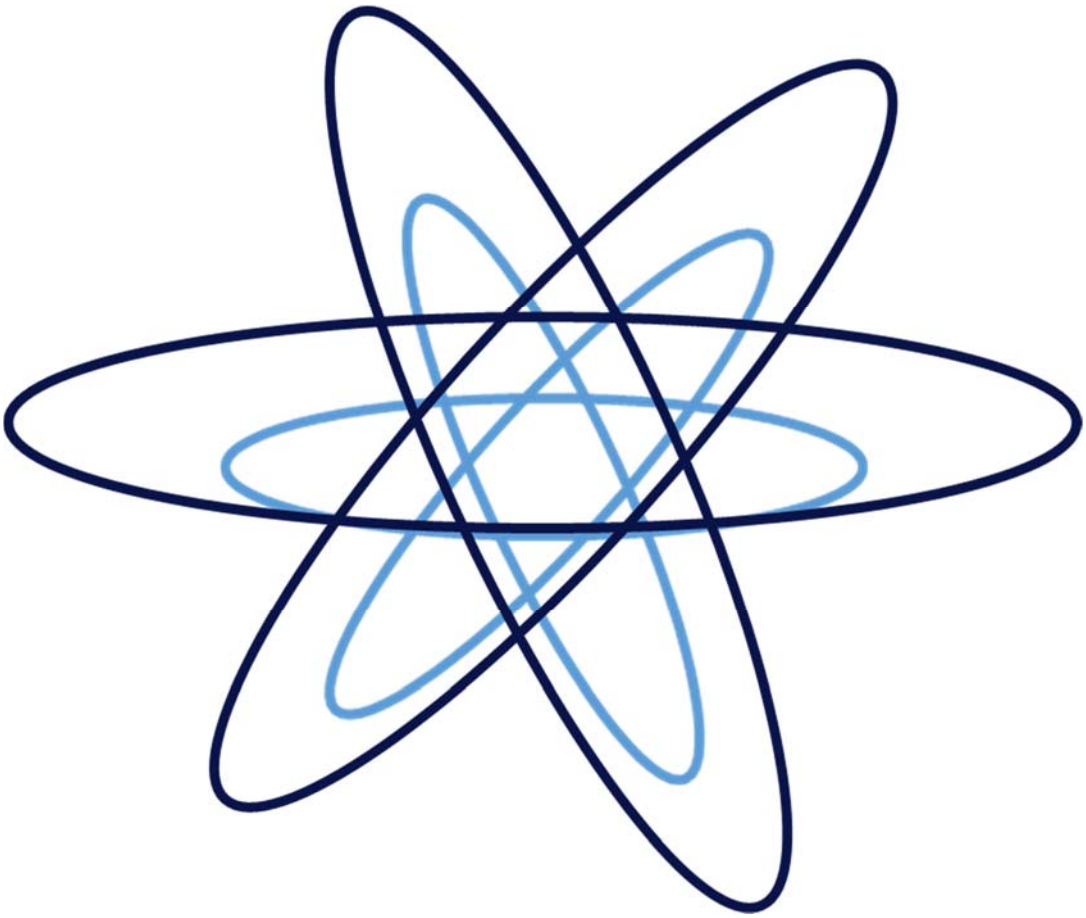
Moving on

Annual report 2017

Department of Nuclear Medicine & PET-Centre, Aarhus University Hospital

AARHUS UNIVERSITY

Aarhus University Hospital



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This past year has been unique in many ways and the department has been moving forward at a high speed both at the clinical, scientific and educational level.

Preface

It is our sincere pleasure to present the annual report 2017 for the Department of Nuclear Medicine and PET-Centre, Aarhus University Hospital. This past year has been unique in many ways and the department has been moving forward at a high speed both at the clinical, scientific and educational level.

The Department of Nuclear Medicine & PET Centre is entering a very important transition phase with completion of the new buildings at Aarhus University Hospital, which will house our new large department where we merge 3 sections into one new department. In addition to this process, we have successfully been able to expand our infrastructure in the existing facilities. This is a demanding task and only possible through dedication, flexibility and loyalty from everyone in the department. We therefore thank our engaged staff for all their commitment and hard work during the past year.

In March 2017 we inaugurated PET/CT scanner no. 5, which provided a necessary increase in the infrastructure and reflects the continuing increase in the clinical demand for PET/CT examinations. The PET/CT scanner was funded as part of an effort made by Central Region Denmark to increase the diagnostic capacity and efficiency towards earlier detection of cancer. During the past year, we are also very proud to look at the continuing growth of clinical activities, always with the patient in focus. Close collaborations with most departments at Aarhus University Hospital is a key driver in keeping up the high quality in all clinical activities. An effort made possible through active participation in a large number of frequent multidisciplinary conferences.

The 2017 annual report is also dedicated to present some of our research and the impact of successful research-training programs of talented young scientists supervised by strong senior researcher making strong team-works. Thus, the Department of Nuclear Medicine and PET Centre is proud to present an array of highly original research projects from PhD students, Postdocs and research year students, which successfully contribute to increase our knowledge of important diseases and the quality of patient management. Together, this palette of projects also demonstrates our unique ability to facilitate research from the very basic level to the highly complex integrated clinical level. This is only possible due to an impressive infrastructure, our highly dedicated staff and collaborators.

Excellence is part of our vision in every way our department performs. In particular, this is a key focus for our research strategy and it is the basis for attracting financial support, talented scientists and clinicians as well as for the production of high impact publications. Importantly, we therefore also focus on continuous training and education of each staff member combined with sharing of knowledge to obtain the highest standard. This together with continuous efforts to optimize procedures and workflows ensure the most efficient use of equipment and staff resources.

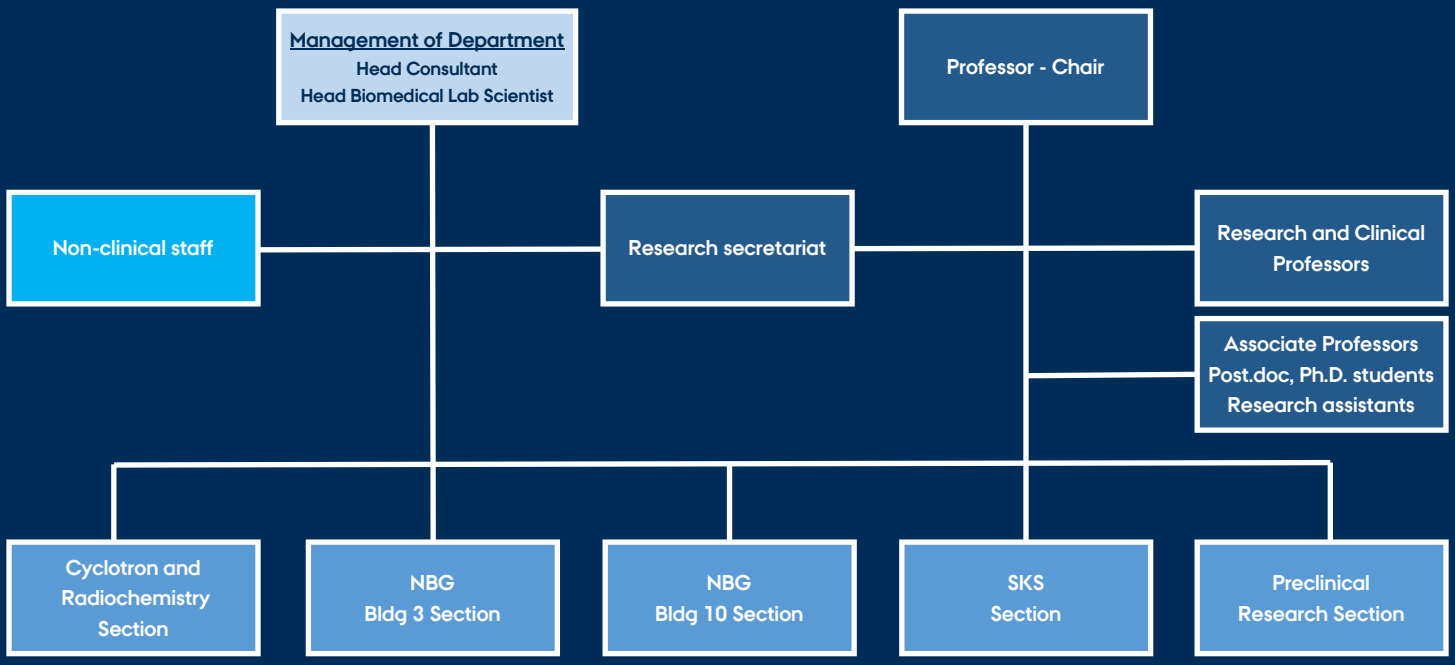
We are grateful for the generous external financial support to our department, which is necessary to secure a highly efficient development of novel examinations based on research. The close collaboration with many colleagues at both Aarhus University Hospital and Aarhus University as well as other national and international partners is fundamental for the excellent research achievements. And most importantly, we are also very thankful for the extensive support we have received from the management at both Aarhus University and Aarhus University Hospital during 2017.

Jørgen Frøkiær
Professor, Head of Department, MD, DMSc

Michael Werenberg Mikkelsen
Head Biomedical Laboratory Scientist


Sedgwick Museum
of Earth Sciences

Organization



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Equipment 2017

Equipment type	Model	Year of purchase
Gamma camera	Mediso TH-45	2005
	Mediso TH-45	2015
	DDD Nephrocam	2016
SPECT cameras	Picker Axis	2000
	Philips CardioMD	2007
SPECT/CT scanners	GE Discovery NM/CT 670	2011
	Siemens Symbia T-16	2011
	Siemens Symbia T-16	2012
PET brain scanner	Siemens HRRT	2005
PET/CT scanners	Siemens Biograph 40 True Point	2007
	Siemens Biograph 64 True Point	2009
	Siemens Biograph 64 True Point	2009
	GE Discovery 690	2009
	GE Discovery MI Digital Ready	2017
Cyclotrons	GE PETtrace	1993/2010
	IBA Cyclone 18/18	2009
Pre-clinical equipment		
Phosphor imager	FujiFilm BAS-5000	2002
SPECT camera	Philips BrightView	2009
MicroPET/MRI	Mediso Nanoscan	2014

Staff

Afsaneh Otroosh, *Medical Laboratory Technologist* • **Alessandro Miani**, *Msci* • **Ali Khalidan Vibholm**, *MD, PhD Student* • **Allan Kjeldsen Hansen**, *MD, PhD Student* • **Anders Floor Frellsen**, *Chemist, PhD* • **André H. Dias**, *MD, Specialist Registrar* • **Andres Muñoz-Jensen**, *Cleaning/Support Worker* • **Anja Abildgaard Gregersen**, *Medical Laboratory Technologist* • **Anna Christina Schacht**, *Radiochemist* • **Anne Charlotte Bekker,** *Medical Laboratory Technologist* • **Anne Kirstine Arveschoug**, *Senior Consultant* • **Anne Marlene Landau**, *Associate professor, Assistant Professor* • **Anne Sofie Møller Andersen**, *PA to David Brooks/ Research Coordinator* • **Anne Sophie Koldkjær Sølling**, *Registrar* • **Anne-Mette Nørby Rasmussen**, *Medical Secretary* • **Annette Dysterdich**, *Department Medical Laboratory Technologist* • **Arne Møller**, *Associate Professor, MD* • **Ate Haraldsen**, *MD, Senior Consultant* • **Birgitte Maria Nielsen**, *Secretary* • **Birthe Hedegaard Jensen**, *Research Coordinator* • **Bjarke Brokhøj**, *Electronics Engineer Student* • **Bórgny Skúlardottír**, *MD, Registrar* • **Brita Kragh**, *Medical Laboratory Technologist* • **Camilla Molich Hoff**, *MD, PhD, Registrar* • **Carsten Gleesborg**, *PhD student* • **Casper Schmidt**, *PhD student* • **Cecilie Dorthea Rask Clausen**, *Student* • **Charlotte Koldsø**, *Medical Laboratory Technologist* • **Christian Fløe**, *Medical Physicist* • **Christian Skyum A. Juhl**, *Medical Laboratory Technologist* • **Christina Vang Staal Larsen**, *Medical Laboratory Technologist* • **David James Brooks**, *Professor, MD, DMSc* • **Dirk Andreas Bender**, *Chief Radiochemist, QM, PhD* • **Dorte Hvid Schmidt**, *Medical Laboratory Technologist* • **Dorte Mikkelsen**, *Medical Laboratory Technologist* • **Dorte Schmidt Jespersen**, *Medical Laboratory Technologist* • **Dorthe Hoffmann**, *Medical Secretary* • **Elisabeth Jemima Rønne**, *Medical Secretary* • **Emil Holm Kirk**, *Chemist* • **Erik Holm Toustrup Nielsen**, *Radiochemist* • **Eva Amalie Nielsen**, *MD, Registrar, PhD* • **Frederik Husum**, *Student* • **Gertrud Høher Kiil Jørgensen**, *PA to Susanne Keiding /Research Administrator* • **Gitte Bjerggaard Kall**, *Medical Laboratory Technologist* • **Gitte Jensen**, *Medical Secretary* • **Gitte Lund Nielsen**, *MD, Specialist Registrar* • **Gitte Munkebo Kodahl**, *Medical Laboratory Technologist* • **Gitte Skou**, *Medical Laboratory Technologist* • **Hanne Døssing Prahl**, *Medical Laboratory Technologist* • **Hanne Juul Nielsen**, *Medical Secretary* • **Heidi Poggianti**, *PA to Jørgen Frøkiær/Research Coordinator* • **Heidi Thomsen Kristensen**, *Medical Laboratory Technologist* • **Hélène Audrain**, *Radiochemist, Production Manager, PhD* • **Helle Danielsen**, *Medical Laboratory Technologist* • **Helle Søgaard**, *Medical Laboratory Technologist* • **Hendrik Johannes Harms**, *Postdoc, PhD* • **Henriette Dam Heinsvig**, *Medical Laboratory Technologist* • **Henrik Bluhme**, *Medical Physicist, PhD* • **Irene Qvistgaard**, *Medical Laboratory Technologist* • **Jacob Horsager**, *Student worker* • **Jan Jacobsen**, *Radiochemist* • **Janni Thor**, *Medical Laboratory Technologist* • **Jeanette Würts** •**Jeannette Elkjær Jensen**, *Medical Secretary* • **Jenny Ann Phan**, *PhD student* • **Jens Kristian Graverholt**, *Electronics Engineer* • **Jens Sørensen**, *Professor, MD, DMSc* • **Jeppe Lund Schaldemose**, *PhD Student* • **Jeppe Madsen**, *Medical Laboratory Technologist* • **Jeppe Wehner**, *Medical Laboratory Technologist* • **Jette Holberg Rasmussen**, *Medical Laboratory Technologist* • **Joan Fledelius**, *MD, PhD student* •**Joel Fredrik Astrup Aanerud**, *MD, Specialist Registrar* • **Jørgen Frøkiær**, *Professor, Head of Department, MD, DMSc* • **Karen Margrethe Kristensen**, *Cleaning/Support Worker* • **Karin Fenger Beck**, *Chief Medical Secretary* •**Karin Hjorthaug**, *MD, Senior Consultant* • **Karina Højrup Vase**, *Radiochemist, QA, PhD* • **Karina Stensgaard Bjørnholdt** • **Karoline Knudsen**, *PhD student* • **Kaspar Pahira Vraa**, *Department Medical Laboratory Technologist* • **Kathrine Stokholm**, *PhD Student* • **Khalida Akbari**, *Medical Laboratory Technologist* • **Kim Frisch**, *Chemist, Senior Scientist, PhD* • **Kim Vang Hansen**, *Master of Engineering* • **Kirsten Bouchelouche**, *Senior Consultant, Associate Professor, MD, DMSc* • **Kirstine Petrea Bak-Fredslund**, *MD, PhD student* • **Kristian Platz Petersen** •

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Academic staff

Allan Kjeldsen Hansen, MD, PhD-student at the Department of Nuclear Medicine & PET Centre and the Department of Clinical Medicine, Aarhus University. Allan Kjeldsen Hansen's area of research is tau imaging in dementia and Parkinsonian disorders. In 2017 he received research support from the International Parkinson and Movement Disorder Society (travel grant) and the Lundbeck Foundation.

