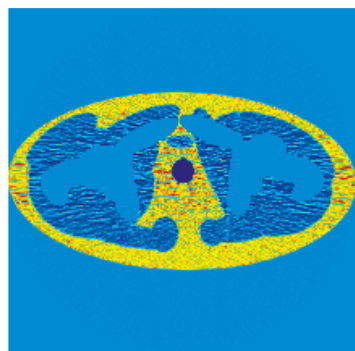
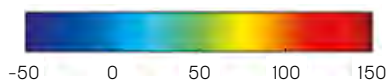
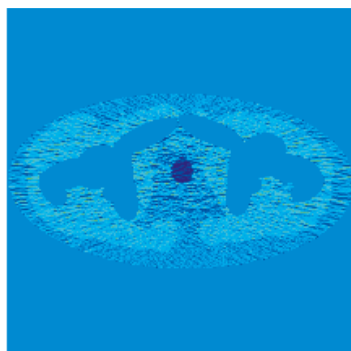


FIGURE 1. Suppression of the beam hardening artifact for the mathematical pelvic phantom. The image reconstructed via conventional filtered back-projection with water beam hardening correction (left) and the corresponding image obtained via DIRA in iteration 8 (right).

Lipid (%), iter=8



Protein (%), iter=8



Water (%), iter=8

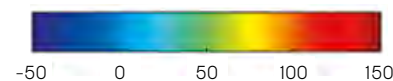
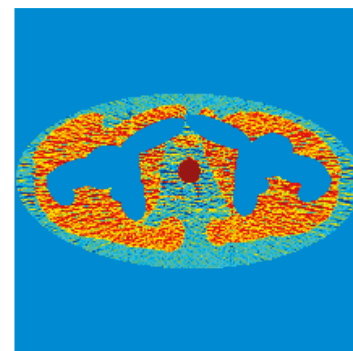
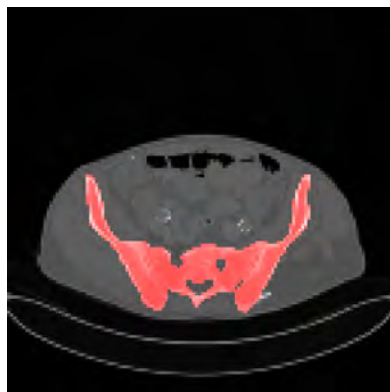


FIGURE 2. Soft tissue classification into lipid, protein and water (LPW) after 8 iterations of DIRA.

A



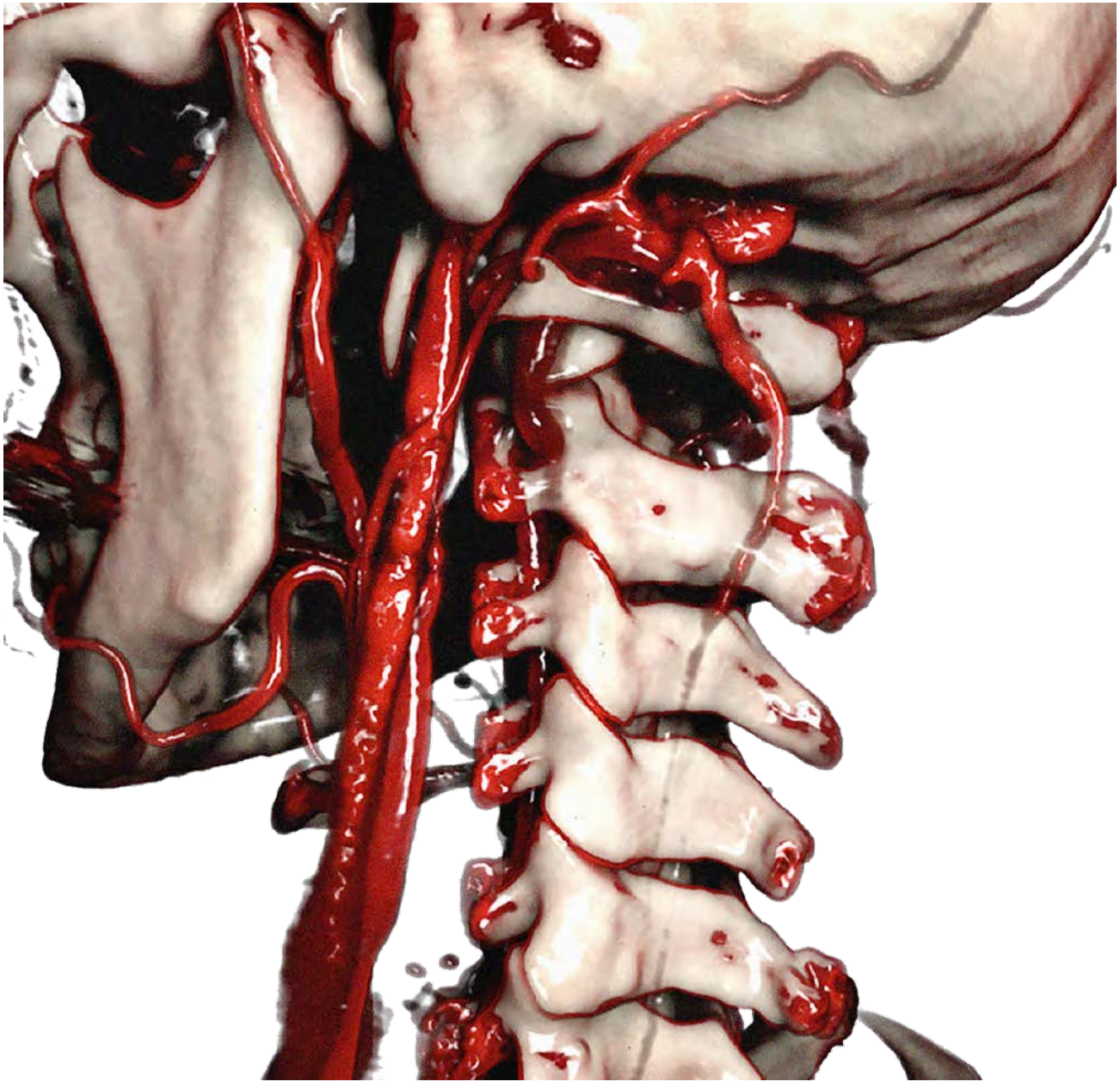
B



C



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



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. The overall goal of this projects is to develop methods for the creation of image-driven patient specific organ models. The models will allow for exploratory simulation of function that enable groundbreaking medical research on organ function. The long-term goal is clinical use of patient specific functional organ models in the diagnostic workflow.

This challenging goal calls for concerted efforts on development of novel technical approaches in all the stages of the image-based creation of the organ model. Also important is the execution of the simulation incorporating the boundary conditions derived from the patient-specific imaging data. The work is conducted in an interdisciplinary medical-technical cycle intimately linking medical research, clinical use, and technical development and is summarized in the following key areas.

Data Acquisition

Myelin is crucial for efficient signal transmission over long ranges in the nervous system. Degradation of myelin impairs the signal transmission and eventually leads to brain atrophy and brain dysfunction. We have developed a new model for estimating the brain volume, degree of myelination and degree of oedema, which is now available for MR-scanners worldwide. We have also developed a novel method for multi-fiber reconstruction based on a mixture of non-central Wishart distributions, which better captures the true fibre orientation distribution and outperforms the previ-

ously proposed probabilistic models.

Patient-Specific Modeling and Simulation

A novel numerical framework was developed for patient-specific modeling and simulation of blood flow and muscle function based on imaging data. With segmentation of the whole heart as boundary conditions, simulation of cardiac hemodynamics was obtained with outstanding geometrical detail. In addition, simulations of deep brain stimulation (DBS) have been used for investigation of optimal positioning in DBS for Tourette syndrome obsessive compulsive disorder.

Exploring and Explaining Multimodal Data in Clinical Populations

Multimodal data are acquired to understand brain-body interactions involved in for example the sleep and pain disorders narcolepsy and irritable bowel syndrome (IBS). We have developed a novel framework for mechanistic modelling of time dependent neuroimaging data. The framework has the ability to explain the measured hemodynamic responses to neural activity e.g. fMRI data, in terms of activity in for example excitatory and inhibitory neurons. The model explains and predict brain function and can thus have the potential to become biomarkers of disease. To further aid scientific reasoning and hypothesis formulation in these brain co-cohort studies, we have developed a data analytics and exploration environment allowing neuroscientists to visually explore all data in a single application. This visual environment fills an important gap when it comes to analyzing patient group data having both a spatial and an abstract nature. ■

Computed Tomography

MRI

Cardiovascular

Neurology

Modeling

Visualization

Simulation

PROJECT INFORMATION

Project Name

Seeing Organ Function

Project Leader

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

Main Project Participants

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

Grants

KAW

Key publications

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

Lantz J, Gupta V, Henriksson L, Karlsson M, Persson A, Carlhäll C-J, Ebber T. "Impact of pulmonary venous inflow on cardiac flow simulations: Comparison with in vivo 4d flow MRI." *Annals of biomedical engineering*, 47(2):413–424, 2019.

Jönsson D, Bergström A, Forsell C, Simon R, Enström M, Ynnerman A, Hotz I. "A Visual Environment for Hypothesis Formation and Reasoning in Studies with fMRI and Multivariate Clinical Data." *Eurographics Workshop on Visual Computing for Biology and Medicine*, 2019, Honorable mention for best paper.

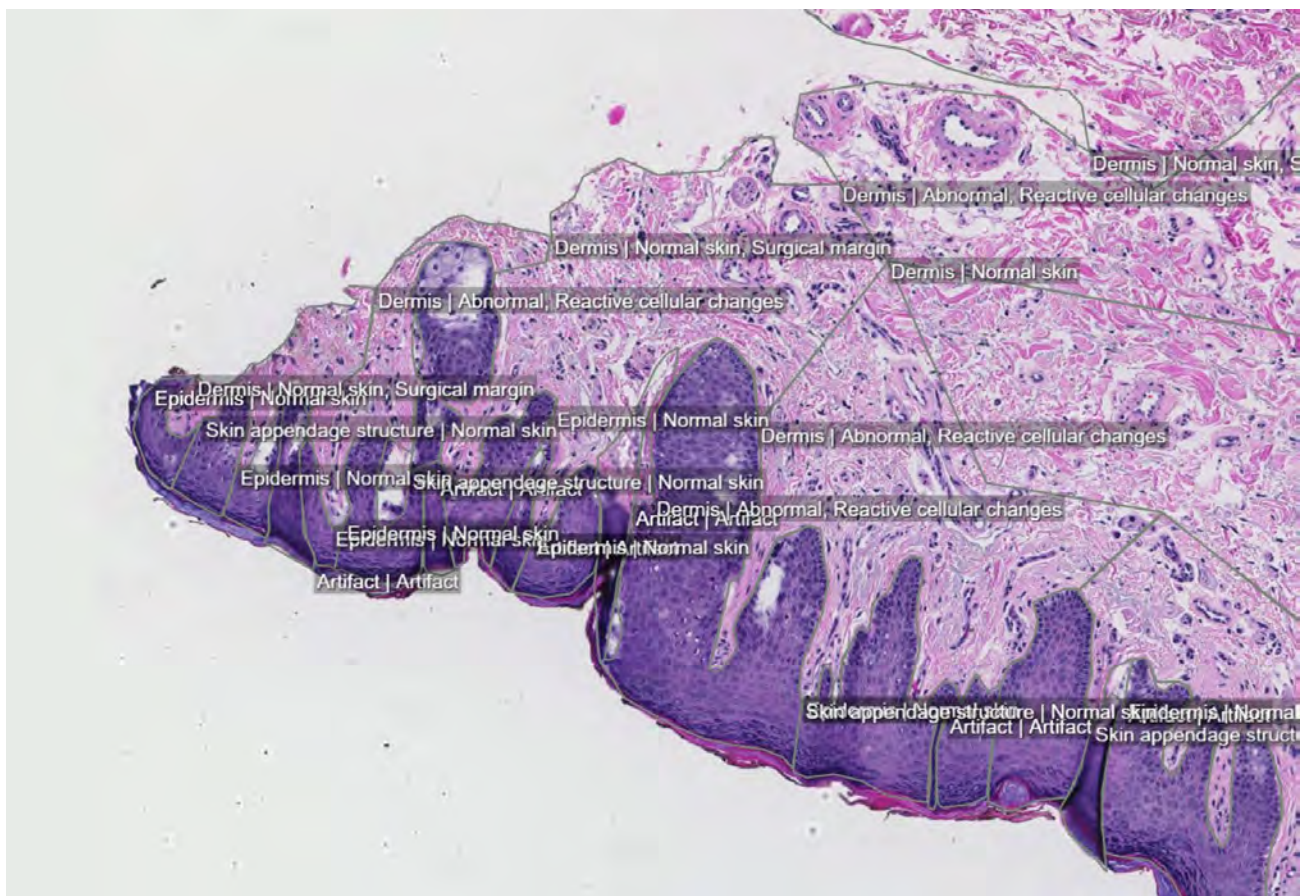


FIGURE. Annotation of a histopathology sample.

Digital Pathology

Diagnostic pathology is of crucial importance for health care, especially cancer care. Pathologists analyze tissue, histology, and cell samples, cytology, from the patient. 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 imaging diagnostics in pathology 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 artificial intelligence and human-computer interaction.

The CMIV research agenda in digital pathology tackles several image analysis challenges. An important groundwork is to create systematically annotated collections of imaging data to be used as ground truth for training of artificial intelligence models. The

project has developed four large, systematically annotated data collections that are shared through the AIDA Data hub, in total about 800 GB of image data with 25,000 annotations.

Several clinical applications of AI in a human-in-the-loop setting are being explored: Increasing precision and efficiency in breast cancer histological grading, the same for cancer detection in lymph nodes, and smart assistance in skin cancer diagnostics. We also develop methods to accelerate the cumbersome process of creating training

Digital Microscopy

Oncology

Gastrointestinal

Gynecological

Pulmonary

AI/Data analytics

Visualization

PROJECT INFORMATION

Project Name

Digital Pathology

Project Leader

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

Main Project Participants

Darren Treanor, Jeroen van der Laak, Sven-Patrik Hallsjö, Anna Bodén, Karin Lindman, Sofia Jarkman, Jesper Molin, Martin Lindvall, Caroline Bivik Stadler, Martin Falk, Marie Waltersson, Stina Garvin, Martin Hallbeck, Arrigo Capitanio, Helén Richard

Grants

Vinnova AIDA 2017–2021
WCMM 2018–2022

Key publications

Lindman K, Rose J F, Lindvall M, Lundström C, Treanor D. Annotations, ontologies, and whole slide images-Development of an annotated ontology-driven whole slide image library of normal and abnormal human tissue. *Journal of Pathology Informatics*, 2019.

Asa S L, Bodén A C, Treanor D, Jarkman S, Lundström C, Pantanowitz L. 2020 vision of digital pathology in action, *Journal of pathology informatics*, 2019.

Falk M, Ynnerman A, Treanor D, Lundström C. Interactive Visualization of 3D Histopathology in Native Resolution. *IEEE transactions on visualization and computer graphics*, 2018.

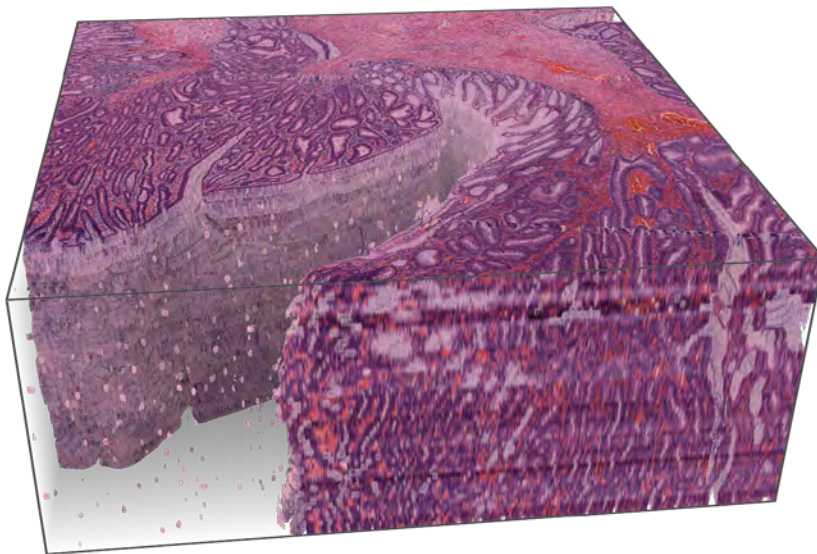


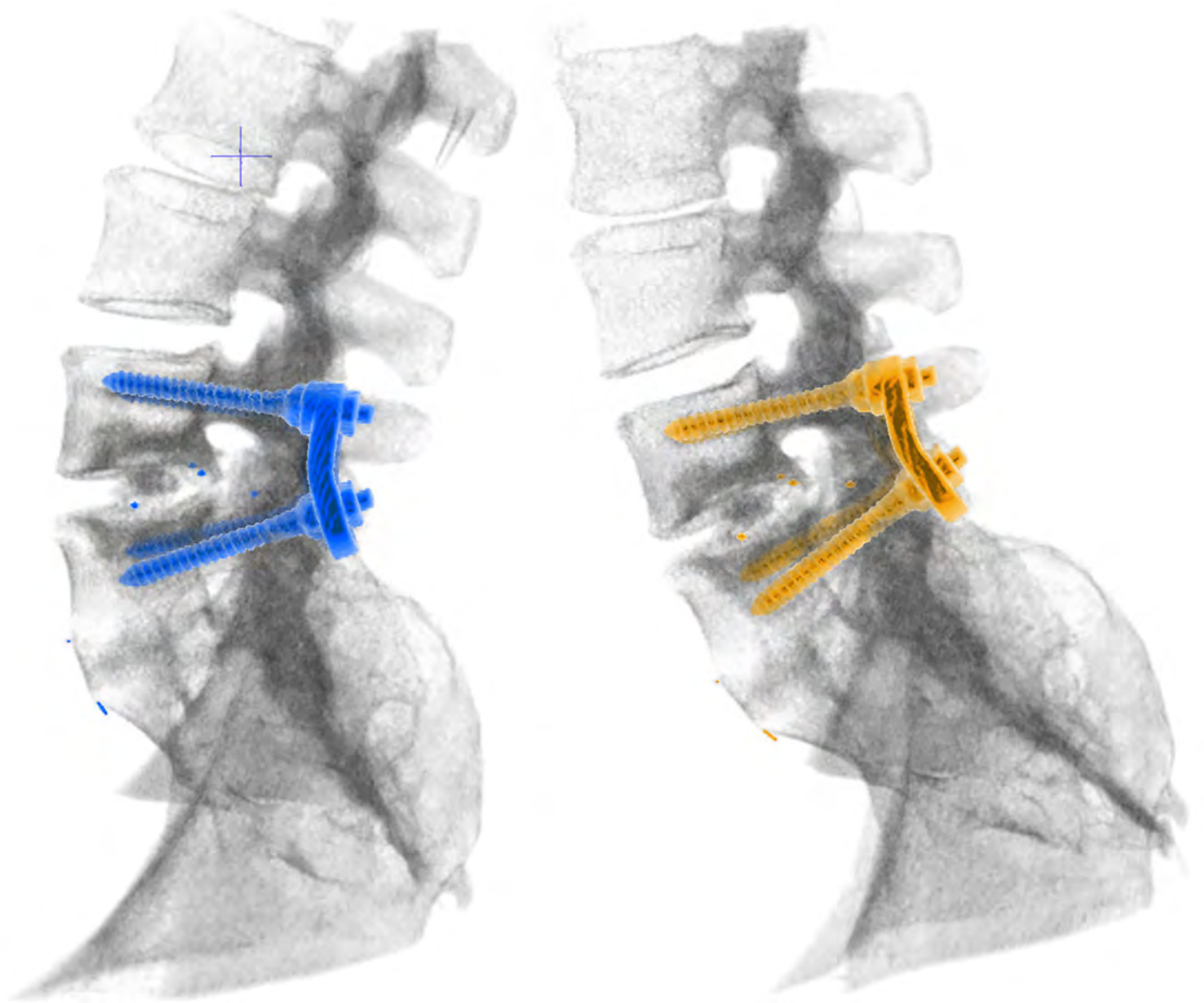
FIGURE. 3D histology where thin histopathology images from a tissue sample have been combined to show a three dimensional volume on the microscopic level.

data for initial AI development and for tuning AI models in clinical use. Furthermore, methodology to validate digital clinical work is developed and deployed. A common ground for these research projects is the focus on finding digital solutions that will work in the clinical setting.

A noteworthy result from the project is also a solution for visualization of 3D histology, handling these very large data sets at high speed and with ample interaction possibilities.

The CMIV pathology group consists

both of medical and technical researchers from the university and pathologists and lab assistants from the clinical pathology department at the hospital, all working together on research and development efforts close to clinical practice. The group is very active in the international community to promote advances in the field. Examples include the organization of the Nordic Symposium on Digital Pathology and contributions to the Computational Pathology Symposium at the European Congress of Pathology. ■



Precision Orthopedics

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

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

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

Traditionally, the orthopedic surgeon's workflow for physical material

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

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

A noteworthy achievement in the CMIV part of the project concerns the patient movement effort, led by Hans Tropp. The groundbreaking idea pursued is to combine a CT scan with marker-based motion capture, to create a dynamic model of the individual patient. There now is a working high-precision solution, that was demonstrated at the Swedish orthopedic congress. It is being used in studies of femoroacetabular impingement and other orthopedic applications. ■

Computed Tomography

Musculoskeletal

Acquisition

Modeling

AI/Data analytics

Visualization

Simulation

PROJECT INFORMATION

Project Name

PRECIIS – Groundbreaking Precision for Orthopedic Surgery

Project Leader

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

Main Project Participants

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

Grants

Vinnova 2017–2019

Key publications

Vavruch L, Brink RC, Malmqvist M, Schlösser TPC, van Stralen M, Abul-Kasim K, Ohlin A, Castelein R M, Tropp H.

Surgical Outcomes of Anterior Versus Posterior Fusion in Lenke Type 1 Adolescent Idiopathic Scoliosis. Spine, 2019.

Brink RC, Vavruch L, Schlösser TPC, Abul-Kasim K, Ohlin A, Tropp H, Castelein R M, Vrtovec T.

Three-dimensional pelvic incidence is much higher in (thoraco) lumbar scoliosis than in controls. European Spine Journal, 2019.

Brodén C, Giles JW, Popat R, Fetherston S, Olivecrona H, Sandberg O, Maguire Jr G Q, Noz M E, Sköldenberg O, Emery R. Accuracy and precision of a CT method for assessing migration in shoulder arthroplasty: an experimental study. Acta Radiologica, 2019.

Quantitative MRI as a Tool for Post Mortem Imaging

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

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

the gold standard for acquisition of relevant post-mortem data, especially in determining natural causes of death such as acute heart attack.

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

It was found that each relevant pathology such as infarction, inflammation or tumors exhibit unique combinations of parameters. Therefore, the measured values can provide the

radiologist and the forensic pathologist with relevant information for the determination of the cause of death.

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

PROJECT INFORMATION

Project Name

Quantitative MRI as a Ground-Breaking Tool for Post Mortem Imaging Diagnoses

Project Leader

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

Main Project Participants

Wolf-Dieter Zech, John Bäckman, Malgorzata Pietrzak

Key publications

Schwendener N, Jackowski C, Persson A, Warntjes MJ, Schuster F, Riva F, Zech W-D. 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.

Schwendener N, Jackowski C, Schuster F, Persson A, Warntjes MJ, Zech W-D. Temperature-corrected post-mortem 1.5 T MRI quantification of non-pathologic upper abdominal organs. *International journal of legal medicine* 131 (5), 1369–1376. 2017.

Warntjes JBM, Persson A, Berge J, Zech W. Myelin detection using rapid quantitative MR imaging correlated to macroscopically registered luxol fast blue-stained brain specimens. *American Journal of Neuroradiology* 38 (6), 1096–1102, 2017.

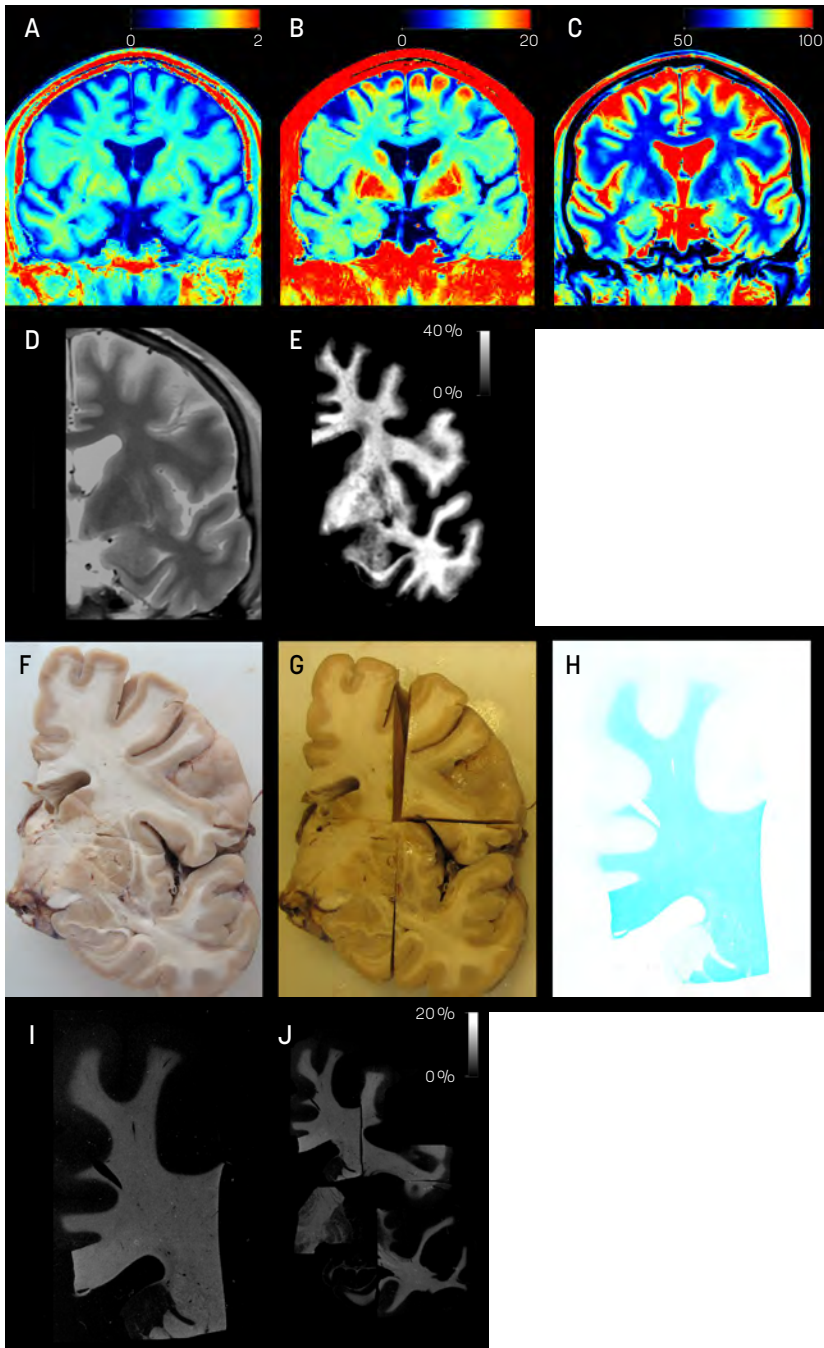


FIGURE. The process for myelin evaluation on a male subject, 69 years old, acquired at a temperature of 10 degrees.