Anders Floor Frellsen, Chemist, PhD, Member of The Danish Chemical Society, is currently undergoing continuing education at the Eidgenössische Technische Hochschule (ETH) Zürich in Radiopharmaceutical Chemistry/Radiopharmacy. He oversees daily productions in the radiopharmacy for classical nuclear medicine productions, and constantly works to implement new internal radiotherapies at the department.

André H. Dias, MD, Nuclear Medicine Specialist at Department of Nuclear Medicine & PET Center, Aarhus University Hospital. André H. Dias is a nuclear medicine physician, trained in Portugal that has been working at the Department of Nuclear Medicine at Aarhus University Hospital since 2015, in both clinical and research functions.
Member of both Portuguese and Danish Nuclear Medicine Associations as well as the European Nuclear Medicine Association. Former member of the "Young EANM Committee" of the European Association of Nuclear Medicine. Currently a member of the "Inflammation and Infection Committee" of the European Association of Nuclear Medicine.
In 2017 he received research support from The Danish Cancer Society (Kræftens Bekæmpelse, Knæk Cancer) for a project on perfusion imaging of prostate cancer in relation to response to endocrine therapy.

Anna Christina Schacht, Radiochemist, M.Sc., Quality Control

Anne Kirstine Arveschoug, Consultant, head of the Nuclear Medicine section at Nørrebrogade and responsible for Therapy and diagnostics. Responsible for the postgraduate education of physicians in the Department, she has been representing DSKFNM in the Danish Health and Medicines Authority's committee for specialist planning of Clinical Physiology and Nuclear Medicine. At present representative of DSKFNM in Educational Committee in all three educational regions of Denmark.

Anne M Landau, Associate Professor in Translational Neuroscience, PhD, Department of Nuclear Medicine and PET Center and Translational Neuropsychiatry Unit. Anne and her group perform preclinical imaging and autoradiography in rodent and minipig models of neurodegenerative diseases and neuropsychiatric disorders. Currently, her team's main goal is to develop and validate novel PET tracers towards elucidating disease progression and evaluating the efficacy of experimental therapeutics in animal models. In 2017, Anne received research support from the Parkinsonforeningen, and other ongoing projects are currently funded by the Innovation Fund Denmark/Eurostars, EU/FP7 Multisyn, Lundbeck Foundation and Fonden af 2/7 1984 til Bekæmpelse af Parkinsonsyge. Anne is a member of the Scientific Advisory Board of BrainMatTrain (Marie Curie Initial Training Network funded by the European Commission Horizon2020 Programme) and an Associate Editor of Acta Neuropsychiatrica.

Arne Møller, MD, Associate professor. Translational research manager at Department of Nuclear Medicine & PET Center, Aarhus University Hospital. Arne is heading the research group for Pathological Gambling at NUK/PET and CFIN, and coordinator for neurotransmission research at CFIN. He is coordinator and lecturer at the neuroscience program at the university partnership Denmark-China, SDC. Together with prof. Therese Ovesen and Morten Kringelbach is he member of the board of directors at the Flavour Institute, Aarhus University.

Ate Haraldsen. Consultant. Member of European Society for Radiotherapy and Oncology (ESTRO) and Dansk Selskab for Klinisk Fysiologi og Nuklearmedicin (DSKFNM). Teaches at specialist courses for nuclear medicine physians, radiologists and oncologists.

Camilla Molich Hoff, Senior Registrar, PhD. Chairman of YNK (Association of Young Nuclear Medicine physicians in Denmark) and thereby board member in DSKFNM (Danish Society of Clinical Physiology and Nuclear Medicine). Member of European Association of Nuclear Medicine (EANM). Course director and teacher at the national course for young nuclear medicine physicians. Functions as UKYL (training coordinating junior doctor). Research areas are nuclear cardiology, head and neck cancers.

Carsten Gleesborg, MSci Neuroscience, PhD student

Casper Schmidt, psychologist and PhD student at the Dept. Clinical Medicine, Aarhus University. Casper's research focuses on self-control and on devising new strategies to assess and treat different forms of addiction, with foci on the neural and behavioural mechanisms underlying impulsive and compulsive disorders within behavioural addictions in the general population. This incorporates use of methods such as cognitive neuroscience, neuroimaging, cognitive-behavioural testing and pharmacological modulation. In 2017, he received research support from the Augustinus Foundation.

Christian Fløe, Medical physicist, M.Sc., member of the Danish Society for Medical Physics.

David J Brooks MD DSc FRCP(UK) FMed Sci (UK) is Professor of Neurology at Aarhus University, Denmark, Professor of Clinical PET Research at Newcastle University and Visiting Professor of Neurology at Imperial College London, UK. He is Chairman of the European Research Council Neuroscience Panel and is on the Grant Awards Board of Alzheimer Research UK, the Biomedical Research Advisory Panel of Alzheimer UK, and was on the Scientific Advisory Boards of Parkinson's UK, and the German Dementia and the Parkinson Kompetenz Networks. He was Chairman of the NUHS Scientific Advisory Panel, Singapore, in 2015 and is a reviewer for the NMRC, Singapore. He was a member of the Scientific Advisory Board of the Michael J. Fox Foundation for Parkinson's Disease Research (2002-2006), UK Medical Research Council Neuroscience and Mental Health Board (2004-2007), Wellcome Trust Neuroscience Panel (2001-2003) and was Chairman of the Scientific Issues Committee of the Movement Disorder Society (1998-2002). He is an Associate Editor of Brain and is on the Editorial Boards of Annals of Neurology, Molecular Imaging and Biology, Journal of Parkinson's Disease, Synapse, NPJ Parkinson's Disease and Basal Ganglia.

He was on the Editorial Boards of Movement Disorders 1994-1998 and Parkinsonism and Related Disorders 2012-2016. In 2001 he is elected a Fellow of the Academy of Medical Science, UK. His research involves the use of positron emission tomography and magnetic resonance imaging to diagnose and study the progression of Alzheimer's and Parkinson's disease and his work is highly cited with an h index of 108. He has been a recipient of a Danish Alzheimer Foundation Prize, the Kuhl-Lassen award (Society of Nuclear Medicine), and was invited to give the Stahn Fahn (International Movement Disorder Society) and Cotzias (Spanish Neurology Society) Lectures. He is a consultant for GE Healthcare, Biogen, Plexxikon, and GenePod.

Dirk Andreas Bender, Chief-radiochemist, Dr. rer. nat., member of the International Society for Radiopharmaceutical Science.

Erik Holm Toustrup Nielsen, Radiochemist, M.Sc.

Hélène Audrain, Radiochemist, M.Sc., PhD, Production Manager

Hendrik Johannes ("Hans") Harms, is a post-doctoral research fellow at the department of Nuclear Medicine at Aarhus University, on a project funded by a Post-doc grant of the Lundbeck Foundation. Hans is working on developing novel methods of measuring cardiac function using existing dynamic PET images. This work allows us to not only obtain standard cardiac measures, such as myocardial blood flow and left-ventricular ejection fraction, but also measures such as forward cardiac output, left-ventricular mass, atrial volumes and the turnover rate of the central circulation. Currently, he is applying these measures using prognostic data in a collaboration with dr. M.F. Di Carli at Brigham & Women's Hospital in Boston.

Henrik Bluhme, Medical physicist, M.Sc., Ph.D., member of the Danish Society for Medical Physics, member of the Independent Advisory Board to the Public on the Disposal of Radioactive Waste in Denmark under the Ministry of Higher Education and Science.

Jenny-Ann Phan, MD, is a PhD fellow at Department of Biomedicine, Aarhus University and Department of Nuclear Medicine and PET centre, Aarhus University Hospital. Jenny's PhD study focuses on investigating early synaptic changes in a rat model of Parkinson's disease, overexpressing the human alpha synuclein gene. She has applied *in vivo* PET imaging and *in vitro* techniques, including viral vector cloning, immunohistochemistry and autoradiography during her PhD studies. Since PET is the primary instrument in her research, she has also contributed with validation of kinetic models to discriminate specific from non-specific binding of radioligands, displaying complex binding profiles that lack a reference region. In 2017, Jenny went on exchange for six months at Department of Radiology and Radiological Sciences, Section of High Resolution Brain PET imaging at Johns Hopkins Hospital. Here, she worked with kinetic analysis of [^{11}C] raclopride binding to determine D_2/D_3 receptor density and affinity in healthy humans. Furthermore, she helped the group measuring the free fraction of radioligand in plasma.

Jens Sørensen. Professor, MD, PhD, DMSc. Employed part-time. Leads and conducts research in the use of PET/CT in cardiology and oncology with a focus on perfusion imaging. Member of Danish Society of Clinical Physiology and Nuclear Medicine, Swedish Society of Nuclear Medicine, European Association of Nuclear Medicine and European Society of Radiology. Collaborates with Universities in Sweden, Netherlands, Finland and USA.

Jeppe Lund Schaldemose, MSc in Psychology, PhD student at Department of Nuclear Medicine & PET-Centre, Department of Clinical Medicine, Aarhus University. Jeppe Lund Schaldemose's area of research is cognition in neurodegenerative disease. The PhD project has received research funding from the Olav Thon Foundation (Olav Thon Stiftelsen), The Lundbeck Foundation (Lundbeckfonden) and the Parkinson Society (Parkinsonforeningen) in 2017.

Joan Fledelius, MD, Ph.D.-student at Department of Nuclearmedicine, Herning and Aarhus University. Joan Fledelius' area of research is response evaluation with FDG-PET/CT in lung cancer. Funded by the Health Research Fund of Central Denmark Region (Region Midtjyllands Sundhedsvidenskabelige Forskningsfond).

Joel Aanerud, Senior registrar, PhD, teaches neuro-nuclear medicine to medical students and teaches at specialist courses in nuclear medicine for biotechnicians. He is co-supervisor for several PhD students.

Jørgen Frøkiær, Professor, MD, DMSci, Chair of The Department and Head of Research. Jørgen Frøkiær is chairman of The Novo Nordisk Foundation Prize Committee, member of the Novo Nordisk Foundation Committee for Clinical and Translational Research. He is also member of the Program Committee of the Nordic Health and Welfare Program – Nordforsk. Directs a research program in molecular physiology of renal diseases and development of novel molecular imaging tools for kidney diagnostics. In 2017 he received research support from The Danish Council for Independent Research. He is vice-chair of the board of directors at Aarhus Institute of Advanced Studies, and chairman of the Scientific Steering Committee of Danish 7T NMR project. Member of the Academic Council, Health, Aarhus University, member International Scientific Advisory Board of Swedish Biolmaging, member of the board of Hildur and Dagny Jakobsens Mindefond.

Karin Hjorthaug, consultant, chairman for Danish National PET/CT group, teaching at postgraduate courses for medical doctors. In 2017 temporarily employed at Stavanger University Hospital with responsibility for establishing and introducing PET/CT.

Karina Højrup Vase, Radiochemist, M.Sc., Ph.D., QA.

Karoline Knudsen, BMLT MMDI, PhD student. Karoline's research area is gastrointestinal and pancreatic function in Parkinson's disease. The research group received financial support for the PhD project in 2015 and 2016 from the Jascha Foundation (Jascha Fonden), the Parkinson Foundation (Parkinsonforeningen), and the Foundation of July 2nd 1984 (Fonden af 2. juli 1984 til Bekæmpelse af Parkinsonsyge).

Kim Frisch, Chemist, Senior Scientist, PhD

Kim Vang Hansen, M.Sc.EE.

Kirsten Bouchelouche, Senior Consultant, Clinical Associate Professor, DMSc, MD, is member of the Leader Group and the Research Council, and clinical section leader. She is responsible for PET/CT in urologic and gynecologic malignancies, and PET/CT in cardiology. She is invited speaker at national and international meetings and congresses, and teaching pre-and post-graduate medical doctors, students, and technologists. She is involved in several clinical research protocols and is supervisor for PhD students, medical doctors and a medical student at the new Research Honours Programme at Health, Aarhus University. She is referee in more than 25 scientific international journals. Evaluator and expert referee for the Danish Society of Clinical Physiology and Nuclear Medicine on applications for consultant positions. She is member of the Danish Society of Clinical Physiology and Nuclear Medicine, Danish National PET/CT group, the working group Danish Penile Cancer Database ("DaPeCa"), Danish Society of Cardiology, working group of Cardiac Imaging, European Association of Nuclear Medicine (EANM), and Society of Nuclear Medicine and Molecular Imaging (SNMMI). She has collaboration with Molecular Imaging Program at National Cancer Institute (NCI), National Institutes of Health (NIH), USA. In 2017 she was nominated and selected to be Editor of Seminars in Nuclear Medicine, starting as Ass. Editor 2018, and Editor from 2020.

Lars Christian Gormsen, Consultant, MD, PhD. Board member of the Danish Endocrine Society, member of the Danish Society of Clinical Physiology and Nuclear Medicine, member of National Working Groups for Lymphoma (Imaging Section) and Merkel Cell Tumors (PET/CT). Associate professor at Aarhus University teaching pre-graduate students and at PhD courses.

Kirstine Bak-Fredslund, MD, PhD student

Kristian Stær, MD, Research Assistant

Lars Poulsen Tolbod, Medical physicist, M.Sc., PhD, member of the Danish Society for Medical Physics.

Mads Ryø Jochumsen, MD, PhD student at Department of Nuclear Medicine & PET and Department of Clinical Medicine, Aarhus University. Mads Ryø Jochumsens area of research is perfusion imaging in prostate cancer. In 2017 he received research support from The Danish Cancer Society (Kræftens Bekæmpelse, Knæk Cancer), Health Research Fund of Central Denmark Region (Region Midtjyllands Sundhedsvidenskabelige Forskningsfond), Harboe Foundation (Harboefonden), Dagmar Marshalls Foundation (Dagmar Marshalls Fond), Knud and Edith Eriksens Foundation (Knud og Edith Eriksens Mindefond) and Agnes and Poul Friis Foundation (Agnes og Poul Friis Fond).

Majken Borup Thomsen, MSc Med., PhD student

Martin Byskov Kinnerup, MSc Eng, PhD student at Department of Nuclearmedicine & PET Center, Aarhus University. Martin Byskov Kinnerups area of research is noradrenaline dysfunction in Parkinsons Disease. In 2017 his project received support from the Lundbeck Foundation, and the Parkinson's Foundation.

Mette Marie Fode, MD, PhD student

Michael Winterdahl, Associate Professor in Neuroimaging, Ph.D. Michael Winterdahl leads a multidisciplinary research group at the Department of Nuclear Medicine and PET Center, which aims at understanding the effects of neuropeptides on human behaviour, by using a combination of state-of-the-art brain scanning methods, cognitive neuroscience theory and animal models. This research has the potential to significantly influence our understanding of human behaviour in heathy individuals and in neuropsychiatric patients. Michael Winterdahl's group consists of students and volunteers and an international network of collaborators who engage in a wide range of activities within neuroscience. International collaborators include Professor David Yeomans, Stanford, US, Professor Paul Zak, Claremont University, US, and Professor N.J. Shah, Forschungszentrum Jülich, Germany. Michael Winterdahl has supervised numerous students and currently coordinates and teaches "The Interdisciplinary Summer School on Neuroimaging" and "The Interdisciplinary Summer School on Cognitive Neuroscience". He has recently been elected Union Representative for "magistre" at the Institute of Clinical Medicine.