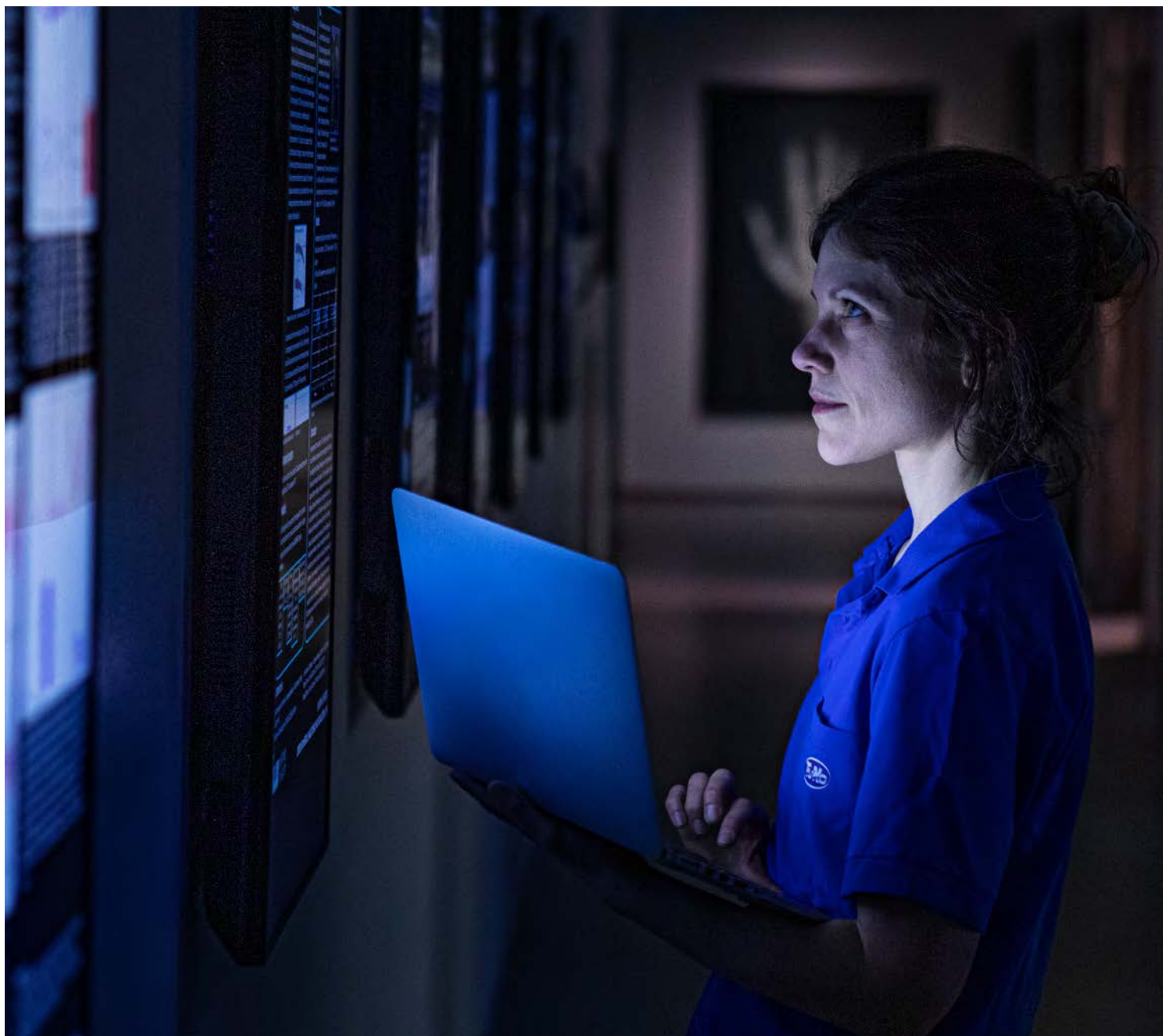




Quantitative Data

– Key to Precision Medicine

Precision medicine is an emerging approach that takes individual variability into account. By using clinical and environmental information not only from the patient at hand but also from a large group of previously treated patients, individuals can in more detail be classified into subpopulations that differ in how they respond to a specific treatment. Precision medicine and big data fits perfectly into the concept of artificial intelligence (AI). Some even state that in order for precision medicine to reach full potential it must embrace artificial intelligence and in particular, deep learning.



Traditionally, treatment strategies have been developed to fit the average patient, not focusing on individual differences. Although this works in many cases the consequence is often a fair share of patients for whom the treatment is not optimal but they are still suffering from possible side effects. These cases of over-treatment do also post an economical burden on the health care system.

Precision medicine is an emerging approach that takes individual variability into account. By using clinical and environmental information, not only from the patient at hand but also

from a large group of previously treated patients, individuals can in more detail be classified into subpopulations that differ in how they respond to a specific treatment. In this way doctors can more accurately predict which treatment strategy that will be effective in a specific group of patients, sparing side effects and costs for those who will not benefit. In other words, precision medicine provides the right treatment to the right patient at the right time.

The progress seen in precision medicine lately is related to fast development within a number of important research and technology areas such as large-scale genetic sequencing, high resolu-

tion imaging, biosensors, large scale data transfer and artificial intelligence.

Although precision medicine is promising in the possibility to increase prevention, early diagnostics and effective therapies, it is still in its infancy. Much work remains to be done before it can really be part of the every-day business in healthcare.

To be effective, precision medicine relies on large amounts of data from different sources being stored and processed.

Big Data

Big data is the term used for data sets that are either too large or so complex

“The aim of my thesis has been to develop quantitative methods for analyzing muscle size and fat infiltration.”

Anette Karlsson

that commonly used software tools are unable to handle them. With the use of big data, it is possible to see trends and associations that are not evident when looking at smaller data sets. At first glance, the advantages for medicine should be direct. However, at a closer look the picture reveals more complexity.

Big data can be categorized as unstructured or structured. Structured data consists of information that is collected in a categorized way and is often numeric. The data is frequently found in spreadsheets. This is the kind of data that large industries as Google and Amazon are using in many of their

successful analyses. Although these data sets are definitely big they are often of low information density.

Structured data does exist in medicine too but it is more common with unstructured data. For example, in a big data context, notes from patient records or radiology images would be considered unstructured as the information is not possible to retrieve directly. For images there is of course a spatial structure, but traditionally the content is only suitable for visual inspection. Often, several forms of data are combined, adding to the complexity.

The Challenge with Unstructured Data

Medical images can originate from a wide range of imaging methods. Hence, the output can vary in resolution and number of dimensions from two up to four, as in the case of time-resolved images. In addition, the dimensionality increases when there is more than one value per pixel, such as in flow studies. With increased resolution and dimensionality, the volume of data grows dramatically. These data volumes in combination with potential integration of different modalities require advanced analytical methods and high-performance computing.

Medical images suffer from different levels of disturbances as noise, artefacts and missing data that if not handled with preprocessing will distort the analysis. The images also need segmentation to extract the region of interest. This is often done manually by a radiologist but in larger data sets an automatic solution is necessary.

Quantified Imaging Data

With the rising interest in big data analytics comes an increased demand for quantification of imaging data. The traditional analysis of radiology or pathology images is a subjective approach where the radiologist or pathologist looks at the images and guided by what they see determine the diagnosis. Apart from being a time-consuming effort often with a low reproducibility the data produced is problematic in big data analytics. The data needs a lot of pre-processing in order to be useful.

Quantitative methods on the other hand, often have a higher level of reproducibility and the automatic nature

makes it faster. A quantitative method can also rely on other channels than the visual and therefore detect things that cannot be seen with the naked eye.

CMIV has the advantage of having access to the whole imaging chain from the actual clinical problems that arise in the day to day business, through on-site research power, to a clinical environment where the solution can be evaluated. The interdisciplinary nature of the research environment makes problems requiring both technical and medical expertise easier to solve.

CMIV Initiatives in Quantification

Anette Karlsson, one of the PhD students at CMIV is an engineer now working as an MR Physicist in parallel to finishing up her thesis.

– In my research I characterize muscles using magnetic resonance imaging. The aim of my thesis has been to develop quantitative methods for analyzing muscle size and fat infiltration in the muscles. Both to be able to use the method for longitudinal studies but also to speed up and automate the process, Anette explains.

The research shows that muscle volume and even more so, fat infiltration seems to be correlated to diseases as muscle dystrophies, cardiovascular diseases and diabetes mellitus.

– Other methods for muscle measurements are often too indirect. For example, the circumference of the thigh or upper arm results in a large variability in muscle volume and says nothing about fat infiltration, Anette says.

The problem with an MR image is that if you don't apply some kind of quantification the value you get for a specific area in the body will not be the same if you redo the analysis at another time. There is no absolute grey-scale. The variability in signal is high and very much dependent on the parameters you choose in the camera.

The signals from fat tissue and water-based organs as muscles behave differently and can easily be separated.

– We have developed a method where we calibrate the fat signal in the MR image in a way that makes the method more robust and insensitive to changed parameters. Using the calibrated fat signal against the total signal we can calculate the functional muscle mass, Anette continues.

The method that Anette and the research group she is part of have developed is now the base of the spin-off company AMRA.

The method has not yet reached clinical practice but is used in clinical research. One of the studies where it is used is in UK Biobank, where 100,000 volunteers are analyzed with the purpose of understanding more about why some people get sick while others do not and how our body composition is related to the risk of getting diseases as diabetes mellitus and cardiovascular disease.

Another quantification method developed at CMIV is the synthetic MRI method. With the technique you can quantify fundamental physical properties of a patient's tissues using MRI. Based on these physical properties a range of conventional MR images can be recreated and 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 to provide more objective means of patient follow-up.

The technique is available commercially through the spin-off Synthetic MR and implemented by most MRI vendors.

Artificial Intelligence

Precision medicine and big data fits perfectly into the concept of artificial intelligence (AI). Some even state that in order for precision medicine to reach full potential it must embrace artificial intelligence and particularly deep learning.

The technical advances in AI have grown immensely in recent years and the progress in machine learning, especially in deep learning, has opened up for great values in medical imaging. With the help of AI large medical data sets can be analyzed much faster and at the same time, more accurate conclu-

sions on treatment options, prognoses and outcomes may be drawn.

In machine learning, mathematical models are developed which have the ability to solve problems by experience. The models are trained to produce useful outputs by being introduced to relevant data sets. The goal is to be able to make correct predictions when using the model on new data. Traditional machine learning is based on human experts pre-defining what features that would be relevant for a prediction – in this context, which image details to look for. Deep learning algorithms, on the other hand, are typically trained without the limiting human intermediary and will automatically identify the true important features.

Training a successful deep learning algorithm requires a substantial amount of data. Medical images are stored digitally in picture archives and are well suited sources for big data sets. When the complications of working



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



Pathologist and CMIV PhD student Sofia Jarkman reviews a digitized histopathology slide.

with medical image data mentioned above is considered and acted on, medical imaging turns out to be a gold mine for big data and the potential for deep learning applications is endless.

– You might think that the hardest part when developing an AI product is to train the AI model. It is not. There are well established methods for that, says Adjunct Professor Claes Lundström.

Claes is the Director of the AIDA initiative and is well aware of what kind of difficulties that may be encountered.

When the model is fully trained a common mistake is to believe that it is ready to be put to work as an independent resource. In reality you need an interaction between the AI algorithm and the expert. One question that needs to be addressed is how to handle false positives. The sensitivity of the AI algorithm is often set high to avoid missing positive cases, with a high level of false positives as a consequence.

– You need a very efficient way of handling false positives or else you have probably lost time on introducing the AI tool. If you do it right I believe that even an AI with relatively low accuracy can be very useful, Claes explains.

At CMIV several AI efforts within

pathology are ongoing where deep learning algorithms are developed for image analysis. In cardiovascular research CMIV researchers have been involved in a study evaluating an AI algorithm estimating fractional flow reserve on coronary CT angiography. In neurology several groups are working with Generative Adversarial Networks (GANs) to generate synthetic images in the training of AI algorithms.

Standardized Acquisition

A key factor to achieve precision in medical imaging research is to have high control of the acquisition process. A standardized, high-quality acquisition means carefully tuned protocols for both modality settings and how the staff perform the examination. This is always in focus at CMIV, which means that research on CMIV-acquired data more easily can pinpoint the disease-specific variations without being disturbed by irrelevant factors.

The benefits of precise acquisition also apply to AI research. Deep learning models may then focus fully on the anatomical and physiological patterns of the patients, learning what the essential differentiating characteristics are.

An important way to disseminate

knowledge is that the protocols and workflows used by CMIV for data acquisition also are being used in clinical practice worldwide.

While this forms standardization to some extent, the typical situation is that the variation in acquisition routines among different sites is high. This is a challenge, not the least for AI solutions, that typically perform worse in a normal clinical setting due to the inherent messiness of the data. Thus, in parallel to standardizing acquisition, AI research must evolve towards better generalization from clean research data to data in the clinical wilderness. Pooling data across many sites is perhaps the most important approach, leading to a strong need for large-scale sharing of medical imaging data at the international level.

Future

The use of machine learning and deep learning in healthcare is still a work in progress. There are several strong initiatives going on both in academia and in the industry but the transfer into clinical use have proven difficult. In this aspect interdisciplinary research centers like CMIV has an important role to play. ■



CMIV PhD student David Abramian together with Ingemar Fredriksson and Josef Wiltzén from Department of Biomedical Engineering.

The CMIV Research School

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

Quantitative Muscle Tissue Analysis using MRI

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

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

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

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

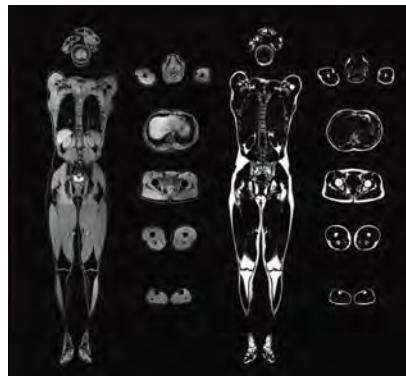


FIGURE 1. A paired magnetic resonance image where the left shows all the water within a whole body and the right shows all the fat.

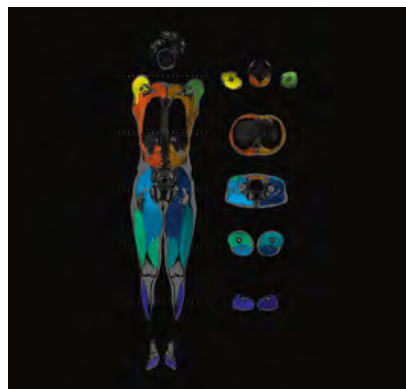


FIGURE 2. A typical result from the automatic method. The different muscle groups are shown in different colors. Grey color indicated that the automatic method has not considered that tissue as muscle tissue.

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. ■

PROJECT INFORMATION

Supervisors

Magnus Borga, Ola Friman, Janne West, Anneli Peolsson

Project

WADIT
MR-based Body Composition

Background

MR Physicist, Department of Medical Radiation Physics, University Hospital of Linköping, 2019–

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

Master of Science, Engineering Biology, The Institute of Technology, Linköping University, 2005–2011

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. Traditionally the degree of stenosis has been used as a measure for risk assessment, but in later years research has shown that the contents rather than the size of the plaque is correlated to plaque rupture. The factors most strongly associated with plaque rupture are blood (intraplaque hemorrhage, IPH) and fat (lipid rich necrotic cores, LRNC).

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

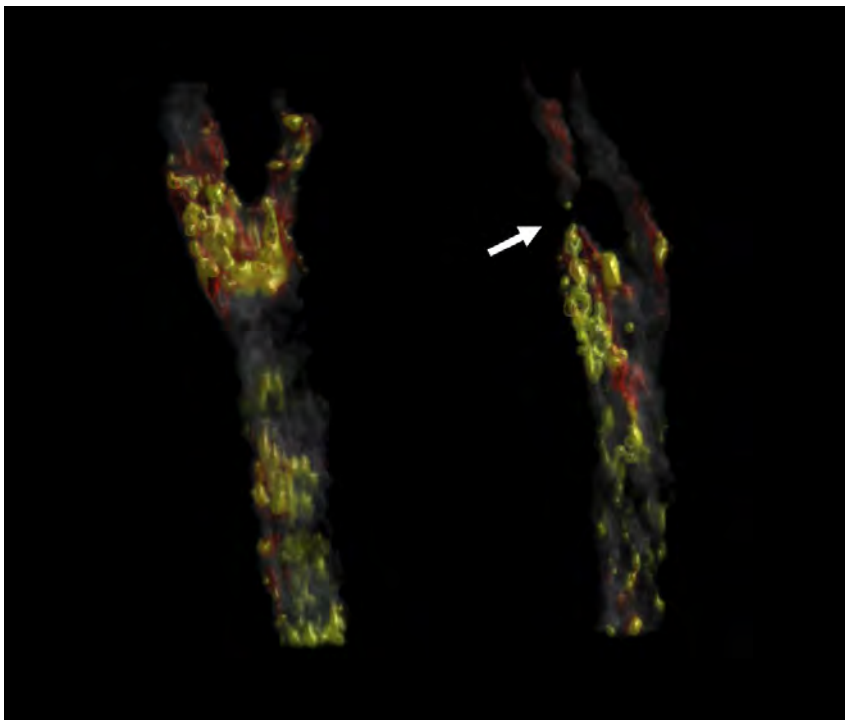
started in 2017 and is finished.

For analysis of the plaques we use a quantitative MRI (qMRI) technique, which is a recently developed method used to quantify the amounts of fat (LRNC) and blood (IPH) inside the vessel walls and plaques. The patients have had a four-point Dixon and cardiac-triggered T1-weighted qMRI-assessment at two points in time, detecting LRNC and IPH by registering the Dixon images against the T1W images. We use a 3T Philips Ingenia scanner located at CMIV.

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

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

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



PROJECT INFORMATION

Supervisors

Ebo de Muinck, Joep Perk, Petter Dyverfeldt

Project

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

Background

Medical school, Linköping University, medical degree 2011

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

Mathematical Modeling of Biological Mechanisms Underlying Brain Responses in fMRI

The brain is an activity-intensive organ which consumes ~20 % of the adult human's total energy production, despite only accounting for ~2 % of the total bodyweight of an average adult. To sustain this high demand for energy, the neural cells in the brain require a continuous supply of molecules used to produce energy, typically glucose and oxygen.

To ensure that an adequate supply of glucose and oxygen is preserved during periods of increased brain activity, the brain directs an increased flow of blood into activated brain areas. This hemodynamic change can be seen in the blood oxygenation level dependent (BOLD) signal captured using functional magnetic resonance imaging (fMRI).

Due to the difficulty of measuring brain activity directly (i.e., the firing of electrical synapses) in humans, researchers often rely on these measurements of hemodynamic responses as a proxy for brain activity. 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). However, the precise mechanisms which translate brain activity to these archetypal hemodynamic responses remain not fully understood. Furthermore, this translation is shown to dysfunction in different neurological disorders.

Here, the use of mathematical modeling, where biologically based hypoth-

FIGURE 1

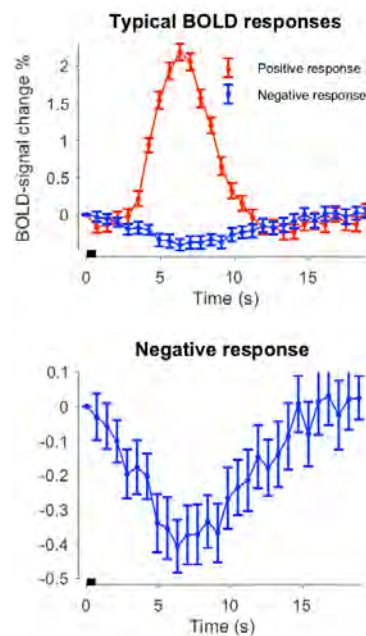
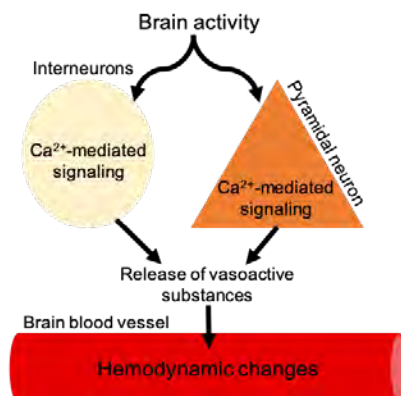


FIGURE 2



eses are translated into mathematical equations and evaluated in a systematic way has been successful. We have previously developed a mathematical model, illustrated in figure 2, which is based on state-of-the-art experimental insights on a cellular level. Using these insights, our model can describe and predict previously published data from different species (humans, rodents, and primates), consisting of many different measurement observables. Furthermore, the model can accurately reproduce the effect of a common anesthetic used in rodent studies. These results pave the way for a better quantitative understanding of how neural activity and hemodynamic responses are connected and provides a new environment that allows for testing of potential therapeutics and their effect on brain hemodynamics. ■

PROJECT INFORMATION

Supervisors

Maria Engström, Gunnar Cedersund, Fredrik Elinder

Project

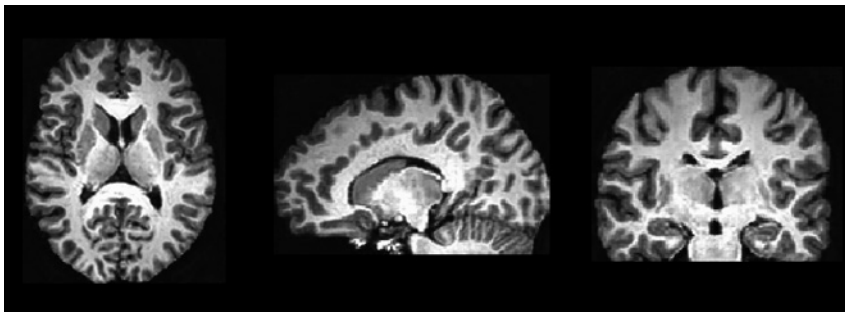
Ab Initio Mathematical Modeling of Mechanisms in the Human Brain

Background

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

Research preparatory course I–II, 2014–2015

Deep Learning Applied to Multimodal Datasets in Psychiatry



A synthetic image of a brain created with a 3D CycleGAN network. Training the algorithm took 12 days using a Tesla V100 graphics card.

Among all medical conditions, major depressive disorder (MDD) is a world leader in terms of years of productive life lost due to illness. This loss of productive life is due to a higher risk of suicide among individuals suffering from depression, but it is also caused by depression's negative effect on work and family relations. Scientists have for a long time tried to understand the underlying brain mechanisms of depression and have made important advances. There are, however, still no good objective biomarkers that can determine if someone suffers from depression or predict whether a patient could benefit from a specific treatment. In this project we will develop deep learning methods that could help us address these challenges.

A deep learning algorithm will be applied to a large, open repository of structural and functional neuroimaging data from depressed and never-depressed individuals. This deep learning algorithm can detect patterns that are often undetectable when using

more traditional “mass univariate” methods.

The algorithm will first be trained and tested using only anatomical data, and next on the neural functional data and, finally, on a combined anatomical plus functional dataset. We can then compare what kind of data that results in the best performance in the deep learning network in terms of distinguishing healthy from depressed individuals.

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

What region or brain function allows us to tell the difference between a healthy and depressed individual? A question like this can be addressed by using a different kind of deep learning network: A network that produces arti-

ficial brains. Specifically, this generative network will be trained to translate from a healthy brain to a depressed brain. Then, by subtracting the fake depressed brain from the real healthy brain we will be able to tell what the deep learning network changed in the healthy brain in order to make it look depressed. By applying the same kind of approach we could, for example, find the neural differences between depressed individuals who respond well to a specific treatment and others who did not respond to this treatment.

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

PROJECT INFORMATION

Supervisors

Markus Heilig, Anders Eklund, Paul Hamilton

Background

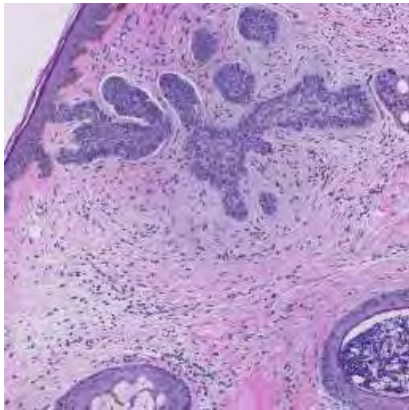
Center for Social and Affective Neuroscience, Linköping University Research Engineer, 3/2015–present

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

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

Master of Science (M.Sc) Medical Physics, Lund University, 9/2009–6/2014. Licensed Medical Physicist, Leg. sjukhusfysiker

XAI Applied to Histopathology Image Analysis



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

This project focuses on the issue of understandability of the AI tools that are developed for assisting the work of pathologists. In order to do this, the methods of explainable AI (XAI) are explored with the aim to apply them in AI solutions for digital pathology. What is Explainable AI? It is an active research field that aims to provide means of explaining the inner workings as well as the reasoning behind the predictions of an AI algorithm. For example, in tumour diagnosis, it would provide an insight into why a whole slide image (WSI) has been labelled as containing “benign

tumour”. The methods achieve this by creating a heatmap on the original image, generating synthetic visualizations or providing some other scores.