Mikkel Holm Vendelbo, MD, PhD, Physician, Department of Nuclear Medicine and PET-Centre, Aarhus University Hospital. Associate Professor, Department of Biomedicine Aarhus University.

Morten Gersel Stokholm, MD, PhD-student at the Department of Nuclear Medicine & PET Centre, Aarhus University Hospital and Department of Clinical Medicine, Aarhus University. Morten's area of research is positron-emission-tomography imaging in patients with idiopathic rapid eye movement behaviour disorder.

Natalie Van Den Berge, Postdoc

Nicola Pavese, MD, PhD, FRCP is Associate Professor at Aarhus University. He is Professor of Clinical Neuroscience at Newcastle University and contract Professor at Pisa University (School of Specialization in Neurology). Nicola Pavese's research focuses on elucidating the physiopathology of Parkinson's disease and other neurodegenerative diseases and identifying targets for treatment with structural and functional neuroimaging. He is the Deputy Director of the Clinical Ageing Research Unit at Newcastle University and leads the Parkinson's disease research team. He is also a standing member of several study groups in movement disorders for the International Parkinson and Movement Disorder Society. Nicola Pavese serves as member of the Advisory Panel for The National Institute for Health Research - Research for Patient Benefit Programme. He is Section Editor for Neuroimaging for Current Neurology and Neuroscience Reports and Regional Editor for the American Journal of Neuroscience. In 2015, he received research support from The Danish Council for Independent Research to use imaging techniques to investigate early pathological changes in patients at high risk to develop Parkinson's disease and relate disorders. He has also received grants from Parkinson UK, the MJF foundation (PPMI study), and the Italian Ministry of Health.

Niels Henrik Stubkjær Hansson, PhD student

Ole Lajord Munk, Medical physicist, M.Sc., PhD. Member of the Danish Society for Medical Physics.

Ove Noer, Master in Biomedical Engineering and Informatics. Ove is a research assistant working with the preclinical imaging group. His background in information technology development, support and programming and his extensive experience with PMOD, SPM, C++ and Matlab have made him a very valuable member of the team. He is primarily working with the analysis and pharmacokinetic modeling of PET data acquired from scans of different animal models. He has focused on optimizing analysis techniques, e.g. implementing scripting and Statistical non-Parametric Mapping (SnPM), an applied form of permutation theory.

Per Borghammer, Consultant associate professor, MD, PhD, DMSc. Chief responsible for clinical brain diagnostics. He is research group leader in the Movement Disorder PET research group, and directs a research program in advanced multi-modal imaging of pathophysiological mechanisms in patients with prodromal and manifest Parkinson's disease. Per Borghammer holds a Lundbeck Foundation research fellowship. He is member of the "Non-motor symptoms in Parkinson study group" under the auspices of the International Parkinson and Movement Disorder Society, and sits on the scientific board of the Danish Parkinson's Disease Association.

Peter Frøhlich Staanum, Medical physicist, M.Sc., PhD, member of the board of the Danish Society for Clinical Physiology and Nuclear Medicine, member of the Danish Society for Medical Physics.

Peter Iversen, Consultant. Member of Danish Society of Clinical Physiology and Nuclear Medicine (DSKFNM). Teaches at specialist courses for nuclear medicine physicians (endocrinology). Research areas: Nuclear diagnostics in endocrinology and radionuclide therapy in endocrinology, thyroid cancer and neuroendocrine cancer.

Peter Parbo, MD, PhD. Registrar in the department, and member of the Alzheimer research group lead by Professor David Brooks.

Rola Ismail, MD, PhD student

Simon Maretti Tornbjerg, MD, Registar

Steen Jakobsen, Radichemist, PhD

Stine Kramer, Consultant, member of Dansk Selskab for Klinisk Fysiologi og Nuklearmedicin (DSKFNM), member of the Board of Danish Esophagus, GEJ & Gastric Cancer Group (DECV), teaches at specialist courses for gastroenterologists.

Søren Baarsgaard Hansen, MSc, PhD, medical physicist, is chairman of the Scientific committee for the Norwegian Association for Medical Physicists symposium 2020, lecture and course organizer for several medical imaging courses at Aarhus University and Sino-Danish Center for Education and Research.

Thea P. Lillethorup, MD, PhD

Tine Nygaard Gregersen, MD, PhD. Member of term management group, for medical candidate students at Aarhus University. Teaching medical doctors in their internship regarding career, collegial supervision and educational documents in Region Nord. Research area, gastroenterology and hepatology in NUK and PET, in particular neuroendocrine tumor and bile acid malabsorption.

Aage Kristian Olsen Alstrup, Honorary associate professor, veterinarian, PhD. Laboratory animal veterinarian for the department and its two animal facilities. Aage Kristian Olsen Alstrup performs preclinical research at the PET Center, and his primary research area is to investigate factors of importance for scanning of experimental animals, including their anesthesia, monitoring and surgery. He also teaches in laboratory animal science, is censor and academic writer.

PhD and Postdoc projects

PhD

Non-invasive measurement of Tumor Perfusion with ^{82}Rb PET/CT in Prostate Cancer

Mads Ryø Jochumsen
MD, PhD student

Mads' area of research is perfusion imaging in prostate cancer

Supervisors
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Jørgen Frøkiær, Professor, DMSc

Michael Borre, Professor, DMSc

Kirsten Bouchelouche, MD, DMSc

Jens Sörensen, Professor, DMSc

Angiogenesis and blood flow is known to be elevated in tumor tissue, consequently imaging of tumor blood flow (TBF) has been used for characterization of aggressiveness and monitoring of treatment response in a range of cancers. The main purpose of the Ph.D.-project is to validate and qualify non-invasive tumor perfusion imaging with ^{82}Rb PET as a new diagnostic method for quantitative measurement of TBF, and subsequently for evaluation of tumor aggressiveness and monitoring of treatment response in prostate cancer (PCa) patients.

The initial study has been completed, comparing TBF in 15 high-risk PCa patients with 15 volunteers without known disease of the prostate. TBF measured by ^{82}Rb SUV in the fifteen patients were significantly higher than blood flow measured by ^{82}Rb SUV in healthy prostate tissue of the controls, both when the tumors were drawn by PSMA guidance ($p<0.001$) and when applying the 60% threshold method on the ^{82}Rb PET hot spot ($p<0.001$). The ^{82}Rb uptake are thereby consistent with increased flow, and we consider the study to be a proof of concept of ^{82}Rb PET/CT as a tool for quantitative TBF measurement.

As blood flow is the underlying basis for growth in a tumor, absolute quantification of TBF might be a valuable tool in the risk evaluation and monitoring of PCa. In the following study the correlation between TBF, MRI guided biopsies and post prostatectomy Gleason score will be examined as well as the connection between TBF and other tumorbiological characteristics, such as the grade of angiogenesis, androgen receptor density and Na-K-ATPase. Furthermore, the response in TBF to chemo-hormonal treatment will be investigated, including the predictive value of the initial perfusion response regarding long-term treatment effect. Finally, a test-retest study is planned.

If we find that TBF correlates with Gleason score and hence aggressivity of PCa, there will be a huge potential for using ^{82}Rb PET in risk stratification and monitoring of patients with PCa. TBF measurement could thereby become a potential valuable tool in selecting which patients will benefit from treatment and which patients could safely enter active surveillance programs. Furthermore, if we find that initial response in TBF are associated with long term treatment response, ^{82}Rb PET can be a potential tool for early treatment response evaluation in PCa. ^{82}Rb PET thereby has the potential to contribute to a more personalized medical treatment of the increasing number of patients with PCa.

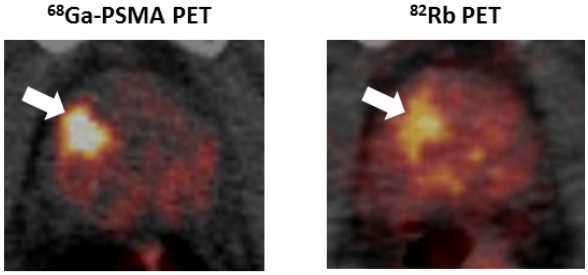
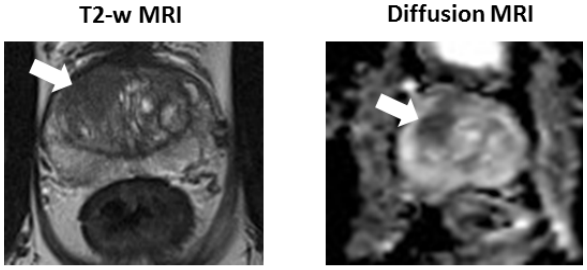


Figure 1 Tumor diagnosed on ^{68}Ga-PSMA PET (left) shows highly increased blood flow on ^{82}Rb PET (right).



Tumor visualized on T2w-MRI (left) shows markedly restricted diffusion (right), matching findings on ^{68}Ga-PSMA PET and ^{82}Rb PET respectively.

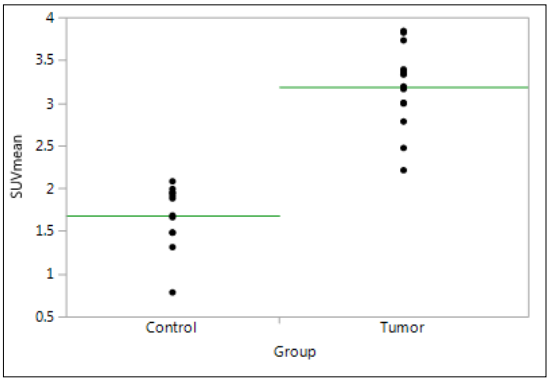


Figure 2 SUV mean of the tumor of the 15 patients drawn by PSMA guidance compared to the SUVmean of the prostate gland of the healthy controls.

PhD

[18F]AV-1451 PET imaging of Parkinson's disease, Dementia with Lewy Bodies, and Progressive Supranuclear Palsy

Allan Kjeldsen Hansen
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Supervisors
Per Borghammer,
MD PhD DMSc

Karen Østergaard,
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David J Brooks,
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The prevalence of dementia in Parkinson's disease (PD) is around 30%, but 80% of PD patients will develop dementia if they have the disease for over 20 years. The characteristic pathology in PD, PD dementia (PDD) and Dementia with Lewy Bodies (DLB) is fibrillar α-synuclein. However, up to 50% of patients with DLB or PPD also have enough amyloid-β plaques and tau-containing neurofibrillary tangles (NFT) for a secondary diagnosis of Alzheimer's disease (AD) to be made at autopsy. Importantly, two studies have shown that levels of tau-containing NFTs may be a stronger correlate of dementia in PD than α-synuclein pathology. However, this conclusion was based on cross-sectional post-mortem data and the in vivo time-course of pathological NFT deposition and its relation with onset of cognitive decline in Lewy body syndromes is still unclear.

With the advent of tau-selective positron emission tomography (PET) probes, such as [18F]AV-1451, it is now possible to measure in vivo levels of pathological tau-aggregation in the brains of living patients. At the Aarhus University Hospital PET-Center, we are currently using [18F]AV-1451 PET to elucidate the associations between pathological tau-deposition and cognitive decline in PD patients. In a longitudinal study, we aim to compare levels of cortical [18F]AV-1451 uptake in cognitively impaired PD with non-impaired PD patients who would be expected to have low [18F]AV-1451 binding.

At clinical presentation, idiopathic PD can be difficult to separate from atypical PD, such as progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD). The histopathological hallmark of PSP is aggregation of globose tau-inclusions in the lentiform nucleus, substantia nigra, oculomotor nuclei, cerebellar dentate nuclei, locus ceruleus, thalamus, and cortical regions including the motor- and premotor cortex. A specific PET tau-tracer could have immediate clinical utility for supporting the differential diagnosis of early parkinsonian cases into tauopathies such as PSP and CBD, so separating them from idiopathic PD. In our proposed study, we intended to scan clinically probable PSP and CBD cases with [18F]AV-1451 PET imaging and compare their tau load and distribution with that in PD, Unfortunately, [18F]AV-1451 appears to have reduced affinity for the tau species characteristic to PSP and CBD. Future generations of tau tracers may offer improved differential diagnostic capabilities in parkinsonian disorders.

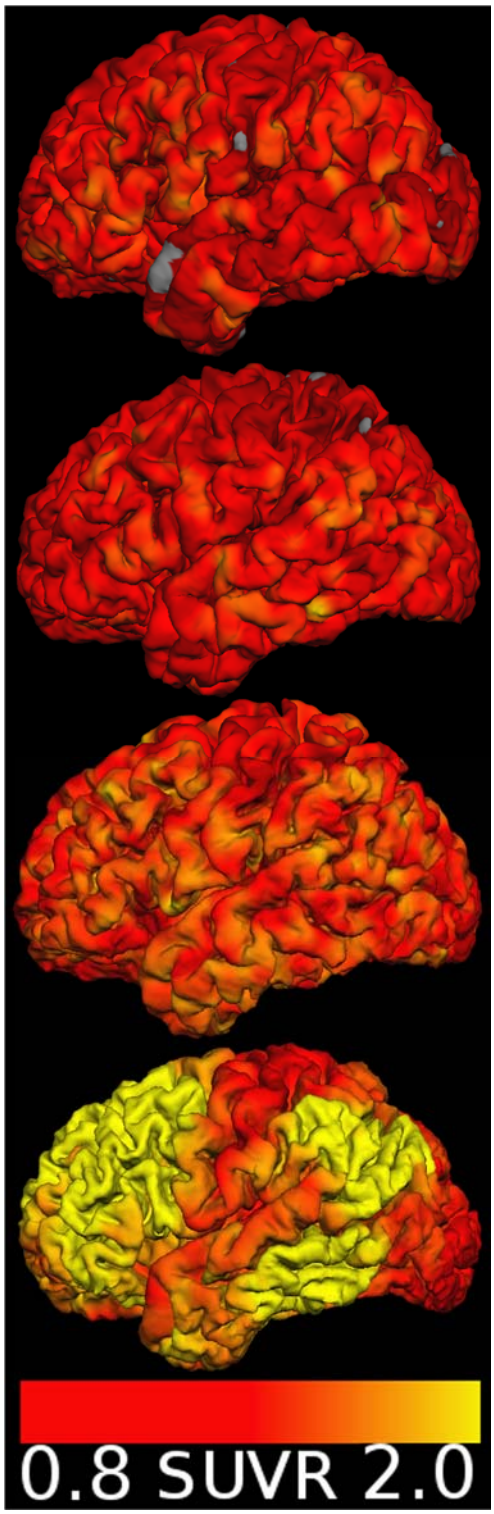

Figure 1: Tau PET (18F-AV-1451) from four subjects. From top to bottom: Healthy control, Parkinson's disease with no cognitive impairment, Parkinson's disease with mild cognitive impairment and finally a patient with Alzheimer's disease.

PhD

Myocardial oxygen consumption and efficiency in aortic valve stenosis patients with and without heart failure

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Myocardial external efficiency (MEE, %) describes the coupling between mitochondrial energy production and mechanical work, and is defined as the ratio of left ventricular stroke work and myocardial oxygen consumption (MVO2, mL/min/g). Thus, MEE has the potential to provide critical insight into the pathophysiology of heart failure. Therefore, we investigated potential differences in MVO2 and MEE in patients with aortic valve stenosis (AS). We included AS patients throughout a wide clinical spectrum of the disease and healthy controls. Furthermore, we validated methodological simplifications and the repeatability for non-invasive MEE-evaluation to facilitate the use of MEE in future studies. The main findings are presented below:

Paper I
Left ventricular volumes and mass estimated from ECG-gated 11C-acetate PET correlate excellently with CMR but are consistently underestimated. Despite excellent correlation for stroke volume and mass, calculating MEE from a single ECG-gated 11C-acetate PET study cannot yet be recommended.

A more elaborate software approach for left ventricular border definition is likely to improve accuracy, which is highly influenced by the presence of concentric hypertrophy.

Paper II
Quantification of myocardial efficiency is largely dependent on the image modality and technique used for evaluation. Overall, CMR derived MEE and WMI display superior repeatability compared with echocardiography or PET. Consequently, the use of CMR instead of echocardiography or PET improves reliability of study results and reduces the estimated sample size by up to 60 %.

Paper III
In patients with AS, MVO2 remains unaltered regardless of symptomatic status, systolic function, degree of hypertrophy, and NT-proBNP. These results indicate that the pressure overloaded heart has a comprehensive ability to preserve normal rates of oxidative phosphorylation and that the onset of systolic failure is unlikely to be caused by mitochondrial dysfunction. Interestingly, MEE only deteriorates after the onset of severe systolic dysfunction (LVEF < 50 % or GLS > -12 %) proving a sustained ability to maintain normal mechanoenergetic coupling in patients with normal-flow AS.

In contrast, patients with low-flow, low-gradient AS, MEE was reduced to a similar level as for patients with LVEF < 50 %. This is the first study to demonstrate a potential cause of poor clinical outcome in this subgroup of AS patients.

Consequently, MEE and MVO2 provide limited value in the search for markers which could aid the challenging task of differentiating symptomatic from asymptomatic AS patients. However, the large differences in MEE between AS groups and the excellent repeatability of MEE imply that serial MEE-measurements may conceal important prognostic information in AS patients.

PhD

FDG-PET/CT for Response Evaluation in Non-Small Cell Lung Cancer Patients

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Supervisors
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Hanne Linnet,
MD, PhD, Chief Physician

The thesis was finished November 31rd 2017 and consist of an overview and five original papers, three of which are published in international peer reviewed journals, and the last two manuscripts have been submitted for publication, but are not published yet.

The first paper entitled: "Using positron emission tomography (PET) response criteria in solid tumours (PERCIST) 1.0 for evaluation of 2'-deoxy-2'-[18F] fluoro-D-glucose-PET/CT scans to predict survival early during treatment of locally advanced non-small cell lung cancer (NSCLC)", is published in the *Journal of Medical Imaging and Radiation Oncology.* This showed that response evaluation with 18F-FDG-PET/CT, using both visual evaluation and PERCIST 1.0, is feasible as long as strict attention is paid to minimizing the variation in uptake time between scans and that both methods can separate responders from non-responders.

The second paper entitled: "Inter-observer agreement improves with PERCIST 1.0 as opposed to qualitative evaluation in non-small cell lung cancer patients evaluated with F-18-FDG PET/CT early in the course of chemo-radiotherapy", is published in the *European Journal of Nuclear Medicine and Molecular imaging Research* and shows that the inter-observer agreement for evaluating early response to treatment with 18F-FDG-PET/CT is strong (using both visual evaluation and PERCIST 1.0) and that PERCIST 1.0 provides a higher inter-observer agreement than the visual evaluation.

The third paper entitled:"^{18}F-FDG-PET/CT after induction chemotherapy for prediction of survival after radical chemo-radiotherapy in locally advanced NSCLC patients" (not yet published) showed that in this setting, ^{18}F-FDG-PET/CT is not an obvious tool for selecting patients who will or will not benefit from radical radiotherapy. We found indications of a correlation between OS and early ^{18}F-FDG-PET response, but contrary to our expectations, with longer survival for patients with SMD than PMR, although the difference is not statistically significant. Percentage change in the semi-quantitative parameters does not perform better than the qualitative visual evaluation when evaluated by an experienced nuclear medicine specialist.

In the fourth paper entitled: "18F-FDG-PET/CT for very early response evaluation predicts CT response in erlotinib treated NSCLC patients – A comparison of assessment methods" published in *Journal of Nuclear Medicine* we found that total lesion glycolysis analysis seems to perform better than other semi-quantitative methods and visual evaluation. The optimal cut-off level can identify approximately 40% of patients that will not benefit from erlotinib treatment as early as 1-2 weeks into the treatment.

Finally, the fifth paper entitled: "Predicting survival using very early response evaluation with ^{18}F-FDG-PET/CT in erlotinib treated NSCLC patients – A comparison of assessment methods" (not yet published), showed that an early change in ^{18}F-FDG-uptake during erlotinib treatment is correlated to both PFS and OS. The choice of method for analysis is not clear-cut, but percentage change in TLG as suggested by the PERCIST 1.0 is not inferior to other methods, and visual evaluation seems to be less sensitive at this very early time-point.

Taken all together, we believe that the evidence presented in this thesis provides an important contribution towards implementation of ^{18}F-FDG-PET/CT for early response evaluation during the treatment of NSCLC patients in routine daily clinical practise, particularly in the palliative setting, as is already the case for the evaluation of lymphomas. This could become an important step toward personalized treatment planning for these patients

PhD

Early markers of parkinsonian disorders in patients with prodromal Parkinson's disease – follow-up

Morten Gersel Stokholm
MD, PhD

Morten's area of research is positron -emission-tomography imaging in patients with idiopathic rapid eye movement behaviour disorder.

Kristian Stær
MD,, Research Assistant

Main Supervisor
Dr. *Nicola Pavese*
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Co-Supervisors
David J Brooks,
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Karen Østergaard,
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Per Borghammer,
MD, Associate Professor

Arne Møller
Associate Professor

Objectives

The objectives of this international research project is to better characterize the functional changes associated with REM sleep behaviour disorder (RBD) or -glucocerebrosidase (GBA) mutation carrier status to understand the earliest features of the pathological process in Parkinson's disease (PD), Dementia with Lewy Bodies (DLB), and multiple system atrophy (MSA) disease development.

Study description

Studies have indicated that RBD and GBA mutation carriers can represent patients in a pre-symptomatic phase of PD, DLB, and MSA.

Using 11C-PK11195 PET, a marker for activated microglia involved in neuroinflammation, in RBD patients, our team found increased levels of neuroinflammation in substantia nigra, putamen and caudate (brain areas typically involved in PD) in these patients, suggesting that neuroinflammation occurs in the early stages of the development of Parkinsonian syndromes.

Activated microglia was also found in the visual associative cortex, potentially explaining the difficulties that RBD patients have in tests assessing visio-spatial skills. In the same cohort, 18F-dopa PET, a marker of monoamine function, showed that a subgroup of RBD patients had widespread dopamine dysfunction in striatal sub-regions including the caudate, possibly suggesting that these subjects are in an early stage of DLB rather than PD. Additionally, 18F-dopa uptake was reduced in the thalamus of RBD patients compared to controls, possibly reflecting dysfunction of the monoaminergic projections from the locus coeruleus and raphe nucleus.

We will perform an imaging and clinical follow-up in the RBD patients who have participated in our baseline study to determine if the changes that we have found in these patients progress over time and whether they can be used as early imaging biomarkers of Parkinsonian disorders.

We predict that this will provide significant insight into the earliest pathological mechanisms of PD and provide targets for pharmacological interventions aiming to halt or slow down the development of both motor and non-motor symptoms. In particular, it could help to better understand the extent and time-course of degeneration of non-dopaminergic systems, the onset of inflammation, and their contribution to clinical status.

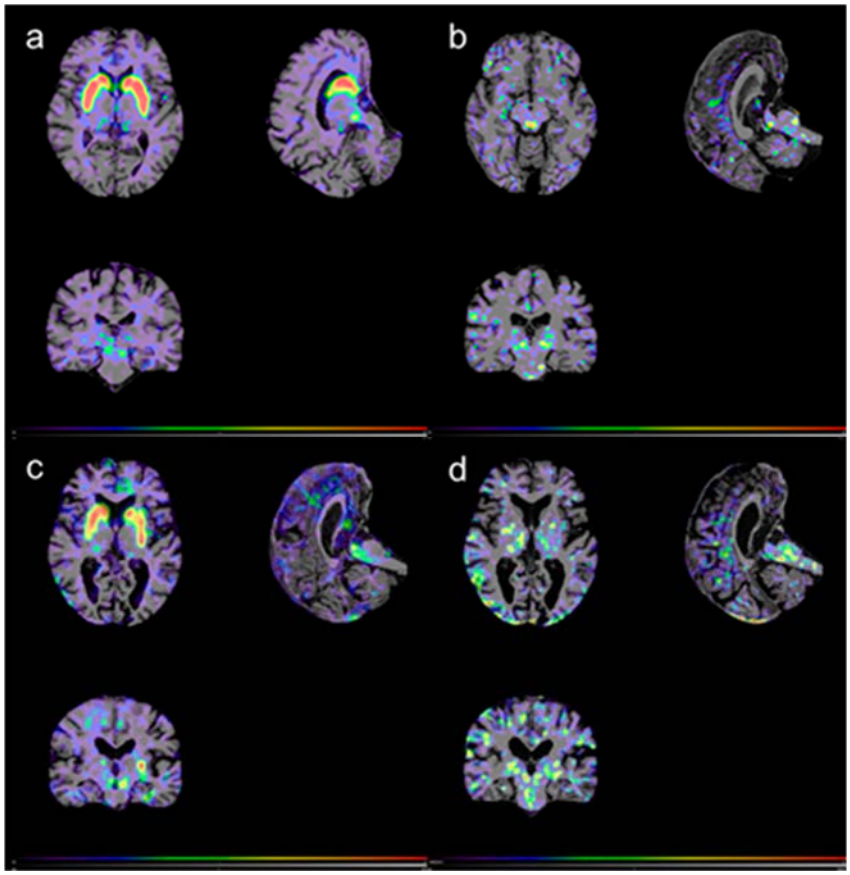

Figure 1: 18F-DOPA PET of a healthy control subject (a) showing normal tracer uptake in the striatum and a REM sleep behaviour disorder patient(c) showing a mild reduction in tracer uptake on the left side. 11C-PK11195 PET of a healthy control subject (b) and a patient with REM sleep behaviour disorder (d) showing increased tracer uptake in the brainstem region representing increased microglia activation in the latter.

PhD

Optimization of stereotactic body radiation therapy for liver metastases

Mette Marie Fode
MD, PhD

Supervisors
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Professor, PhD, MD

Michael Sørensen,
PhD, MD

Jørgen Petersen,
MSc.

Stereotactic body radiotherapy (SBRT) is a special kind of radiotherapy, where a very large radiation dose is delivered to the tumor in a few fractions with a very precise technique based on CT that does not account for functional variation in the liver tissue. Radiation -induced liver disease (RILD) is a rare but serious condition and therefore it is an essential limiting factor in SBRT treatment planning. PET scanning of the liver using the galactose analog [^{18}F]-fluoro-2-deoxy-D-galactose (FDGal) is used to image and quantify regional metabolic function of the liver and we tested if this PET method can be used to optimize the treatment strategies for SBRT liver tumors (functional treatment planning).

In a retrospective study of seven patients referred for SBRT of liver tumors, we investigated if functional treatment planning using FDGal PET/CT can assist the construction of SBRT treatment plans in a manner by which radiation exposure to the best functioning liver tissue could be reduced. In this group of patients, the mean dose delivered to the liver was reduced by up to 15% when based on functional treatment planning compared to conventional treatment planning. We conclude that it was technically feasible to construct functional treatment plans and to spare the best functioning liver tissue (I).

In a prospective phase I study including 14 patients referred for SBRT for liver metastases, we examined the clinical feasibility of functional treatment planning and the relationship between the regional radiation dose and reduction of metabolic liver function in normal liver tissue after treatment. FDGal PET/CT was performed prior to and one month after SBRT. We found that by incorporating pre-treatment FDGal in the treatment planning, the radiation dose was reduced by approximately 2 Gy to the best functioning liver tissue compared to the total liver volume subtracted the tumor volume (Figure 1). Normalized data showed a linear dose-response relationship one month after treatment with 50% reduction in liver function at 23 Gy delivered in three fractions and 12% reduction in liver function for each 10 Gy increase in dose. The study demonstrates the clinical use of construction and delivery of SBRT functional treatment planning for liver metastases (II).

The concept of functional treatment planning in patients treated with SBRT for liver metastases could be expanded to patients with larger tumor burden (more metastases or larger metastases) without increase in morbidity. It seems favorable to escalate the radiation dose to the tumor to increase the local control without increase in morbidity. Furthermore, patients with pre-existing parenchymal liver disease have a higher risk of developing RILD and it is likely that they would benefit considerably from SBRT functional treatment planning, but this remains to be confirmed.

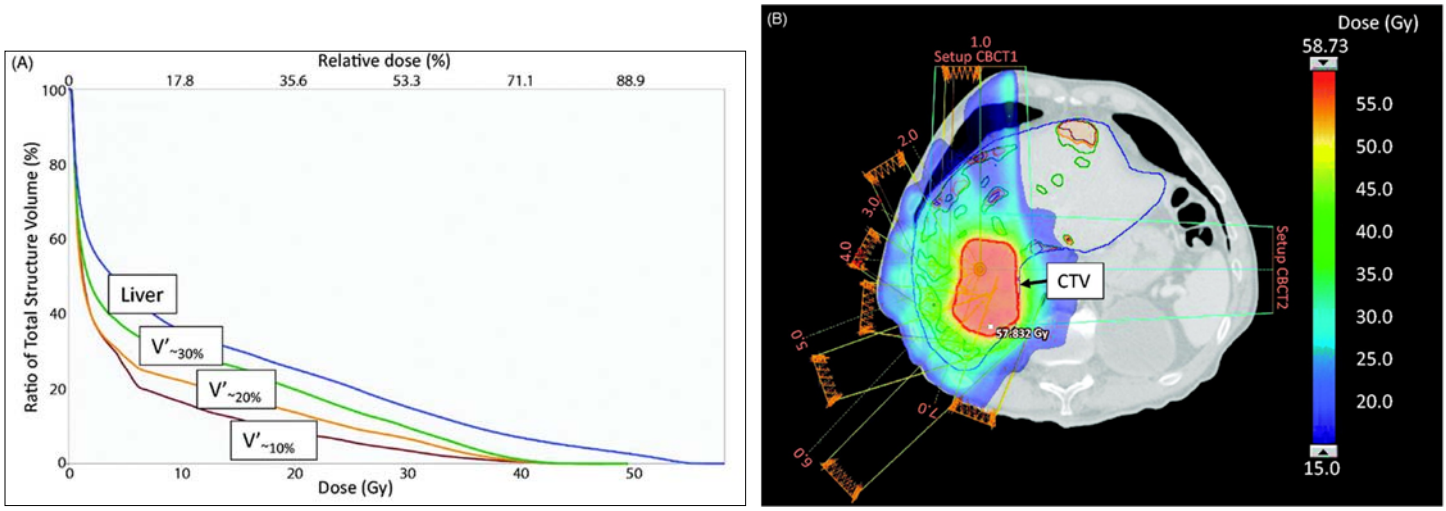

Figure 1:
A: Dose-volume histogram of patient #10 visualizes the radiation dose delivered to the total liver subtracted the tumor (Liver) is higher than the dose delivered to the 10, 20 and 30% best functioning liver tissue (V'_{10}, V'_{20} and V'_{30}).
B: The dose distribution to the tumor (CTV) and the normal liver tissue avoiding the sub-volumes of best functioning liver tissue (brown, orange, green)

PhD

Imaging synaptic density in rat and pig brain

Majken Borup Thomsen
MSc Med,
PhD student

Majken's area of research involves preclinical imaging and validation of a novel tracer of synaptic density, and the development of rodent models of Parkinson's disease. Majken is funded by a Lundbeckfonden PhD scholarship.