Grad-CAM is a commonly used technique for explaining AI. It determines which pixels in the image have contributed most to the predicted outcome. In this project we have trained two AI algorithms to predict if a patch from a skin WSI contains tumour cells (figure to the left). On purpose, we trained one algorithm to perform better than the other. Then we generated Grad-Cam visualisations to understand which parts of an image are most important for each algorithm to determine if the image contained tumour cells (figures to the right). Comparing the visualisations produced on the same patch by the both AI algorithms, we could distinguish which algorithm that had performed better in this task, why an algorithm made a mistake or a correct prediction. The future work will aim to apply Grad-CAM as well as other XAI methods to help making AI solutions for other problems more transparent. ■

PROJECT INFORMATION

Supervisors

Claes Lundström, Stina Garvin, Gabriel Eilertsen

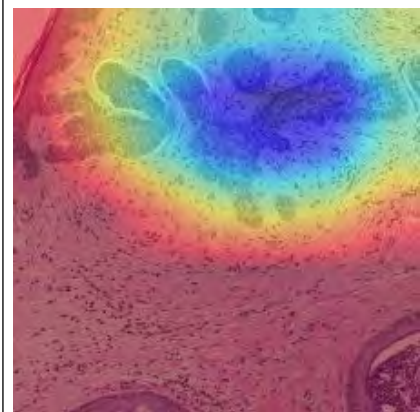
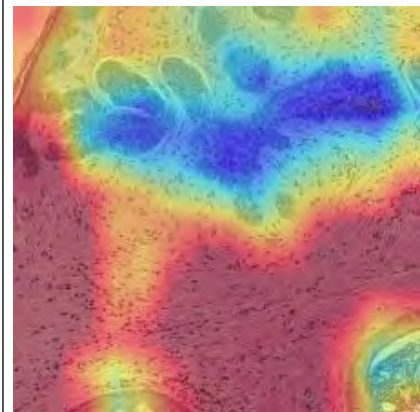
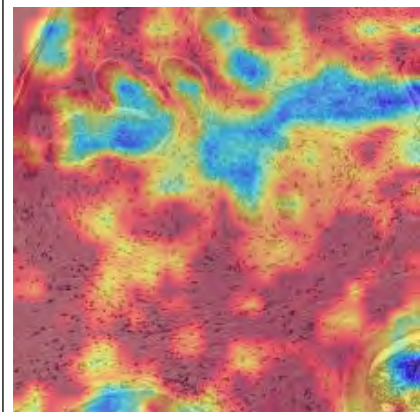
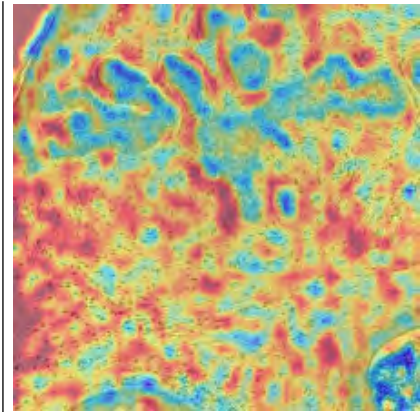
Project

Explainable AI in digital histopathology (XAI-Path)

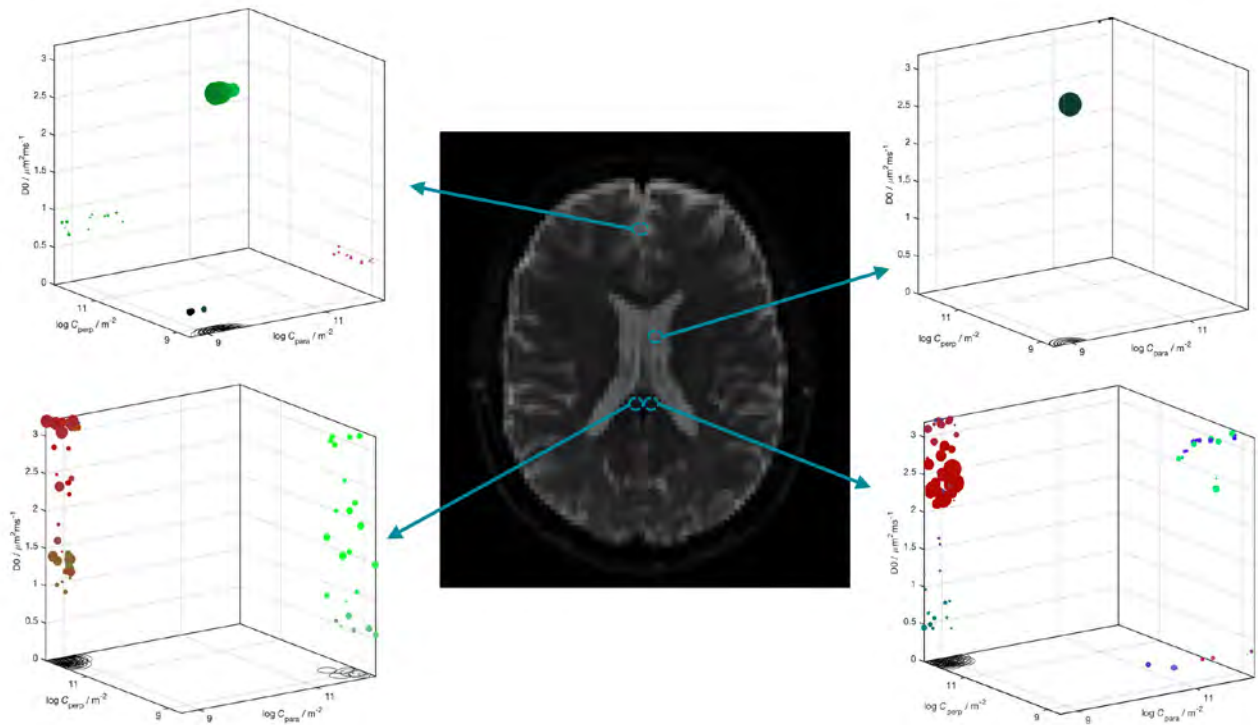
Background

Lancaster University, BSc. Hons Financial Mathematics, 2011–2014

Linköping University, MSc. Statistics and Machine Learning, 2017–2019



Neural Tissue Composition via Diffusion MRI



Diffusion MRI is an imaging technique that allows the study of porous media structures by probing the random motion of water molecules in the scanned specimen. Due to its non-invasive character, it represents a powerful tool for the characterization of the brain microstructure without the use of ionizing radiation.

Its potential as a tool for exploring the brain architecture both in terms of neural connections and local structure has been proven along the years, and many models and methods have been proposed in order to extrapolate meaningful parameters from diffusion sensitized images.

A commonly adopted strategy involves modelling the water molecules' diffusion process as if it was happening freely in space. While this assumption holds in certain scenarios, it constitutes an evident paradox in the recently introduced framework called multidimensional diffusion MRI. Such

framework combines advanced diffusion encoding schemes and maps the brain microstructure at the sub-voxel scale, as a collection of small separate domains in each of which water diffusion is taking place freely, i.e. without any restriction.

To alleviate the free diffusion assumption, we propose to model each voxel as a distribution of compartments in which diffusion is confined. To do so, we replace the currently used paradigm with a model called Confinement Tensor. The figure shows the information that it is possible to retrieve using such approach. Each 3D plot shows the composition of selected voxels in terms of the geometry, displayed in the parameters C_{para} and C_{perp} , the orientation, represented as RGB scale, and diffusivity DO of each pore. All together these parameters provide a description of the neural tissue not achievable with conventional methods which stop at the voxel scale. Ideally, such maps will

provide new insights especially in cases where the neural microstructure is altered due to the presence, for example, of tumors. ■

PROJECT INFORMATION

Supervisors

Evren Özarslan, Ida Blystad, Anders Eklund, Magnus Herberthson

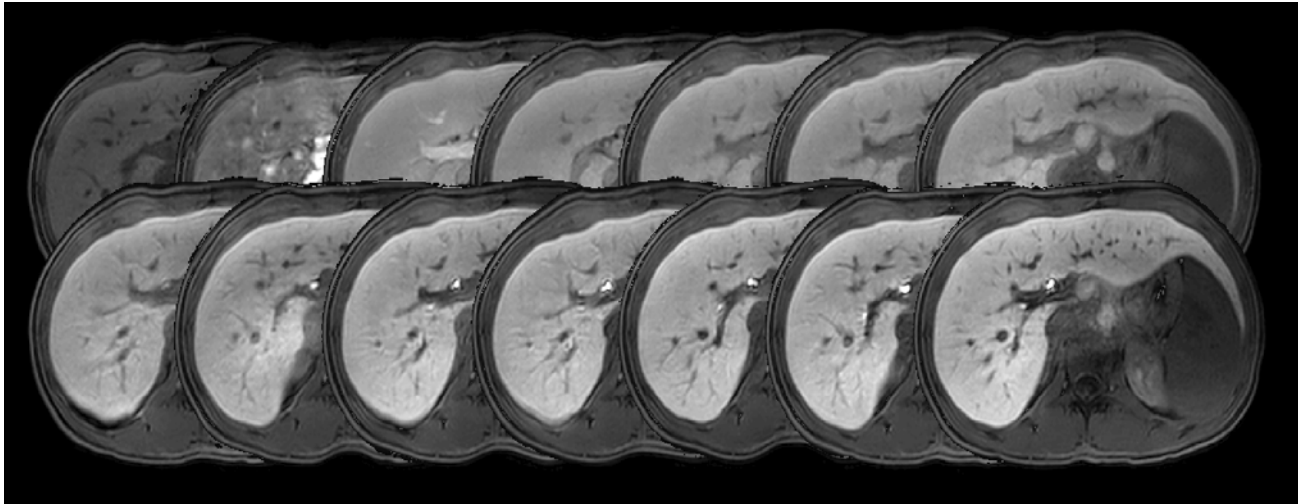
Project

Diffusion MRI with general gradient waveforms (DGGW)

Background

Master's Degree in Biomedical Engineering, 2018, Linköping University

Bachelor's Degree in Biomedical Engineering, 2015, University of Padova



Early Characterization of Hepatic Inflammation, Fibrosis and Function

Today, a patient with liver disease often has to go through a liver biopsy to help the physician diagnose the condition, or see how much fat, iron or fibrosis there is in the liver. However, a liver biopsy is an invasive procedure, which is uncomfortable for the patients and carries some risk for complications.

Therefore, my project is aimed towards using magnetic resonance imaging (MRI) to develop a noninvasive and quantitative tool-kit, which can be used for diagnosing and staging liver diseases. Such a toolkit should include methods for quantifying the amount of fat and iron in the liver, as well as staging how much inflammation and fibrosis there is. For late stages of liver diseases, there should also be methods for quantifying how much the liver function has been affected, e.g. when considering liver transplantations.

So far, my work has mainly focused on measuring liver function. To measure liver function, we use a contrast agent called Gadoxetate. A contrast

agent is a drug that makes parts of the images brighter and is given to a patient during an MRI-examination. Gadoxetate is a special contrast agent, which is accumulated in the liver cells, making the liver brighter than other organs, (Figure). Today, Gadoxetate is commonly used in conventional liver radiology, where radiologists mainly use it to visualize tumors.

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

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

PROJECT INFORMATION

Supervisors

Peter Lundberg, Nils Dahlström, Gunnar Cedersund, Stergios Kechagias

Project

Non-Invasive Liver Biopsy (NILB), Liver Intrinsic Function Evaluation (LIFE), Hepatic Inflammation and Fibrosis Investigation (HiFi), Heart, Adipose Tissue, and Liver Thrust (HEALTH)

Background

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

NASH in Context – a Multi-Level, Multi-Organ, and Translational Perspective

One of the biggest health issues in modern-day society is the prevalence of obesity. It has been shown that obesity is one of the underlying factors contributing to diabetes type 2 (T2DM), the metabolic syndrome (MetS) and other related health issues. Obesity can also lead to the development of other risk factors contributing to MetS, such as non-alcoholic fatty liver disease (NAFLD), which includes a range of liver diseases including non-alcoholic steatohepatitis (NASH). NASH is a form of chronic liver inflammation.

The goal of my project is to develop methods describing the progression and development of chronic liver diseases, NAFLD and NASH. The project centers around a range of available research perspectives in order to provide both holistic and systemic insights into liver disease in relation to T2DM and MetS. This will be done by combining research in developing and applying magnetic resonance (MR) measurements of clinical patients with modeling methods derived from systems biology.

My group has previously used magnetic resonance elastography (MRE), a non-invasive method, to evaluate the degree of liver fibrosis. MRE is used to derive mechanical properties, such as stiffness, from e.g. the liver. In some cases, NASH can be precursor for developing the more serious complication liver fibrosis. During the disease progression the stiffness properties of the liver change. So, for preventive purposes it would be beneficial to be able to detect early on-stage liver inflammation. Thus, my project will focus on the possibility of measuring the degree of inflammation in the liver. One major goal is to create an MR-based assessment of liver inflammation and other related clinical measures using MRE and other non-invasive protocols.

To better understand the progression of NAFLD and NASH my project will also include a systems biology aspect. This part of the project will focus on the creation of mechanistic models describing NASH and NAFLD development using both pre-clinical and clinical data. The goal here will be to create a

systems biology model that is able to describe the underlying mechanisms that cause the change in liver stiffness brought on by NASH and Fibrosis. ■

PROJECT INFORMATION

Supervisors

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

Project

Non-invasive liver biopsy (NILB), Liver intrinsic function evaluation (LIFE), Hepatic inflammation and fibrosis investigation (HiFi), Heart, adipose tissue, and liver thrust (HEALTH), Evaluation of prevalence and severity of NAFLD in primary care (EPSONIP)

Background

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

Coronary Artery Computed Tomography

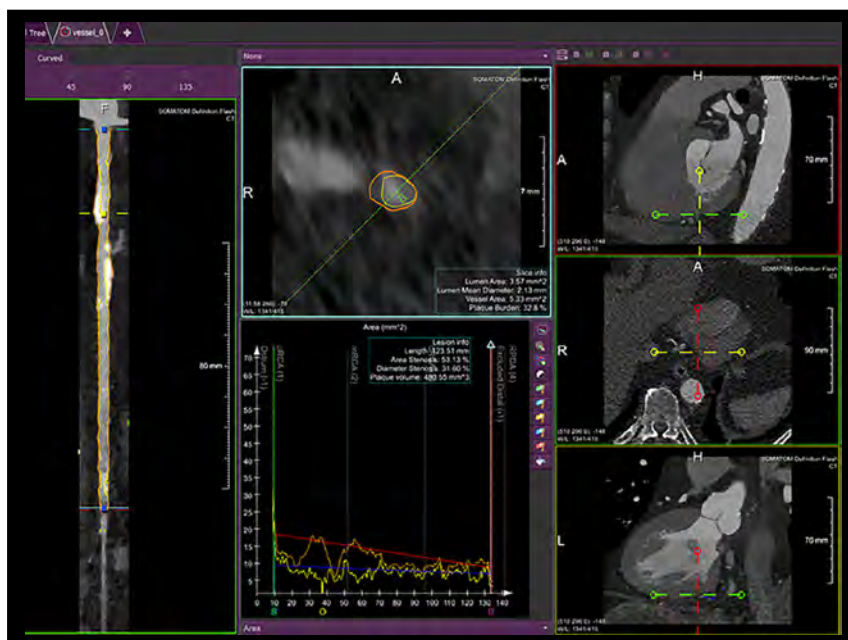
Coronary computed tomography angiography (CCTA) is a non-invasive examination method used to detect coronary artery plaques that might cause a reduction of the blood flow to the cardiac muscle i.e. stenoses. Iodine contrast is injected intravenously during the examination and this makes it possible to see plaques in the vessel wall. CCTA has a high sensitivity for detection of coronary stenoses while the specificity is lower due to a tendency to overestimate the stenosis degree. It is especially calcified lesions that make the evaluation difficult as they cause so called blooming artefacts. These blur the edges of the

plaque thus making it look larger than it actually is. Severe calcifications may even lead to undiagnostic CCTA:s. As a result patients sometimes end up being unnecessarily sent for further evaluation with invasive coronary angiography. This method is considered to be the reference method for stenosis evaluation due to the possibility to measure the fractional flow reserve (FFR) i.e. pressure drop caused by the stenosis.