Supervisors
David J Brooks,
MD, DSc, FRCP (UK), FMedSci (UK), Professor of Neurology

Anne M. Landau,
Associate Professor

The number of functionally active synapses can be used as a measure of neurological health. Reduced synaptic function is present in diseases such as Parkinson's disease, Alzheimer's disease and epilepsy. [11C]UCB-J is a novel positron emission tomography (PET) tracer of synaptic function that binds to synaptic vesicle protein 2A (SV2A), a transmembrane protein located in secretory vesicles in all areas of the brain.

Part of the PhD project is to assess the potential of [11C]UCB-J as a biomarker of global synaptic function in the living rat and pig brain, as a prelude to future studies in animal models of disease. We performed PET scans of anesthetised rats and pigs with [11C]UCB-J while sampling arterial blood for radioactivity and presence of metabolites. We are currently comparing different methods in order to model the tracer kinetics and to identify the regional distribution of the tracer. Furthermore we have performed blocking experiments in where levetiracetam (rat: 100 mg/kg, pig: 30 mg/kg), an antiepileptic drug that binds to SV2A, was administered iv prior to the [11C]UCB-J PET scan.

[11C]UCB-J brain uptake is high and shows fast kinetics in both species. The blocking experiments in the rat showed clear displacement and therefore specific binding, when blocking with levetiracetam (Figure 1).

These preliminary data indicate that [11C]UCB-J may be a good potential *in vivo* marker of synaptic density in the rat and pig brain opening the possibility to non-invasively investigate *in vivo* synaptic function, in a longitudinal manner and in response to therapy, in small and large animal models of neurodegenerative diseases.

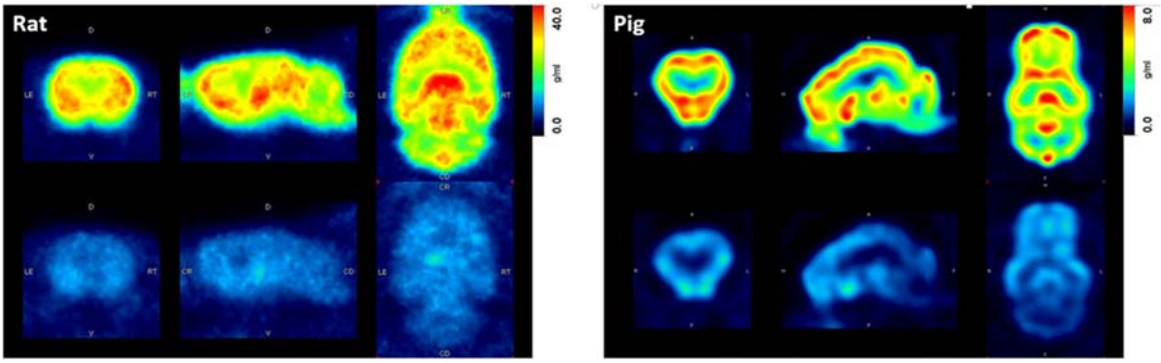

Figure 1 Representative summed SUV images (rat: average of frames from 4-90 min, pig: average of frames from 30-120 min) during baseline condition (top) and after blocking with levetiracetam (bottom) in rat (left) and pig (right).

PhD

Gastrointestinal and pancreatic function in Parkinson's disease

Karoline Knudsen
BMLT MMDI

Karoline's area of research is gastrointestinal and pancreatic function in Parkinson's disease.

Supervisors
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Klaus Krogh, MD PhD DMSc

Karen Østergaard, MD DMSc

Parkinson's disease (PD) is now recognized as a multi-system disorder involving both the sympathetic and parasympathetic nervous system. Most PD patients experience several autonomic non-motor symptoms including constipation, which are often present many years prior to PD diagnosis. The Braak dual-hit hypothesis suggests that PD -synuclein pathology in some cases may initiate in the gut and olfactory system and spread to the central nervous system (CNS) via autonomic nerves; thus, constipation may be among the first prodromal disease symptoms, probably primarily caused by parasympathetic denervation.

Idiopathic rapid-eye-movement (REM) sleep behavior disorder (iRBD) is a sleep condition of dream enactment, and it has been shown that iRBD is a prodromal PD symptom, as the majority of iRBD patients convert to PD or a related synucleinopathy over time. Thus, this patient group gives the opportunity to examine patients in the early pre-diagnostic phase of PD. Despite the high prevalence of gastrointestinal (GI) involvement in PD and iRBD and the importance of this feature in disease and phenotype characterization, it is still poorly understood and not thoroughly examined using objective measures.

Also, the pancreas is highly innervated by the parasympathetic nervous system, and the integrity of parasympathetic innervation can be determined by analysing levels of pancreatic polypeptide (PP) during the initial phase of feeding and serve as a marker of parasympathetic gut innervation.

The purposes of the study were to examine GI function and motility measured by 3 different objective methods in PD, iRBD, and healthy control subjects (HC). Also, PP levels after sham feeding (chew-and-spit procedure) were measured in PD and HC as an estimation of GI parasympathetic innervation.

Significantly affected GI function was found in both PD and iRBD patients using all three applied objective measures. GI transit time using the radio opaque marker (ROM) technique was significantly longer in both study groups compared to controls, and 79% of PD patients and 33% of iRBD patients displayed delayed transit time.

The same significance pattern was seen in CT segmented colonic volume, and 66% of PD patients and 48% of iRBD patients displayed increased volume of the colon (Figure 1). Using the 3D-Transit electromagnetic capsule system, delayed transit was seen in the small intestine in PD (colon transit not obtained) and in the colon in iRBD (Fig. 2).

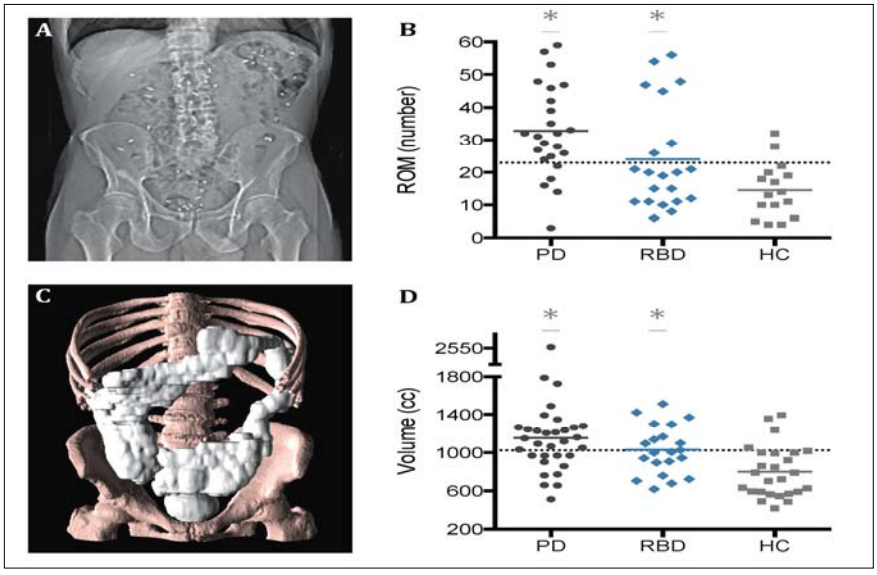


Figure 1 A. CT scan of retained radio opaque markers (ROM) as a measure of gastrointestinal transit time. **B.** Total number of retained ROM in PD, iRBD, and HC. **C.** Outline of the colonic volume defined on CT scan. **D.** Total colonic volume in PD, iRBD, and HC. *indicates $p<0.05$ compared to HC.

Colonic motility was evaluated as time to first propagating colonic movement and found significant in both patient groups, most pronounced in the PD patients. The GI dysfunction was in general more severe in PD compared to iRBD, possibly due to both a more severe neurodegeneration and use of anti-parkinsonian medication.

Subjectively scored constipation symptoms were present in 18% of iRBD and 38% of PD.

Plasma PP levels after sham feeding were significantly decreased in PD compared to HC (Figure 3). This difference was most pronounced at the 10-minute time point.

So far, the study has shown a significant involvement of the GI tract in both iRBD and PD patients, most prominent in the latter. Objectively measured dysfunction was more prevalent than subjective constipation symptoms in both patient groups. Also, plasma PP levels after sham feeding were significantly decreased in PD compared to controls as an indicator of parasympathetic denervation of the gut organs.

In conclusion, the present study provides the most comprehensive information about GI function in PD and iRBD until now. It is of great importance to understand and establish the phenotypic characteristics of PD, including GI function, as a very early diagnosis will be of the utmost importance once neuroprotective drugs become available.

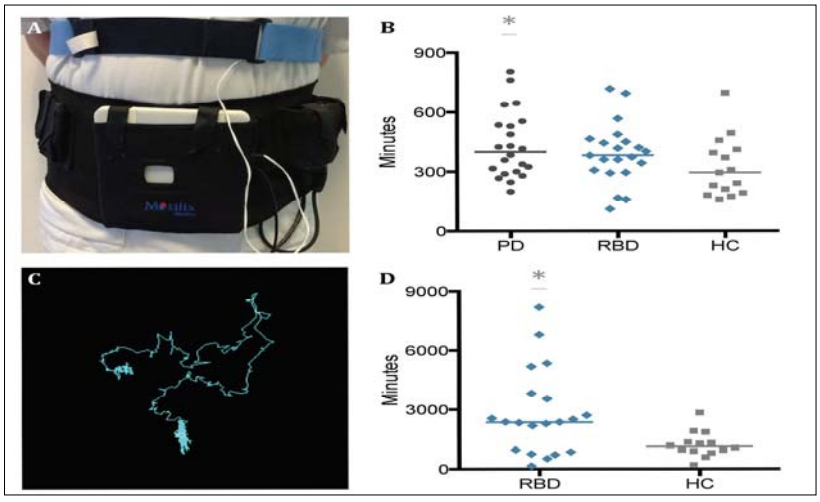


Figure 2 A. 3D-Transit abdominal monitoring system. **B.** Small intestinal transit time in minutes in PD, iRBD, and HC. **C.** Illustration of 3D electromagnetic capsule passage of the colon. **D.** Colonic transit time in iRBD and HC in minutes. *indicates p<0.05 compared to HC.

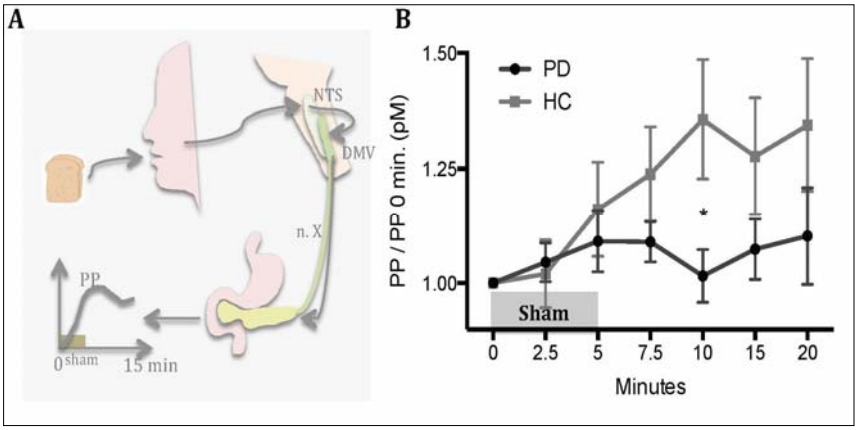


Figure 3. A. Schematic illustration of early cephalic phase peak of the hormone Pancreatic Polypeptide (PP) mediated by the vagus nerve (n. X) via the nucleus tractus solitarius (NTS) and the dorsal motor nucleus of the vagus (DMV). PP plasma levels after sham feeding is a validated marker of vagal integrity. **B.** PP concentration ratio at 0-20 min. during and after sham feeding 0-5 min. *indicates p<0.05.

PhD

Neuroimaging biomarkers of mild cognitive impairment in neurodegenerative disease

Jeppe Lund Schaldemose
MSc in Psycology, PhD student

Jeppe's area of research is cognition in neurodegenerative disease.

Supervisors
David J Brooks, MD, DSc, FRCP (UK), FMedSci (UK), Professor of Neurology

Adjmal Nahimi, MD, PhD

Malene F. Damholdt, MSc in Psychology, PhD

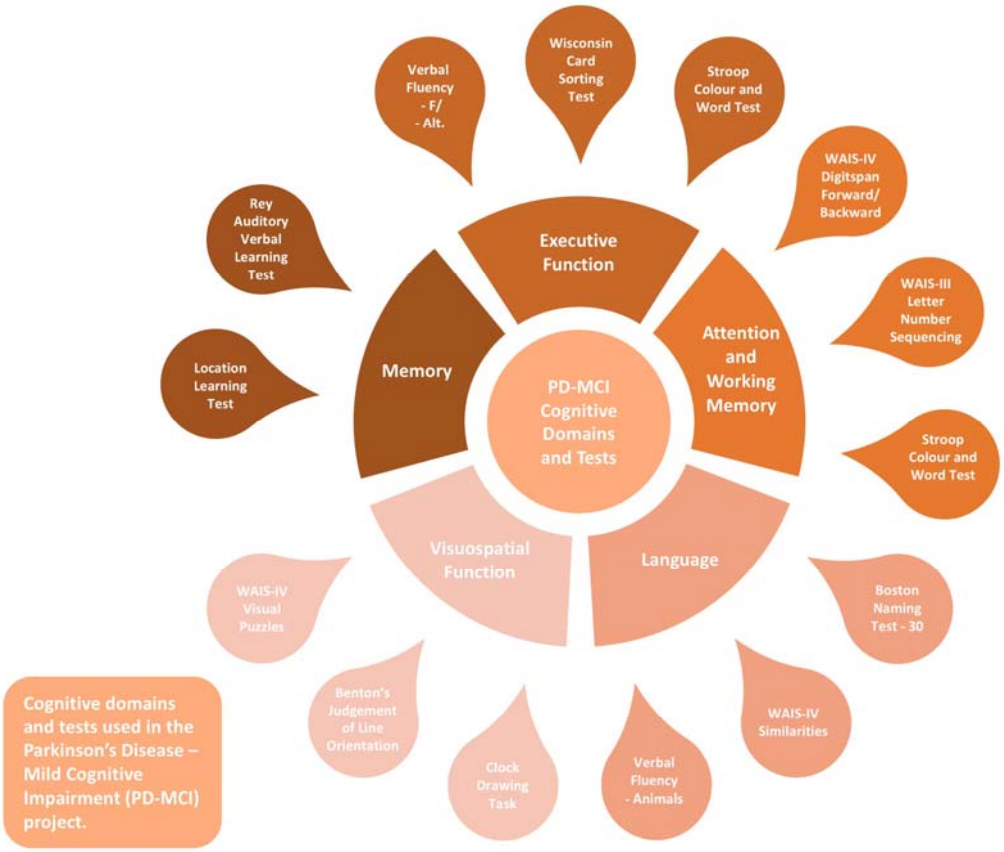
Collaborators:
Peter Parbo, MD, PhD student

Alzheimer's disease (AD) and Parkinson's disease (PD) are characterised by trajectories of cognitive decline and dementia. Unfortunately, there is a lack of knowledge on how to prevent or cure cognitive decline and dementia in these neurodegenerative diseases. Therefore, the purpose of the PhD-project is to clarify the relationship between cognitive decline and objective neuroimaging biomarkers in AD and PD and hereby bring this research forward. The PhD-project will assess the progression and characterise the neuropsychological (NP) profiles of mild cognitive impairment (MCI) and dementia in patients with AD and PD. These measures will be compared to objective neuroimaging biomarkers of beta-amyloid, tau and inflammation in AD and noradrenaline in PD, in two separate studies with longitudinal designs.

The AD-study was initiated by Profesor David Brooks and MD, PhD student Peter Parbo in 2014. Participants had PET-scans of beta-amyloid (11C-Pittsburgh compound B), tau (18F-AV1451) and inflammation (11C-(R)-PK11195), MRI-scans, blood samples and NP assessments. Baseline data have been collected for 44 participants with MCI, 4 patients with AD and 23 participants with normal cognition. We are currently doing follow-up scans and assessments and expect to finish data collection in late 2018. Data analysis into the cognitive measures and characterization of NP profiles will begin this spring.

The PD-study was initiated in 2017 and participants will undergo PET-scans of noradrenaline (11C-MeNER), MRI-scans, MEG/EEG-scans and extensive NP assessments in accordance with the Movement Disorder Society guidelines for PD-MCI. So far, we have collected PET-scans, MRI-scans and NP assessments from 10 patients with PD and 14 healthy controls. Recruitments are ongoing and follow-up data will be collected after one and two years.

If we manage to identify early objective neuroimaging biomarkers of cognitive decline in AD and PD, it could be of great importance for the future research into the treatment of these neurodegenerative diseases. Potentially, it would provide the opportunity to enable early intervention in an attempt to slow down or halt cognitive decline before progression into MCI and eventually dementia in AD and PD.



PhD

Noradrenergic dysfunction and slowing of cortical oscillatory activity in Parkinson´s disease patients with mild cognitive impairment

Martin Byskov Kinnerup
MSc Eng,
PhD-student

Martin's area of research is noradrenaline dysfunction in Parkinsons Disease. In 2017 his project received support from the Lundbeck Foundation, and the Parkinson's Foundation.

Supervisors
David J Brooks,
MD, DSc, FRCP (UK), FMedSci (UK), Professor of Neurology

Adjmal Nahimi
MD, PhD

Birger Johnsen
MD, PhD

Malla Chakravarty
Assistant Professor, PhD

Mild cognitive impairment (MCI) is highly frequent in patients with Parkinson's Disease (PD) and may appear before the cardinal motor symptoms in some patients. MCI primarily includes progressive dysfunction in executive, visuospatial and in working memory functions; however, the full spectrum of cognitive deficits and the underlying mechanisms of progression of MCI to dementia in PD patients are not clearly understood. Preclinical and in-vitro studies suggest that loss of noradrenaline producing neurons from the locus coeruleus in the brainstem may play a key role in the prevalence and severity of cognitive deficits. Thus, depletion of noradrenergic innervation may lead to pathological slowing of cortical oscillatory activity and worsening of cognitive deficits in PD patients. However, no studies have examined the role of noradrenergic deficits in the occurrence of neurophysiological abnormalities in PD patients with MCI in a clinical setting. Here, we employ [^{11}C]MeNER PET in a longitudinal clinical multimodal imaging study to elucidate its role in cognitive impairment and neurophysiological abnormalities in patients with PD.

We are conducting a longitudinal study where 50 patients with PD and 50 age matched healthy controls(HC) will undergo extensive annual neuropsychological evaluations, together with quantification of deficits of noradrenergic neurotransmission by means of positron emission tomography with [^{11}C] MeNER, a highly selective antagonist of noradrenaline transporters. Pathological slowing of cortical oscillatory activity and morphological changes in cortical and subcortical structures will be quantified with recordings of magnetoencephalography, electroencephalography, and magnetic resonance imaging, respectively. PD patients and HC will be assessed for autonomic disorders using Valsalva and tilt -test and they will be assessed for REM Sleep Behaviour Disorder using polysomnography.

The main aims of the current project are to elucidate the underlying mechanisms of the insidious progression of mild cognitive impairment to PD dementia. We aim to establish a cognitive profile that can be used as a clinical tool. Through the multimodal approach, we aim to establish biomarkers than can help identify patients that have an increased risk of developing PD dementia.

PhD

Evaluating Göttingen minipig models of Parkinson's disease with PET imaging

Thea P. Lillethorup
MsC Med, PhD

Thea's area of research is evaluating Göttingen minipig models of Parkinson's disease with PET imaging.

Supervisors
David J Brooks, MD, DSc, FRCP (UK), FMedSci (UK), Professor of Neurology

Anne M. Landau, Associate Professor

Dariusz Orlowski, Assistant professor

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by aggregated a-synuclein (a-syn) inclusions in surviving dopaminergic neurons of the substantia nigra, other brainstem nuclei, and association cortex. Patients suffer from both motor and non-motor impairments, which are associated with dysfunction of monoaminergic and cholinergic transmission. The ubiquitin-proteasome system (UPS) is in part responsible for the degradation of misfolded or damaged small proteins such as a-syn and UPS dysfunction is evident in post-mortem tissue from PD patients. By administering UPS inhibitors to rodents, a-syn accumulation associated with loss of dopaminergic neurons and motor impairment has been found.

We have extended rodent models of PD described in the literature to the larger Göttingen minipig and evaluated their validity using *in vivo* positron emission tomography (PET), behavioural analysis and subsequent immunohistochemistry. We followed Göttingen minipigs after either: 1) One direct injection of a high dose UPS inhibitor, lactacystin, into the nigrostriatal pathway, or 2) Weekly injections of lactacystin into a subcutaneous injection port connected to the cisterna magna.

Direct nigrostriatal injections led to decreased binding potential of [^{11}C]DTBZ to the vesicular monoamine transporter 2 (VMAT2) (Figure 1) with associated activation of microglia and behavioural deficits. The chronic ICV injections led to changes in three monoaminergic systems, dopaminergic, adrenergic and serotonergic (Figure 2) tracked with PET imaging markers and motor function became impaired in the animals.

In conclusion, UPS inhibition in a large animal model of PD was evaluated in Göttingen minipigs with PET imaging, behavioural tests and histology and certain aspects related to human PD were observed. The development of pig models of PD to mimic the pathophysiology of PD may prove useful for testing symptomatic and neuroprotective therapies directed at human PD and also for the development of novel PET imaging biomarkers.

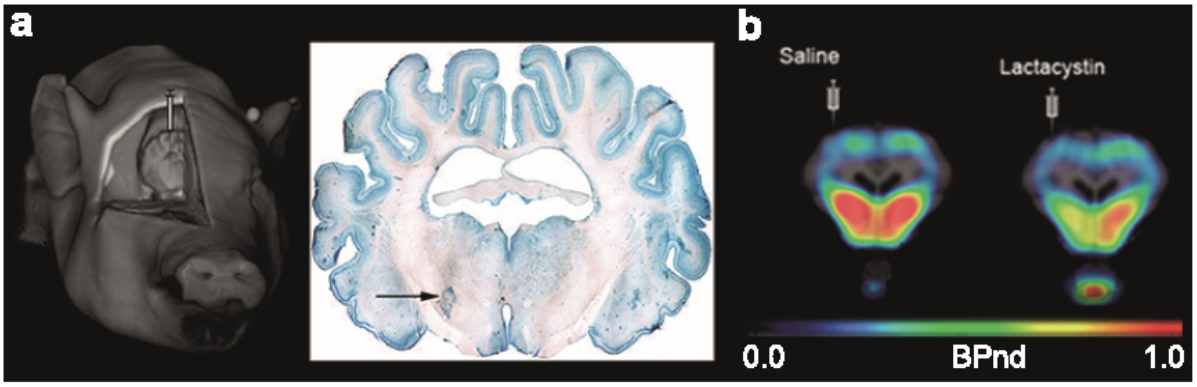


Figure 1 (a) MRI-based stereotaxic injection in the medial forebrain bundle. Arrow marks the visible needle tract. **(b)** VMAT2 binding levels determined by *in vivo* [11C]DTBZ PET. *BPND* values are presented at baseline and 3 weeks post-surgery of ipsilateral and contralateral striatum.

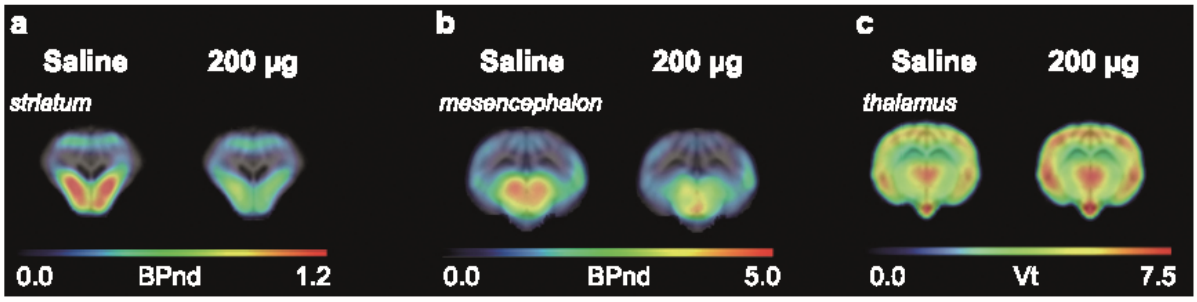


Figure 2 PET images of minipigs injected with saline through the injection port and following 200 µg lactacystin. Parametric maps are displayed for **(a)** [11C]DTBZ *BPND*, a marker of VMAT2, **(b)** [11C]DASB, a marker of the serotonin transporter and **(c)** [11C]yohimbine, a marker of α2-adrenoceptors.

PhD

Noradrenergic dysfunction and slowing of cortical oscillatory activity in Parkinson´s disease patients with mild cognitive impairment

Kirstine Bak-Fredslund
MD, ,PhD student

Supervisors
Susanne Keiding,
MD, DSc, Associate Professor

Michael Sørensen
MD, PhD

Gerda Elisabeth Villadsen
MD, PhD

The galactose analogue 2-^{18}F-fluoro-2-deoxy-*D*-galactose (^{18}F-FDGal) is a liver-specific PET tracer used for 3D quantification of the metabolic liver function and visualization of hepatocellular carcinoma (HCC). In this Ph.D. project, we explored methodological aspects of ^{18}F-FDGal PET/CT in order to simplify the method for implementation in clinical practice:

Paper 1: *We tested if infusion of "cold" galactose during ^{18}F-FDGal PET/CT of patients with HCC improves the detection of intrahepatic HCC.*

This was not the case for neither static nor dynamic examination.

Paper 2: *We determined the day-to-day variation of the hepatic systemic clearance of ^{18}F-FDGal (K_{met}, mL blood/mL liver tissue/min) from dynamic PET of the liver and of the SUV of ^{18}F-FDGal from static PET of the liver. Secondly, we investigated the relationship between these two parameters – to determine if SUV can replace K_{met} clinically in the quantification of the hepatic metabolic function in humans*

There was no significant day-to-day differences of neither K_{met} nor SUV in six healthy subjects and four patients with cirrhosis. SUV had higher intraclass correlation coefficients than K_{met}, 0.92–0.97 vs. 0.49–0.78. The relationship between K_{met} and SUV was linear (Figure 1). Mean Total-SUV (average SUV multiplied by total metabolic liver volume) was significantly higher for healthy subjects than for the patients ($p <$ 0.001). The use of SUV instead of K_{met} simplifies quantification of the metabolic liver function, as K_{met} calculations require a 20 min dynamic ^{18}F-FDGal PET/CT scan with substantial data analysis while SUV can be derived from a simpler 10 min static scan 10 min after tracer injection.

Quantification of the regional metabolic liver function by ^{18}F-FDGal PET/CT may be helpful in the pretreatment evaluation of patients with cirrhosis considered for resection or other substantial treatment to the liver, in order to prevent post-operative liver failure.

Paper 3: *We determined the clinical impact, i.e. change of planned treatment, in 50 patients with HCC of adding ^{18}F-FDGal PET/CT to the standard work-up with contrast-enhanced computer tomography and/or magnetic resonance imaging performed prior to locoregional treatment. Secondly, we compared the results of ^{18}F-FDGal PET/CT with ^{18}F-FDG PET/CT in a subgroup of 29 patients.*

^{18}F-FDGal PET/CT detected previously unknown extrahepatic metastases of HCC in six patients (Figure 2) and had clinical impact in five of the 50 (10%) patients as the planned treatment modality was changed due to these findings. ^{18}F-FDGal PET/CT had higher sensitivities for both intra- and extrahepatic foci than ^{18}F-FDG PET/CT. The overall sensitivity for intrahepatic foci for ^{18}F-FDGal PET/CT was 71% vs 35% for ^{18}F-FDG PET/CT.

^{18}F-FDGal PET/CT may be considered in patients in which the certainty of no extrahepatic spread is paramount as in the case of patients evaluated for liver transplantation.

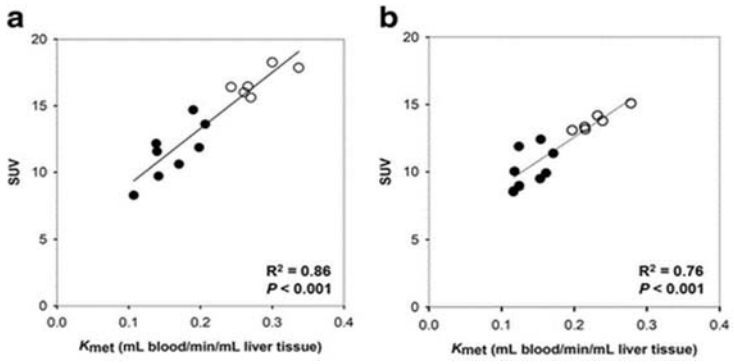


Figure.1 Correlations between regional values of SUV and K_{met} (**a**) and between whole-liver values of SUV and K_{met} (**b**) for ^{18}F-FDGal PET/CT in patients with cirrhosis (black circle) and healthy subjects (white circle). Linear regression lines are also shown.

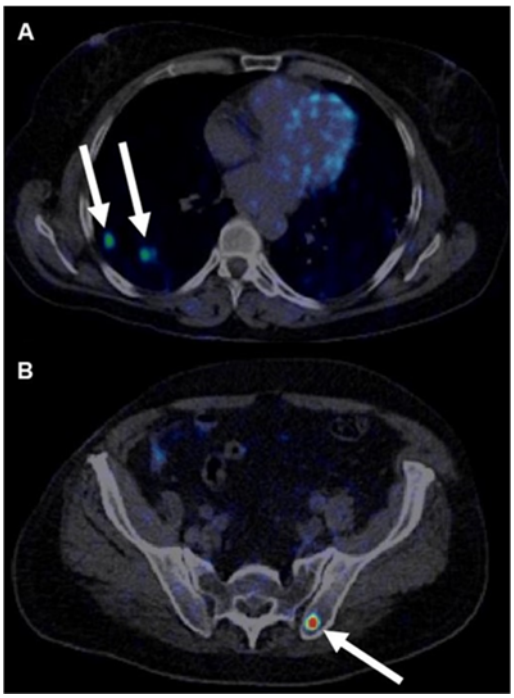


Figure 2. Extrahepatic HCC metastases (arrows) detected by ^{18}F-FDGal PET/CT. (A) Lung and (B) bone.

PhD

Early synaptic dysfunction in a genetic modified rat model resembles the features of Parkinson's Disease

Jenny-Ann Phan
MD, PhD– Fellow

Supervisors
Marina Romero Ramos,
Associate Professor

Albert Gjedde,
Professor, DMSc

Degeneration of dopaminergic neurons in substantia nigra together with the presence of aggregated

alpha synuclein (ASYN) protein are the pathological hallmark of Parkinson's disease (PD). Epidemiological studies have shown that the incidence of sporadic PD increases with age, and PD affects pproximately 1% of the population older than 70 years. From genetic studies, it is known that multiplication of the ASYN gene and also missense point mutations cause autosomal dominant PD with earlier onset and are often related more severe disease progression than sporadic cases.

The focus of this study is to examine the pathological features of a genetic modified model of PD with alpha synuclein overexpression. The overexpression was induced in only one hemisphere, enabling the other as an internal control. We examined the synaptic integrity *in vivo* by using [^{11}C]dihydrotetrabenazine (DTBZ) PET imaging to quantify the presynaptic expression of the vesicular monoamine transporter (VMAT). The findings were further validated with *in vitro* techniques, including autoradiography and immunohistochemistry.