One method that might increase the specificity of CCTA is to measure the transmural attenuation gradient (TAG). The theory is that the contrast attenuation in the vessel reflects the flow of contrast through that vessel.

By measuring the attenuation at small intervals throughout the vessel it is possible to calculate the linear regression coefficient. A stenosis will decrease the contrast flow and thereby increase the regression coefficient. The needed measurements can be made using specialized software or the same software used for the ordinary CCTA evaluation.

There is no standardized method established regarding the CCTA for TAG measurements. One factor that probably affects the results is whether the CCTA was acquired during one or multiple heart beats since every heart beat changes the contrast attenuation slightly. This retrospective study will include one heartbeat CCTA:s that have been followed up with invasive coronary angiography and FFR. All examinations have been acquired between August 2009 and March 2017 here in Linköping. The primary aim is to evaluate if TAG improves the specificity of CCTA:s acquired during one heartbeat. ■



PROJECT INFORMATION

Supervisors

Anders Persson, Jan Engvall,
Tino Ebbers, Mischa Woisetschlager

Background

Radiology nurse 2005, Masters
Degree 2013

fMRI Methods for Brain Tumor Treatment

Functional magnetic resonance imaging (fMRI) is a method used to reveal the location of brain activity when the subject performs a certain task. The analysis of fMRI data has revealed a great amount about the localization of specific functions in the brain. In clinical practice fMRI has become essential for the planning of brain tumor removal surgeries. Since fMRI shows the parts of the brain that are

still working it makes it easier for the surgeons to remove the tumor without damaging those parts.

The analysis of fMRI data relies heavily on signal processing and statistics. The data needs to be denoised by a filtering process, and afterwards a statistical test reveals what parts of the brain that were active. During the 2000s a “Bayesian” framework was introduced that unifies the procedure for

denoising the data and performing the statistical test, which produces better results in the analysis.

Due to the particular structure of the brain, with many folds in its surface, regions that are physically close together are not necessarily functionally related. The most common procedures for analyzing fMRI data do not take this anatomical information into account, but advanced “adaptive” methods exist which are capable of doing so. However, such methods have not yet been introduced in the new Bayesian framework.

In our work we have developed two different extensions to the Bayesian framework that make it anatomically adaptive. They differ in the precision of the anatomical information which they are capable of representing and in the amount of computing power that they require, with one of them being simpler and less precise and the other more complex and demanding. We have shown that both methods are capable of enforcing anatomical boundaries on the analysis of fMRI data, which leads to more precise activation maps. ■

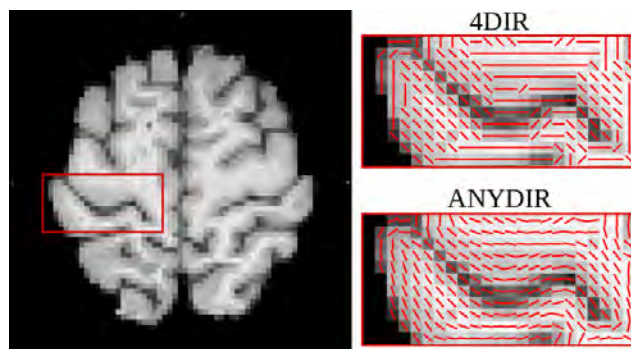


FIGURE 1. Comparison of the representations of anatomical orientation from both of the developed methods. The 4DIR methods is capable of representing fewer orientations but requires less computational resources.

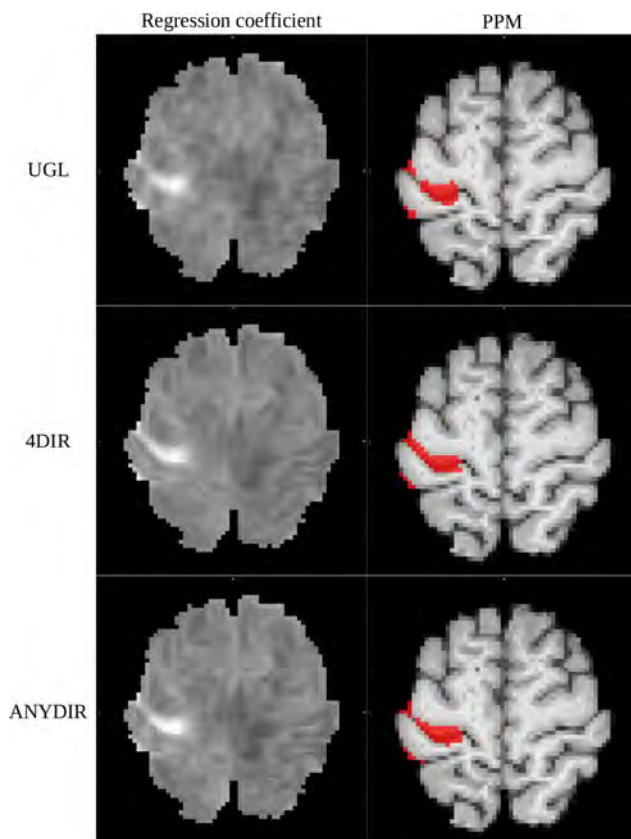


FIGURE 2. Comparison of regression coefficients and activation maps obtained from the original Bayesian framework and the two adaptive extensions. Both adaptive extensions reflect the anatomical information from the brain folds and result in more accurate activation maps.

PROJECT INFORMATION

Supervisors

Anders Eklund, Evren Özarslan, Ida Blystad, Hamid Behjat

Background

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

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

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

Human-AI Interaction for Medical Imaging

The last decade's advancements in machine learning (ML) has led to a dramatic increase in AI capabilities and the viability of learning by example. However, despite impressive technical advances and many successful research projects, machine

algorithms for medical diagnostics are to a very small extent used in healthcare today. One challenge is that for ML algorithms with less than 100% sensitivity and specificity the clinical user needs effective means to assess the validity of results and incorporate this knowledge

within the broader context of their diagnostic process.

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

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

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

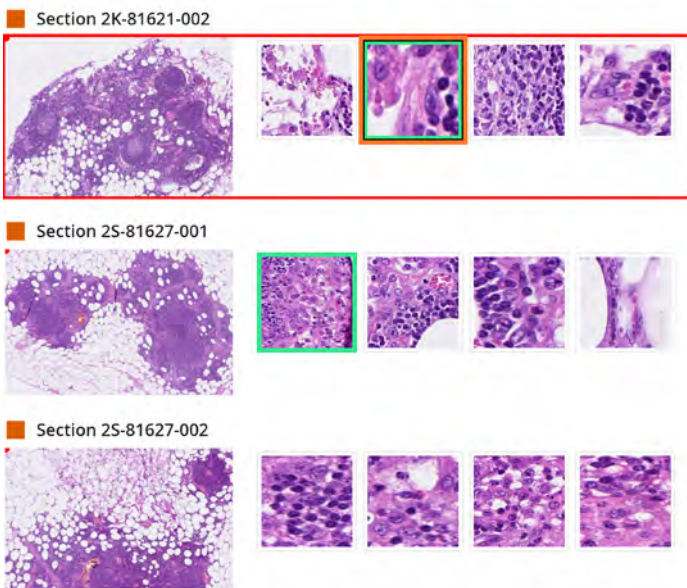


FIGURE 1. User interface for rapidly staging lymph node sections for metastasis. The pathologist is guided through a ranked list of detection candidates. The sensitivity can be increased if the preliminary results indicate the patient is close to a decision-cut-off. This allows an adaptable pace of work, working fast when possible and slow when needed.

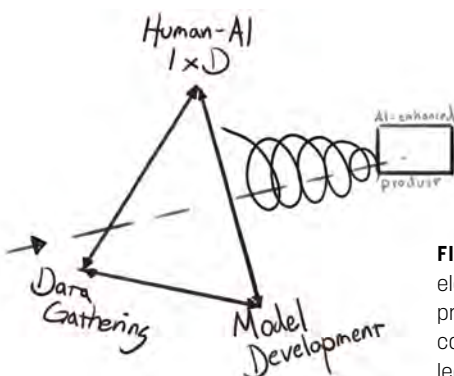


FIGURE 2. Description of the key elements for an iterative design process for software with predictive capabilities through applying machine learning in the development process.

PROJECT INFORMATION

Supervisors

Jonas Löwgren, Claes Lundström, Darren Treanor, Anders Ynnerman

Project

AIDA

Background

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

Senior Software Engineer at Sectra

Evaluation of an AI-Based, Calcium Scoring Software

Ischemic heart disease is caused by atherosclerotic narrowing of the coronary arteries, impairing blood flow to the heart muscle. It is the leading cause of morbidity and mortality in the world, not seldom associated with diagnostic challenges.

Coronary artery calcification (CAC) is frequent in patients with ischemic heart disease and may occur early in the atherosclerosis process.

Non-contrast-enhanced, ECG-triggered, coronary calcium scoring computed tomography (CSCT) detects CAC and is reliable in predicting future cardiovascular events for asymptomatic patients. The CAC scoring is traditionally performed by experts using semi-automatic softwares which includes manual identification and marking of the calcified coronary artery lesions.

The aim of this study was to compare an automatic AI-based CSCT post-processing software prototype to a traditional, semi-automatic software.

In total 315 CSCT examinations performed at CMIV were included and evaluated with both the traditional

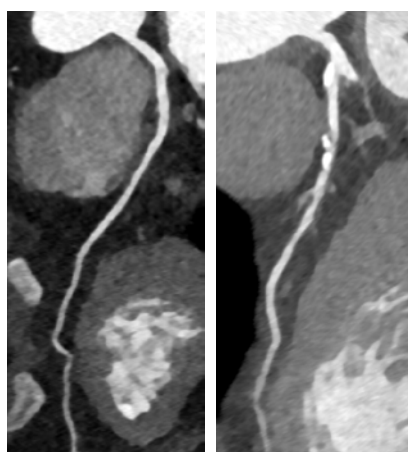


FIGURE. Multiplanar reconstructions of the left anterior descending coronary artery in two different patients.

Left: Normal artery. **Right:** Atherosclerotic narrowing of the proximal part of the artery.

semi-automatic software and the AI-based automatic software. Three calcium scores (Agatston score, Volume score and Mass score) and the number of calcified lesions were registered. Also, time for analysis was measured.

The AI-based, automatic software obtained CAC scores with excellent correlation and agreement compared with the conventional method but was less time-consuming. CAC scoring may thus be an excellent candidate for AI development in the clinical setting, having the potential to reduce clinical workload and increase efficiency. ■