This study revealed that high levels of the native alpha synuclein protein is sufficient to initiate neurodegeneration, as evidenced by reduced density of VMAT in side of striatum with alpha synuclein overexpression, shown both with PET and autoradiography (**Figure 1**). This was a unique feature associated with the toxicity of alpha synuclein aggregation, because overexpression of the control gene, green fluorescent protein (GFP), did not display neurodegenerative changes. To examine the progressive nature of misfolding and aggregation of alpha synuclein, we quantified the aggregates at two time points 4 and 12 weeks after overexpression, demonstrating that the pathological aggregates increased both in number and in size (**Figure 2**). Notably, the pathological aggregates were more severe in lateral than medial striatum, indicating differential regional susceptibility.

In conclusion, we found degeneration of dopaminergic terminals with aggregation of alpha synuclein, which occurred in absence of cell death in substantia nigra. This suggests that the rodent model with alpha synuclein overexpression closely resembles features of PD in human and the model is useful for tests of therapeutics of early interventions for neuroprotection.

More detailed information can be accessed through the following link: doi:10.1038/s41598-017-06724-9

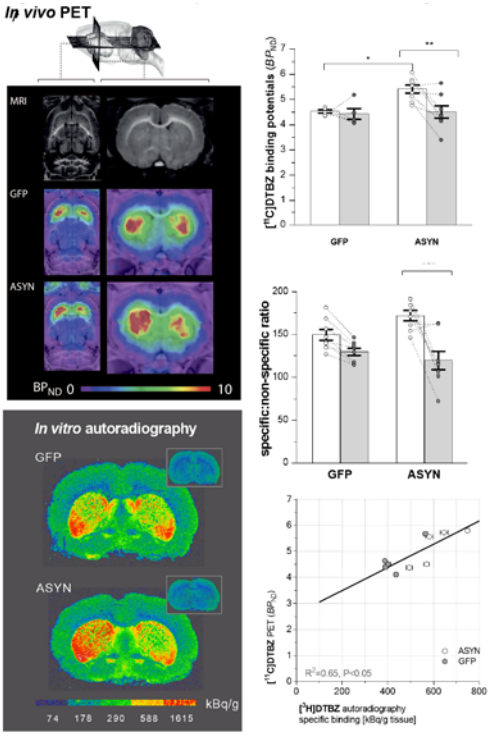


Figure 1 ASYN overexpression induces axonal degeneration

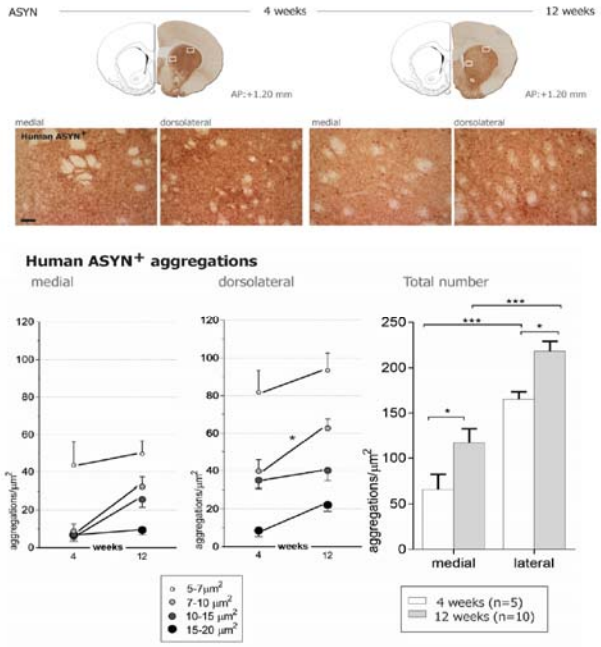


Figure 2 Pathological accumulation of ASYN aggregates

PhD

Positron Emission Tomography of the Enterohepatic Circulation of Bile Salts in Rats

Kim Frisch
Chemist, Senior Scientist, PhD

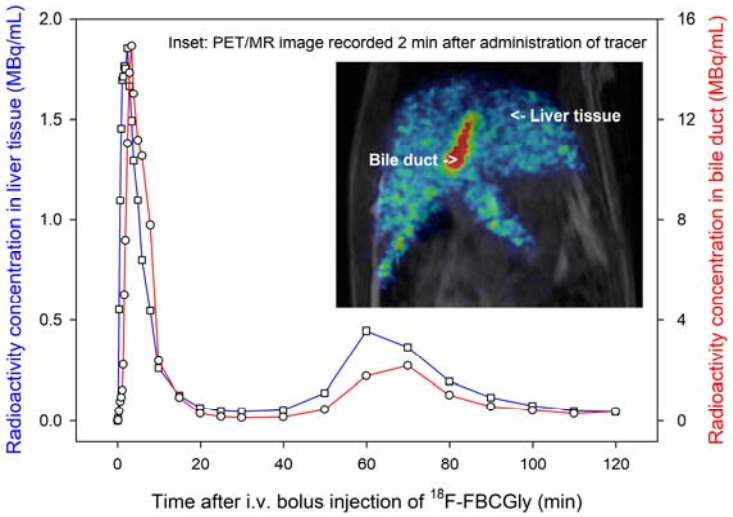
Bile salts circulate continuously between liver and small intestine in a process known as the enterohepatic circulation (EHC). Under normal conditions more than 90% of the bile salt pool is recovered at the distal ileum and returned to the liver with portal circulation. The EHC is important for regulating intracellular concentrations of the potentially cytotoxic bile salts and for bile salts to function as hormones carrying signals between liver and small intestine. Impaired uptake of bile salts in the small intestine leads to elevated concentration of bile salts in the colon that cause severe diarrhea and possibly bile salt-induced colon cancer.

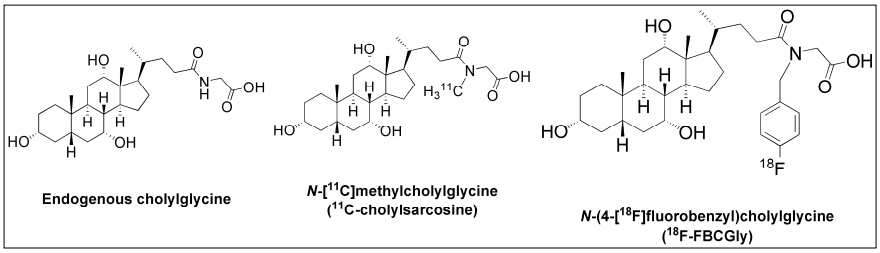
We have previously reported that ^{11}C-cholylsarcosine (*N*-[^{11}C]methylcholylglycine) is a tracer for PET of hepatic transport of conjugated bile salts [1–4]. Unlabeled cholylsarcosine is known to undergo EHC. However, due to the relatively short half-life of the carbon-11 radioisotope (^{11}C; $T_{½}$ = 20.4 min) ^{11}C-cholylsarcosine is unfit as PET tracer of the EHC. We have therefore developed *N*-(4-[^{18}F]fluorobenzyl)-cholylglycine (^{18}F-FBCGly), a novel PET tracer labelled with fluorine-18 (^{18}F; $T_{½}$ = 109.8 min), which has radioactive half-life suited for PET studies of the EHC (Figure 1).

^{18}F-FBCGly is prepared by condensation of 4-[^{18}F] fluorobenzaldehyde on glycine followed by coupling to endogenous cholic acid [5]. The initial part of the development of this radiosynthesis for ^{18}F-FBCGly was done in collaboration with researchers at the Centre for Advanced Imaging at the University of Queensland in St. Lucia, Brisbane, Australia. The design of ^{18}F-FBCGly is based on endogenous cholylglycine, but with an additional 4-[^{18}F] fluorobenzyl group on the nitrogen atom. Besides providing the radioactive label, this group serves two purposes: (1) it makes the tracer stable towards hydrolysis of the amide bond (de-conjugation) by intestinal bacteria and (2) it provides a chromophore for analysis of the tracer by commonly available ultraviolet spectrometry.

PET/MR studies in rats showed that i.v. administrated ^{18}F-FBCGly was rapidly taken up from blood by the liver and secreted into bile with a radioactivity concentration in bile approximately 10 times higher than that in liver tissue. Within 40–60 min after administration, ^{18}F-FBCGly underwent EHC and reappeared in liver tissue and bile duct (Figure 2). Co-injection of the endogenous conjugated bile salt cholyltaurine inhibited the biliary secretion of ^{18}F-FBCGly and delayed the EHC of the tracer, which suggests that ^{18}F-FBCGly use the same hepatic and intestinal transport system as endogenous conjugated bile salts during its EHC.

To the best of our knowledge, ^{18}F-FBCGly is the first PET tracer shown to undergo EHC. We envision that ^{18}F-FBCGly PET can be used as tool for non-invasive *in vivo* investigations of the pathological mechanisms of diseases affecting the EHC and of drugs inhibiting hepatic and intestinal transport of conjugated bile salts.





PhD

Research in Alzheimer's disease

Peter Parbo
MD, PhD

Rola Ismail
MD, PhD

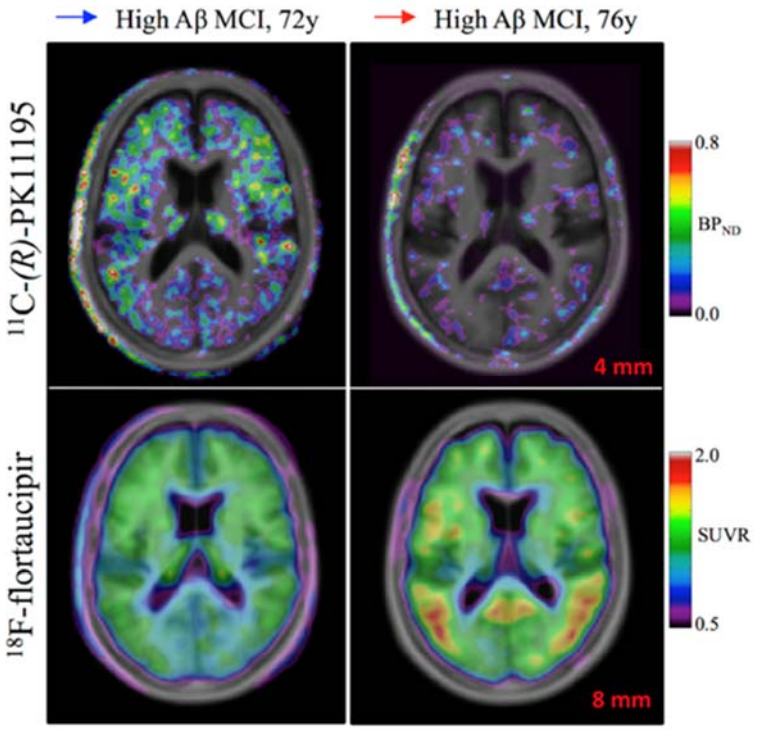
Main supervisor
David J Brooks,
MD, DSc, FRCP (UK), FMedSci (UK), Professor of Neurology

Co-supervisor
Joel Aanerud
Senior Registrar, PhD

We have been studying baseline levels of β-amyloid fibrils with ^{11}C-PiB PET, tau tangles with ^{18}F-flortaucipir PET, and inflammation with ^{11}C-PK11195 PET in healthy controls, subjects with mild cognitive impairment (MCI) capable of independent activities, and early Alzheimer disease (AD). Peter Parbo has found that two thirds of MCI cases show evidence of amyloid deposition and 80% of these also show areas of brain inflammation. He reported that levels of cortical β-amyloid and inflammation are correlated in multiple areas (Parbo P et al. Brain 2017; 140 (7): 2002-2011). He has also investigated the relationship between β-amyloid plaques, inflammation, and tau tangles. Amyloid plaques could be seen in the absence of tau tangles in MCI but nearly all cases with cortical tau had amyloid. This suggests that cortical tau tangles require the presence of cortical amyloid to seed them though hippocampal tau could be seen in the absence of amyloid plaques. There was no clear correlation between levels of tau and inflammation in this series. Tau but not inflammation correlated with cognitive decline (P Parbo – in preparation).

Finally, Peter Parbo has studied the relationship between white matter small vessel disease (SVD) and Alzheimer pathology in MCI cases. In his MCI cohort of 42 subjects there was no correlation between vascular lesion, amyloid, and tau load - SVD correlated primarily with subject age. Peter Parbo successfully defended this work and has been awarded his PhD.

Our MCI cases and healthy normal controls are currently being followed longitudinally in the follow-up PhD project of Rola Ismail and are being re-scanned to determine the different time courses of Alzheimer, vascular, and inflammatory pathology.



PhD

Impulsivity and compulsivity: the roles of dopamine and serotonin in rewards

Casper Schmidt
Psycologist, PhD student

Supervisors
Arne Møller
Associate Professor, MD

Valerie Voon
MD, PhD

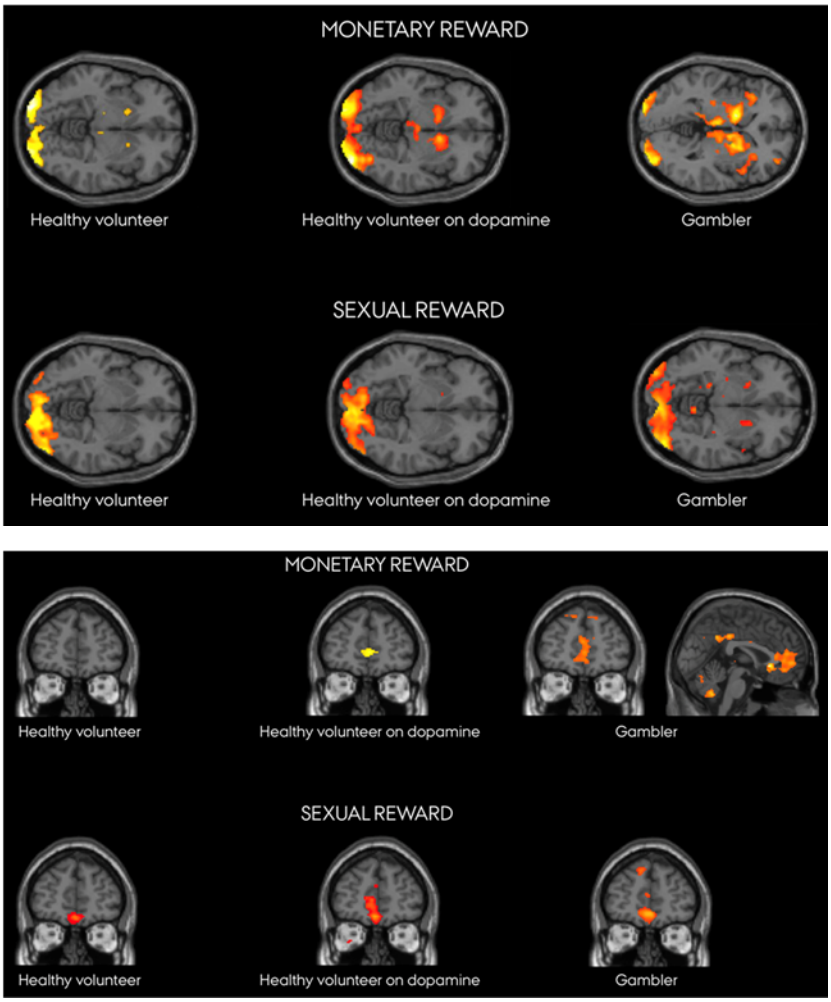
Within the neuroscience of addiction, there is lack of evidence both in terms of assessing its mechanisms and treating its different forms. This Cambridge-Aarhus PhD project currently seeks to delineate the relationship between the roles of dopamine and serotonin in rewards, and their roles in the neuropsychological measurements of impulsivity and compulsivity. Although a lot is known about these separate roles, no research has been devoted to the basics of these neurochemical mechanisms when exposed to humans in combination.