PROJECT INFORMATION

Supervisors

Anders Persson, Joakim Alfredsson, Jan Engwall, Magnus Janzon

Background

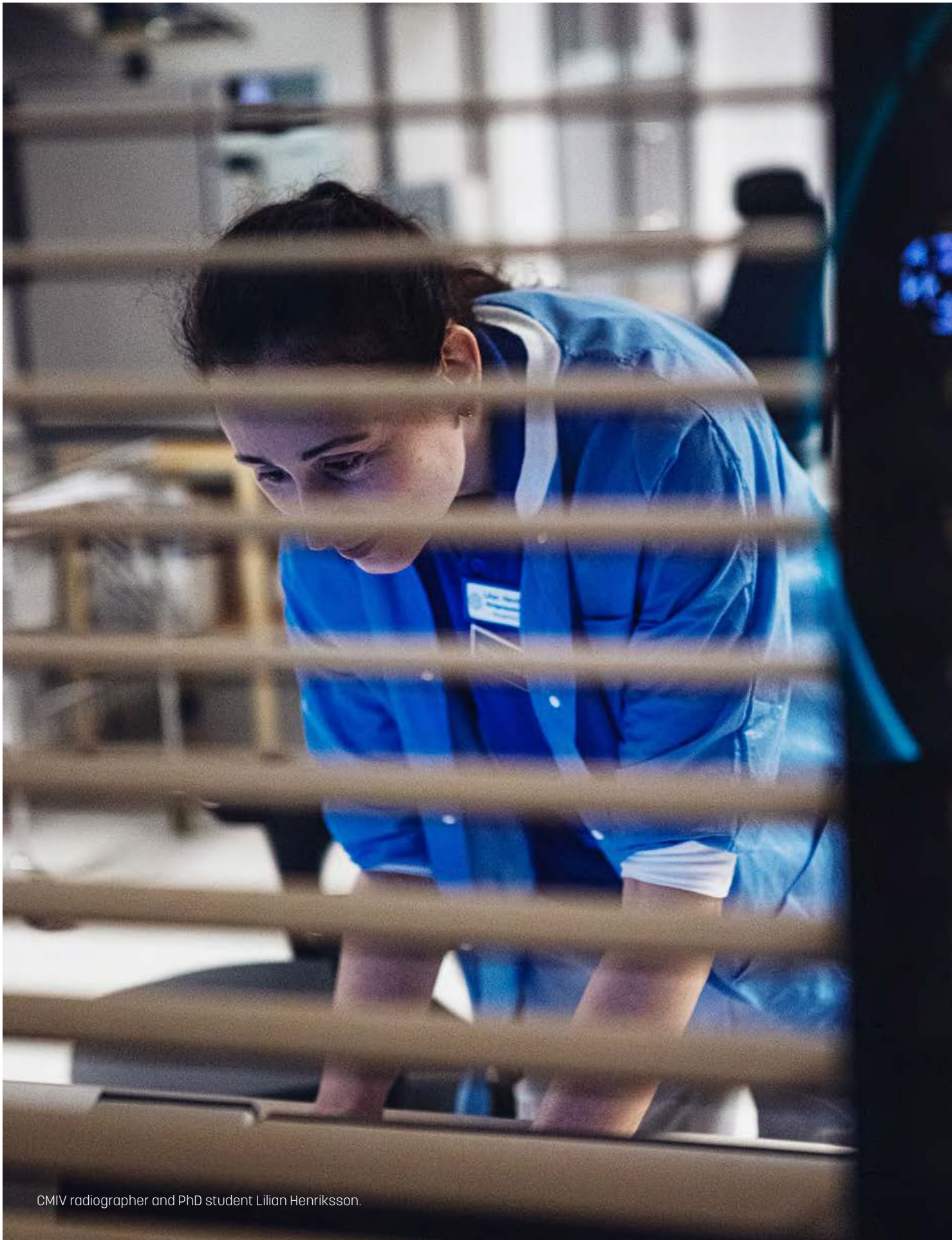
Specialist in medical radiology, 2008





Dissertations

During 2019 six of the CMIV PhD students have finished their studies and defended their theses. The PhD students and the research school are an important part of CMIV and we are proud to present their theses here.



CMIV radiographer and PhD student Lilian Henriksson.

Bharti Kataria

Visual Grading Evaluation of Reconstruction Methods and Dose Optimization in Abdominal Computed Tomography

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

An increase in the number of CT examinations has raised concerns about the negative effects of ionizing radiation as the dose is cumulative over the life span of the individual. Image quality in CT is closely related to the radiation dose, so that a certain dose with an associated small, but not negligible, risk is a prerequisite for high image quality. Typically, dose reduction in CT results in higher noise and a decrease in low contrast resolution which can be detrimental to the image quality produced. New technology presents a wide range of dose reduction strategies, the latest being iterative reconstruction (IR). The aim of this thesis was to evaluate two different classes of iterative reconstruction algorithms: statistical (SAFIRE) and model-based (ADMIRE) as well as to

explore the diagnostic value of a low-dose abdominal CT for optimization purposes.

This thesis clinically evaluated the effect of IR in abdominal CT imaging and estimated potential dose reductions. The important conclusion from papers I, II and IV is that IR improves image quality in abdominal CT allowing for some dose reductions. However, the clinical utility of the highest strength of the algorithm is limited to certain criteria. The results can be used to optimize the clinical abdominal CT protocol. The conclusion from paper III may increase clinical awareness of the value of the low-dose abdominal protocol when choosing an imaging method for certain patient groups who are more sensitive to radiation. ■

Xuan Gu

Advanced Analysis of Diffusion MRI Data

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

Diffusion magnetic resonance imaging (diffusion MRI) is a non-invasive imaging modality which can measure diffusion of water molecules, by making the MRI acquisition sensitive to diffusion. Diffusion MRI provides unique possibilities to study structural connectivity of the human brain, e.g. how the white matter connects different parts of the brain. Diffusion MRI enables a range of tools that permit qualitative and quantitative assessments of many neurological disorders,

such as stroke and Parkinson.

This thesis introduces novel methods for diffusion MRI data analysis. Prior to estimating a diffusion model in each location (voxel) of the brain, the diffusion data needs to be preprocessed to correct for geometric distortions and head motion. A deep learning approach to synthesize diffusion scalar maps from a T1-weighted MR image was proposed, and it was shown that the distortion-free synthesized images can be used for distortion correction. An

evaluation of six methods for susceptibility distortion correction, involving both simulated and real data, was also performed.

A common problem in diffusion MRI is to estimate the uncertainty of a diffusion model. Therefore, an empirical evaluation of tractography, which is a technique that permits reconstruction of white matter pathways in the human brain was presented in this thesis. ■

Magnus Ziegler

Improving Assessments of Hemodynamics and Vascular Disease

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

Blood vessels are more than simple pipes, passively enabling blood to pass through them. Their form and function are dynamic, changing with both aging and disease. Magnetic Resonance Imaging (MRI) offers a unique platform for investigating both the form and function of the vascular system. The form of the vascular system can be examined using MR-based angiography, to generate detailed geometric analyses, or through quantitative techniques for measuring the composition of the vessel wall and atherosclerotic plaques. To complement these analyses, 4D Flow MRI can be used to quantify the functional aspect of the vascular system, by generating a full time-resolved three-

dimensional velocity field that represents the blood flow.

This thesis aimed to develop and evaluate new methods for assessing vascular disease using novel hemodynamic markers generated from 4D Flow MRI and quantitative MRI data towards the larger goal of a more comprehensive non-invasive examination oriented towards vascular disease.

In the scope of this thesis, methods for visualizing and quantifying flow stasis in abdominal aortic aneurysms were developed and evaluated as well as for quantification of the turbulent shear stresses acting on the vessel wall and quantification of the composition of the vessel wall. ■

Sofie Tapper

Neurotransmitter Imaging of the Human Brain: Detecting γ -Aminobutyric Acid (GABA) Using Magnetic Resonance Spectroscopy

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

In this thesis, MEGA-edited Magnetic Resonance Spectroscopy (MRS) has been used for the purpose of non-invasive detection of γ -aminobutyric acid (GABA) within the brain. GABA is the main inhibitory neurotransmitter in the human central nervous system, and glutamate is the corresponding main excitatory neurotransmitter. A balance between GABA and glutamate is crucial for healthy neurotransmission within the brain, and regional altered concentrations have been linked to certain

neurological disorders. However, it is challenging to measure GABA, and special editing approaches are needed in order to allow reliable quantification. In addition, the GABA measurement is further complicated due to disturbances such as movements during the acquisition that may lead to artifacts in the resulting spectrum.

This thesis can be divided into two sections, where the first section focuses on three clinical applications (narcolepsy, irritable bowel syndrome (IBS), and

essential tremor (ET)), which were all investigated using MEGA-edited single-voxel spectroscopy (SVS). The second section focuses on method development, where two statistical retrospective approaches were investigated for the purpose of improving MEGA-edited data. In addition, a new MRS imaging (MRSI) pulse sequence with the purpose of GABA detection using a high spatial resolution, short acquisition time, and full brain coverage was also investigated. ■

Charalampos Georgiopoulos

Imaging Studies of Olfaction in Health and Parkinsonism

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

Parkinson's disease is characterized by typical motor disorders. In addition, Parkinson's causes non-motor symptoms that greatly affect patients' quality of life. Impaired sense of smell is a common non-motor symptom, which usually occurs several years before the first motor symptoms. The purpose of the studies presented here has been to use different imaging methods to more closely map how odor-specific brain areas are affected by Parkinson's and how examination of the olfactory mind may be helpful

in the diagnosis of parkinsonism.

This thesis focuses on single photon emission tomography (SPECT) and various methods of magnetic resonance imaging (MRI). The results of the first study show that SPECT is effective in distinguishing parkinsonism from non-parkinsonism. A combination of SPECT with regular scent testing can increase diagnostic safety and distinguish Parkinson from atypical parkinsonism. The second study has used a special MRI method that quantifies the random thermal motion of water; this

method has identified very discrete structural changes in certain odor-specific brain regions.

We have also established a reliable MRI method that can be used to look at the brain's function when you smell different scents. Using this method, we have been able to demonstrate two networks with odor-specific brain areas in both the large and small brain. These networks appear less involved after scent stimulation in patients with Parkinson's than in healthy individuals. ■

Natasha Morales Drissi

Brain Networks and Dynamics in Narcolepsy

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

Narcolepsy is a chronic sleep disorder, characterized by excessive daytime sleepiness with frequent uncontrollable sleep attacks. In addition to sleep related problems, changes in cognition have also been observed in patients with narcolepsy and have been linked to the loss of Orexin-A in a number of studies. Results from previous functional and structural neuroimaging studies would suggest that the loss of Orexin-A has numerous downstream effects in terms of both resting state glucose metabolism and perfusion and reduction in cortical grey matter.

The aim of this thesis was to investigate mechanisms and etiology behind the symptoms in narcolepsy through the

application of different neuroimaging techniques.

The results show that the complaints about subjective memory deficits in narcolepsy are related to a misallocation of resources and that this has its seat in defective default mode network activation, possibly involving alterations to GABA and Glutamate signaling. In addition, the findings show a structural deviation in an area of the brainstem previously not described in the etiology of narcolepsy. Furthermore, results from adipose tissue measurements in specific compartments show that weight gain in narcolepsy is characterized by centrally located weight gain and may be specifically related to Orexin changes. ■

A photograph of a medical imaging suite. In the center, a large monitor is mounted on a wall. To the right, a mobile device, possibly a tablet or a specialized monitor, is mounted on a stand. The room is dimly lit, with a blueish tint. The word "Equipment" is overlaid in large white letters across the middle of the image.

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. High speed scanning is necessary for cardiac examinations as well as for restless patients. The two X-ray sources also provide the possibility for dual energy examinations with improved spectral separation.

MRI

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

two parallel RF transmissions (Multitransmit 4D), which adapt the RF signals to each patient. Multitransmit facilitates an increased image uniformity, contrast, and consistency, as well as faster imaging. A full range of receiver coils is available with analog-to-digital converters inside the coils (dStream RF). This samples the MR signal directly in the coil on the patient, and sends it to the reconstructor via a fiber-optic cable.

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

The Siemens 3T Prisma has a 60 cm bore and gradients with 80mT/m@200 T/m/s simultaneously, which facilitate fMRI and DTI studies. The coil concept offers high coil density using parallel transmit technology called TimTx TrueShape for cardiac, abdominal and musculoskeletal examinations.

A full research agreement with Philips Medical Systems and Siemens

Healthcare allows all possible clinical as well as technical research applications.

DIGITAL PATHOLOGY AND ANNOTATION

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

PACS

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

For storage and handling of echocardiographic image data (for both research and clinical use), one of the largest installations of the GE EchoPAC system in the world is available. A



number of advanced diagnostic workstations are available for clinical and research purposes

VISUALIZATION

CMIV has its own Virtual Reality theatre with a capacity of 90 persons. The theatre is built around Barco DP4K-30L 6P Laser projector (21,000 lumens light output), with 4K resolution (4,096 × 2,160). The Barco Laser3D has a native 6-primary color-3D system. The system uses a Barco E2 Image processor, 4K

Native 12 bits/color 3D input/output. The computer to screen connections are run by the Lightware MX-33R Digital Crosspoint matrix. The Wirecast 7.3 Recorder system allows recording and online streaming. During 2018 Wranne was upgraded to an advanced Zoom room enabling remote meetings and education.

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.

INFRASTRUCTURE

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





Computed tomography scan of a goat from the Kolmården Wildlife Park in Sweden. The scanning of the goat was performed in a research collaboration between CMIV and Kolmården. The aim was to document and learn more about the physiology of animals.

Organization

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

RESEARCHERS

Gudrun Alm Carlsson	IMH, Radiological Sciences	Thomas Karlsson	IBL, Disability Research
Ida Blystad	Department of Radiology, Region Östergötland	Johan Kihlberg	Department of Radiology, Region Östergötland
Magnus Borga	IMT, Biomedical Engineering	Eva Klintström	IMH, Radiological Sciences
Mariana Bustamante	IMH, Cardiovascular Medicine	Hans Knutsson	IMT, Biomedical Engineering
Rebecca Böhme	IKE, Center for Social and Affective Neuroscience	Laura Korhonen	IKE, Center for Social and Affective Neuroscien
Carl-Johan Carlhäll	IMH, Cardiovascular Medicine	Maria Kristoffersen Wiberg	IMH, Radiological Sciences
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Gabriel Eilertsen	ITN, Media and Information Technology	Maria Magnusson	ISY, Computer Vision
Gillian Einstein	TEMA, Gender Studies	Alexandr Malusek	IMH, Radiological Sciences
Anders Eklund	IMT, Biomedical Engineering	India Morrison	IKE, Center for Social and Affective Neuroscience
Mattias Ekstedt	IMH, Cardiovascular Medicine	Ebo de Muinck	IMH, Cardiovascular Medicine
Maria Engström	IMH, Radiological Sciences	Bengt Norén	Department of Radiology, Region Östergötland
Jan Engvall	IMH, Cardiovascular Medicine	Nina Nelson Follin	IKE, Pediatrics
Björn Gerdle	IMH, Community Medicine	Miguel Ochoa Figueroa	Department of Radiology, Region Östergötland
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Håkan Gustafsson	IMH, Radiological Sciences	Anneli Peolsson	IMH, Physiotherapy
Sven-Patrik Hallsjö	IMH, Radiological Sciences	Irene Perini	IKE, Center for Social and Affective Neuroscience
Paul Hamilton	IKE, Center for Social and Affective Neuroscience	Anders Persson	IMH, Radiological Sciences
Mats Hammar	IKE, Division of Children's and Women's Health	Lennart Persson	IMH, Cardiovascular Medicine
Markus Heilig	IKE, Center for Social and Affective Neuroscience	Hans Ringertz	Karolinska Institutet
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Publications

The CMIV research efforts lead to a steady stream of scientific publications. An overview of the 2019 production is given in the following pages. As papers from CMIV researchers may be primarily registered under other affiliations the listing is not complete, but still shows a good representation of CMIV. The CMIV researchers have presented their work at conferences all over the world during the year, however, conference abstracts are not included in this list unless published as a conference paper.

Bibliometric Analysis

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

TABLE 1. Norwegian Model, 2015–2019

	Number of Publications	Number of Fractions
Journal articles – refereed	290	130.1
Conference publications	32	18.8
Chapters – other academic	0	0.0

Results

% author shares level 2 18

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

TABLE 2. Open Access, 2015–2019

Articles	%
Articles	67
Conference publications	44
Chapters	0

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

TABLE 3. Coverage in Web of Science, 2015–2019

Publications in Web of Science	Number of Publications	Number of Fractions
Articles, reviews, letters, proceedings papers	298	134.6
Coverage		%
Articles		91
Conference Proceedings		79

FIGURE 1. Number of Fractionalized Publications

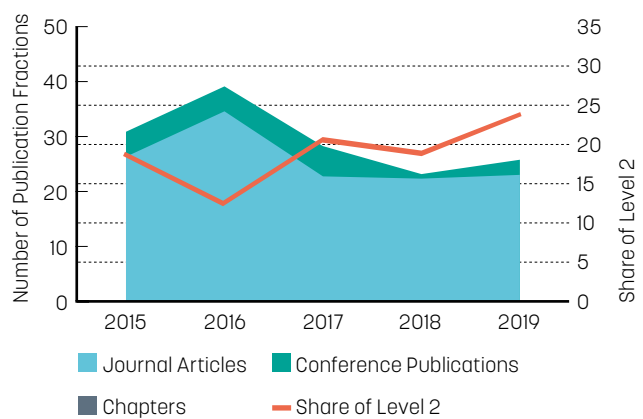


FIGURE 2. Open Access Articles

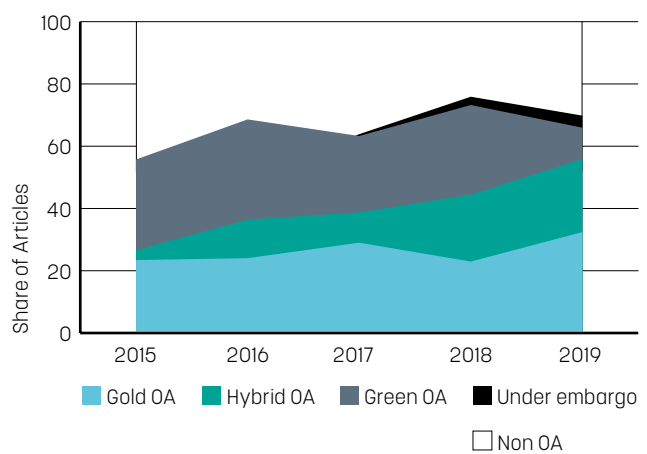


FIGURE 3. Number of Fractionalized Journal Articles: Coverage in WoS, 91%

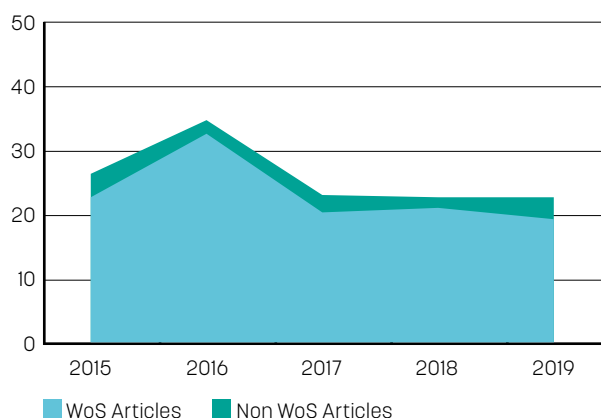


FIGURE 4. Impact

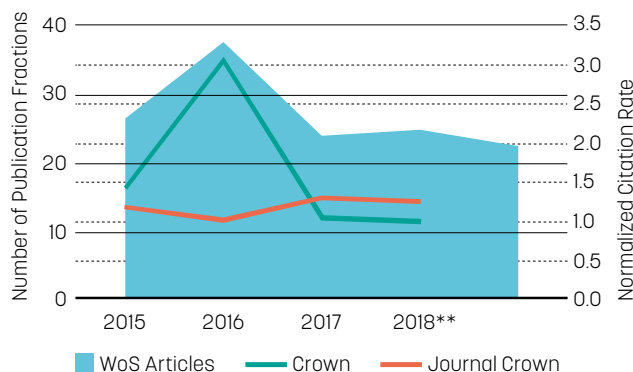


FIGURE 5. Fractionalized Journal Articles in WoS: Co-Authorships

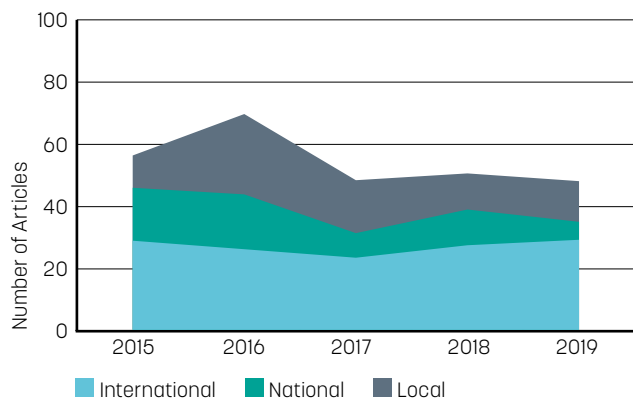


FIGURE 6. Interdisciplinary Publications

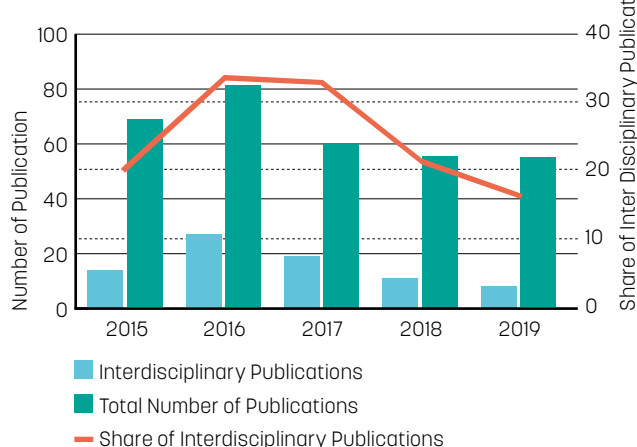


TABLE 4. Citation Analysis, 2015–2018

Publications in Web of Science	Number of Publications	Number of Fractions
Articles, reviews, letters	224	99.4

Results, 2015–2018

Field-normalized citation rate (crown)	1.53
Share of top 10 %	12 %
Share of uncited publications	19 %
Field-normalized journal citation rate (journal crown)	0.98
Journal Impact Factor (JIF) ranking, mean	0.65

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.

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

TABLE 5. Co-Authorship, 2015–2019

	%
Share of articles with international co-authors	50
Share of articles with national co-authors	24
Share of articles with local co-authors	26

TABLE 6. Interdisciplinary Authorship (LiU faculties), 2015–2019

Number	84
Share	26 %

Publications 2019

CMIV affiliated researchers are written in bold.

PEER-REVIEWED ORIGINAL ARTICLES AND PROCEEDINGS

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Ziegler, M. (2019). Improving Assessments of Hemodynamics and Vascular Disease (PhD dissertation). Linköping.

Annual Accounts

During 2019, CMIV had a turnover of more than SEK 56 million. The financial result was SEK 2.7 million.

This fiscal year we have continued to develop our infrastructure by installing the supercomputer Triolith, which was taken over from nsc. Several investments have been made to upgrade and increase the standard on storage servers and also the CMIV booking server. The Philips 1.5T MR was upgraded during spring. To the MR research operations, we also invested in a new fMRI equipment, "VisuaStim Digital". We expanded our office area into a new building, and some new furniture was bought to these new premises.

During 2019 CMIV had several ongoing grant research projects. AIDA – Analytic Imaging Diagnostics Arena continued

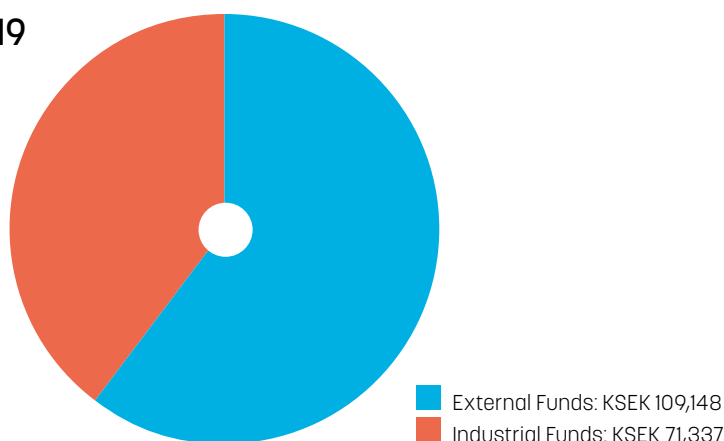
its work, being funded by Vinnova. Nine projects funded by AIDA started up during 2019 and also 2 clinical and 1 technical fellowship. During spring the infrastructure for the SCAPIS project was moved to CMIV. SCAPIS is mainly funded by Swedish Heart-Lung Foundation. The Visual Sweden financed project MeDigiT started during 2019. Vinnova funded a new project – SCAPIS AI platform which started late 2019 and will continue until 2021. Both the Faculty of Medicine and Health Sciences and the Faculty of Science and Engineering continued to support the CMIV initiative within the digital pathology area. ■

ECONOMIC SUMMARY	2015	2016	2017	2018	2019
Total revenue	39,298	40,655	48,165	52,059	56,266
EXPENSES					
Staff expenses	-18,593	-16,978	-15,772	-16,711	-20,390
Cost of premises	-2,869	-9,135	-6,472	-6,657	-5,752
Misc. operating expenses	-11,483	-12,158	-16,765	-18,704	-18,848
Depreciation expenses	-4,980	-6,781	-7,819	-8,129	-8,440
Financial expenses	-123	-132	-36	-151	-126
Total expenses	-38,048	-45,184	-46,864	-50,051	-53,556
Result of operations	1,250	-4,519	1,300	2,008	2,710

NUMBERS IN THOUSANDS OF SEK

Research Funding at CMIV 2010–2019

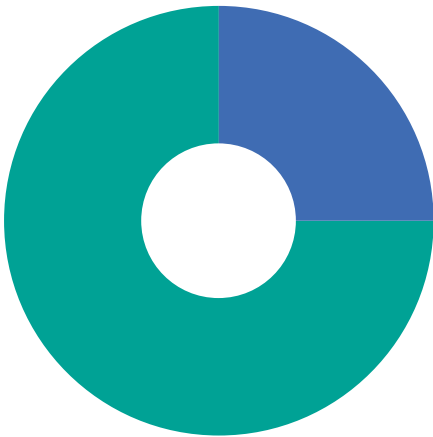
CMIV receives funding from research funds and the industry both directly to the R&D platform and to specific research projects. In addition, the affiliated researchers have their own funding; these grants will, however, not be presented here.



CT Research and Clinic, %

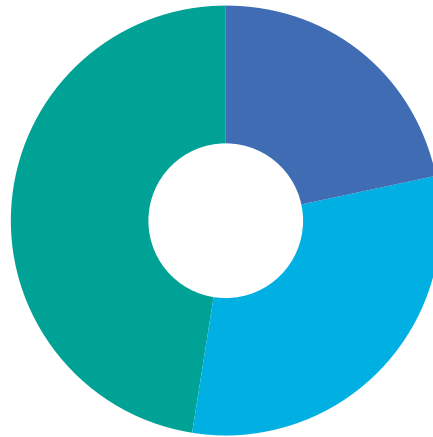
2019

- Combined Research and Clinic, 25
- Clinic, 75



2018

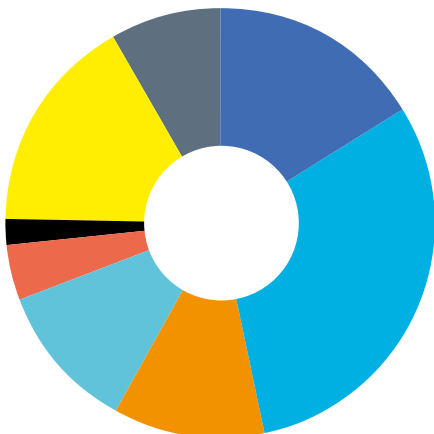
- Combined Research and Clinic, 21.9
- SCAPIS, 30.8
- Clinic, 47.3



Distribution of Research on the MRI Cameras, %

2019

- Full Body Scan, 16
- Logistics, 30
- fMRI Neuro, 11
- Cardiovascular, 11
- Spectro Neuro, 4
- Development Time, 2
- CSAN Neuro, 16
- MSK, 8



2018

- Full Body Scan, 13
- Logistics, 12
- fMRI Neuro, 9
- Cardiovascular, 10
- Combined Clinic/Research, 1
- Spectro Neuro, 3
- Development Time, 3
- CSAN Neuro, 22
- SCAPIS, 6
- MSK, 17
- Neuro, 3