The experiments were carried out during 2017, in a between-subjects double blinded design and contained testing of 127 subjects, including four different arms of appr. 25 healthy volunteers (HV) and a fifth arm of 25 subjects with pathological gambling disorder (PG), a psychiatric patient group with profound deficits in impulsivity and compulsivity. This was done in order to isolate the neural and behavioural correlates of both increasing dopamine and depleting serotonin to investigate:

1) how this affected neural activity in a task-based fMRI experiment on different forms of rewards
2) cognitive components of impulsivity and compulsivity through behavioural testing
3) how these two points relate to a placebo PG group
4) a connectome-based DTI sequence assessing functional neural networks in HV and PG groups

We have so far found preliminary results pointing towards a successful priming of HV towards PG, indicating a potential for reversal of this priming, hopefully being able to reduce addictive symptomatology for addicted populations in the future.

Depending on the potential for extrapolation of the results, we expect to assess a subset of the current subjects for further examination using PET scanning. In conclusion, this project which is currently underway and finished in its initial stages, holds great promise to infer mechanistically about the neural and behavioural processes associated with dopamine and serotonin, thus providing a novel foundation for future treatment options within the neuroscience of addiction.



The pictures shows descriptive priming with L-dopa administered to HV (middle) compared with placebo HV (left) and PG (right) to reward anticipation (top) and outcome (bottom).

PhD

Olfaction in depression

Carsten Gleesborg
MSci Neuroscience, PhD student

Supervisors
Arne Møller
Associate Professor, MD

Morten Kringelbach
Professor

Raymond Chan,
Professor of Neuropsychology and Applied Cognitive Neuroscience

Depression is the leading cause of disability worldwide and is projected to become the primary contributor to the global burden of disease by 2030. Currently it ranks 3rd. It is expected that 15-20% of the population will experience depression at one point in their lifetime.

A common complaint among the patients is that food tastes like cardboard. In 2001 Pause et. al found that MDD patients have reduced olfactory performance, a finding that has been replicated since and recently have caught attention in the research. There is a positive correlation between the reduction in olfaction and severity of depression, and studies also find that treatment of the depressive symptoms leading to relief also leads to increase in olfaction to the point that there is no significant difference between patients and controls.

In my first work, together with my Chinese co-supervisor Raymond Chan we looked at how structural changes in the brain may account for some of the reduced sense of smell. This was done using methods from my co-supervisor in Oxford, Morten Kringelbach, and data from the lab in Beijing. The findings showed that in a depressed brain the structural network between brain regions is out of balance in such a way that the connectivity to the olfactory cortex and in the olfactory network is significantly reduced. Whilst overall there is a loss of connectivity, predominantly on the left hemisphere, a small network including the caudate and putamen have had their connectivity significantly increased.

Following up on these interesting findings, we are have been, and continue to, recruit participants from the department of psychiatry in Aarhus for a study where, using MEG, MRI, and Sniffin' Sticks, we look further into the networks of the brain. This allows us to look into both structural and functional networks in order to see in detail what happens in the brain as you perceive an odor, and how that perception is altered in Depression. Once we get a better idea about where in the brain the changes occur we plan to do a PET study looking further into possible receptor and transmitter imbalances.

PhD

Imaging glutamate ion channel activation

Ali Khalid
MD, PhD

Main supervisor
David J Brooks,
MD, DSc, FRCP (UK), MedSci (UK), Professor of Neurology

Co-supervisor
Arne Møller
Associate Professor

Anne M. Landau,
Associate Professor

Jens Christian H. Sørensen,
Professor, DMSc,

GE179 PET is a use-dependent marker of NMDA glutamate ion channels.

Ali Khalidan Vibholm has shown that in rats, electrical stimulation of the hippocampus led to focal uptake of GE179 that could be blocked by prior administration of ketamine. This confirms that GE179 binds to the phencyclidine site in open glutamate ion channels. Ali Khalidan Vibholm then scanned pigs with GE179 PET during hippocampal stimulation and found a current dependent increase in tracer uptake. Subsequently he has scanned 10 cases of drug resistant focal epilepsy and 18 healthy controls with GE179 PET. Eight of the ten epilepsy cases showed foci, often multiple, of increased glutamate ion channel activity – some of which correlated with their EEG foci. No foci were seen in the healthy controls. He concluded that GE179 PET reveals networks of abnormal glutamate ion channel activity in cases of resistant epilepsy. Ali Khalidan Vibholm successfully defended this work and has been awarded his PhD in 2017.

PhD

Postprandial changes in hepatic bile acid handling

Nikolaj Worm Ørntoft
MD, PhD

Susanne Keiding,
MD, DSc, Associate Professor

Michael Sørensen
MD, PhD

Peter Ott
DSc

The purpose of this project is to quantify the postprandial changes in the hepatic handling of bile acids.

Production of bile is a vital liver function and is needed for lipid absorption and elimination of excess endogenous products and xenobiotics. The main organic constituents of bile are the bile acids. In the gut, bile is needed for intestinal absorption of dietary fat, lipophilic substrates and fat-soluble vitamin (A, D, E, and K). Additionally, it has recently been shown that bile acids have major regulatory effects on the metabolism especially during the feed/fast cycle.

In liver disease bile acid transport and homeostasis is crucial to the development of liver injury. Unfortunately, this aspect is sparsely documented, which limits the possibilities for rational treatment. Due to the importance during digestion, the hepatic transport of bile acids is highly regulated by food intake. Although the theoretical changes are described, the functional changes are unknown, as this has never been studied in humans. Determining the transport fluctuations that occur under normal physiological conditions provides new basic physiological knowledge. This knowledge is needed for assessing the severity and the impact of the specific dysfunctions that occur during liver disease.

The project is performed as two successive PET studies on 6 healthy volunteers. The first PET examination is carried out during fasting and the second after ingestion of a standard meal. Hereby, the changes related to food intake can be identified.

Postdoc

Moving beyond myocardial blood flow imaging with dynamic PET

Hendrik Johannes Harms
PhD, Postdoctoral research fellow

Myocardial blood flow and its increase when stressing the heart is a potent marker of cardiac function. However, it only assesses a single aspect of cardiac function and therefore provides only an incomplete image of a patient's heart. Each dynamic PET study contains a brief early phase in which the injected activity is confined in the blood pool. During this phase, the cavities of the heart are clearly visible, and the displacement of the activity simply reflects the actual displacement of blood, the ultimate purpose of the heart. The main goal of this project is to develop methodology that can measure and quantify novel imaging biomarkers of cardiac disease using this early phase, adding new and more personalized information to just myocardial blood flow.

This study consisted of four separate arms:

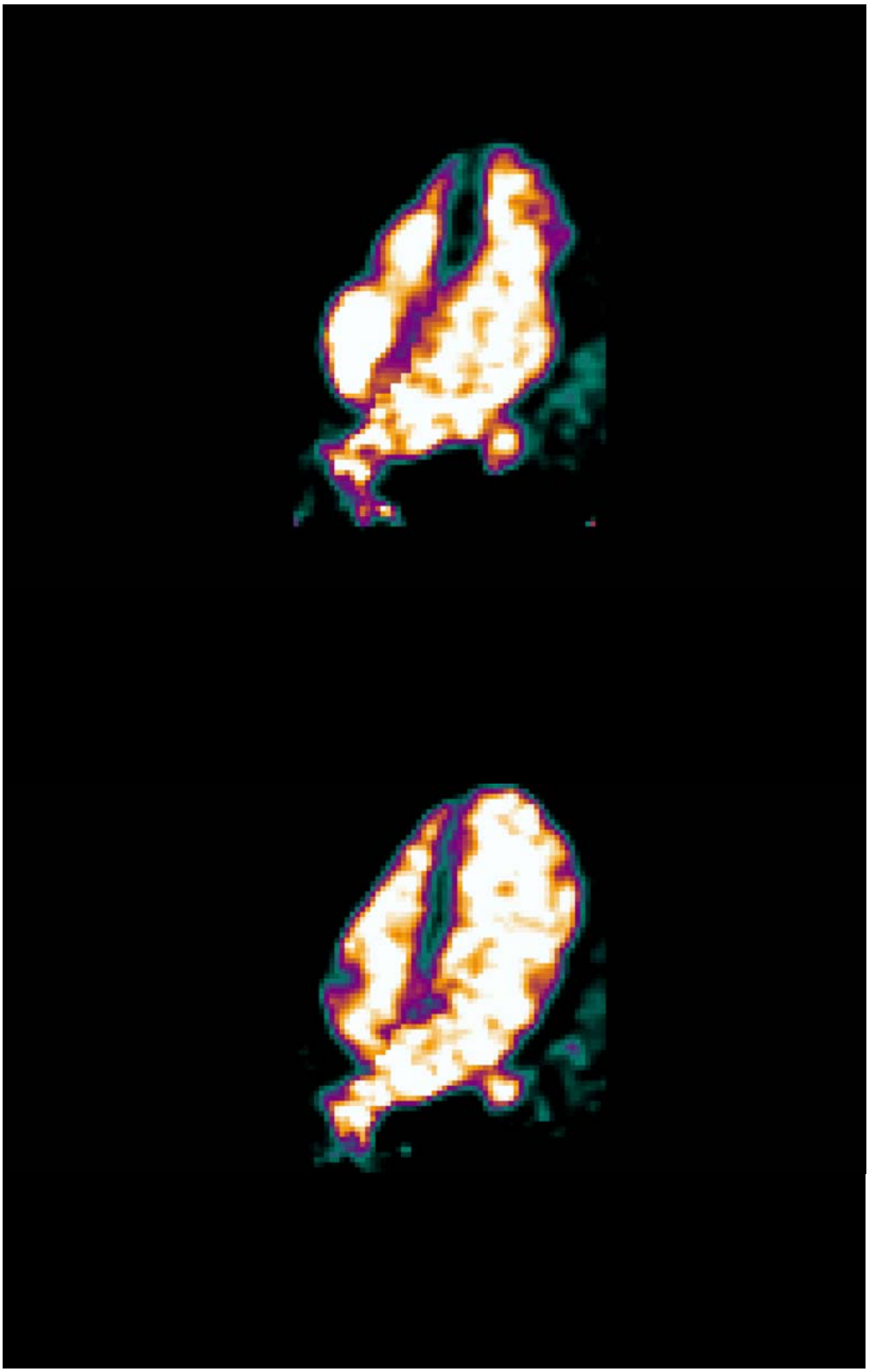
- A study in a porcine model of pulmonary edema
- A validation study in patients that underwent both PET and cardiac MRI
- A reproducibility study in ten healthy volunteers
- A retrospective analysis of myocardial blood flow scans in various patient categories.

In the first study, we managed to reproduce several invasive markers using dynamic 15O-water PET. We managed to measure the effective volume of all the chambers in the pigs' heart under various conditions, as well as the total amount of blood pumped into the circulation by the heart. All of this was obtained by analyzing the arrival time of the injected activity in various regions of the heart. A clear increase in the volume of the heart was measured as the amount of edema increased.

In the second study, we validated a method to measure the forward cardiac output using dynamic PET, a method to measure the total size of the left ventricle itself using the same images and a method combining all of these measures to measure the mechanical efficiency of the heart, again using only a single dynamic PET scan. Correlations were excellent for all measured parameters and the single-PET method showed a clear separation between various patient categories. In addition study 3 showed that all of these measures were highly reproducible.

Finally, in the last study we applied several of these new methods to large clinical cohorts. We learned that we can accurately measure the size of not only the left ventricle, but also the left atrium, and that enlargement of the left atrium was more pronounced with increasing disease severity. In addition, we learned that we can accurately measure the blood flow of not only the left, but also the right ventricle, and that a relative increase in right-ventricular blood flow (compared to left-ventricular) was also more pronounced for increasingly sick patients. Finally, we learnt that the time it takes to move the injected activity through the central circulation (heart and lungs) was associated with disease and disease outcomes, confirming some of the findings of study 1.

In short, in this project we have developed and are further developing novel imaging biomarkers that provide complementary information of a patient's heart and which can be applied to standard dynamic PET scans of the blood flow of the heart.



Highlights 2017

NUK-PET paper selected as paper of the year

The main manuscript of the MELVAS trial is selected as winner of the journal's best paper award for 2017 in Circulation: Cardiovascular Imaging.

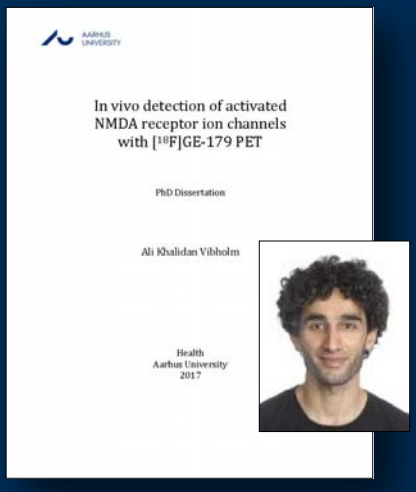
"Nils Henrik Hansson, MD, PhD, of Aarhus University Hospital, Denmark, for the article "Metoprolol Reduces Hemodynamic and Metabolic Overload in Asymptomatic Aortic Valve Stenosis Patients". The editors believe that this is an excellent contribution that uses the power of quantitative multimodality imaging to understand the mechanistic underpinnings of the beneficial hemodynamic effects of left ventricular unloading in asymptomatic aortic stenosis. We expect that this finding may have important implications for the medical management of aortic stenosis."

21 March 2017

New advanced PET/CT scanner is inaugurated at the Skejby facilities.

Patients with cancer, heart diseases and infectious diseases will benefit from the scanner, which is one of the most advanced in the world.

The scanner will provide fast and accurate recordings of cervical tumors and bleeding disorders in i.e. heart diseases.



19 June 2017

Cindy Jørgensen successfully defends her Master of Science thesis entitled "In Vivo Imaging of the Olfactory System: In Vivo Neurochemical Imaging of the Olfactory Bulbs and the Cerebral Olfactory System in Healthy Subjects and Patients with Idiopathic Rapid Eye Movement Sleep Behaviour Disorder: An 18F-DOPA PET Study".

29 June 2017

Ali Khalidan Vibholm, defends his PhD thesis on"Detection of activated NMDA receptor ion channels with [18F]GE-179 PET in patients with focal refractory epilepsy and in electrically stimulated animal models of epilepsy".

Brain publication

July 2017

Researchers Peter Parbo, Rola Ismail, Frederik Mårup, Nicola Pavese, Morten Stokholm, Per Borghammer, Joel Aanerud and David Brooks publish a research article in Brain .

NY CARLSBERG FONDET
NEW CARLSBERG FOUNDATION

Autumn 2017

The Department of Nuclear Medicine & PET-Centre receives a grant from the New Carlsberg Foundation for the decoration of the new facilities at Skejby.

Lancet publication

October 2017

Restless sleep may be an early sign of Parkinson's disease

Researchers from Aarhus University have discovered that patients with the RBD sleep behaviour disorder lack dopamine and have a form of inflammation of the brain. This means that they are at risk of developing Parkinson's disease or dementia when they grow older.

Morten Stokholm and Nicola Pavese's publication is chosen as editor's choice and is mentioned on the cover of The Lancet Neurology, October 2017.

Research year projects

Research year project

Essential liver functions in mini-pigs with radiation-induced liver fibrosis measured by PET/CT

Kristoffer Kjærgaard
Research year student

Supervisor
Michael Sørensen, MD, PhD

Currently, there is an increasing wish for non-invasive methods to assess liver function, especially because of the rising incidence in non-alcoholic fatty liver disease (NAFLD) and general improvement in survival of patients with chronic liver disease. To validate such methods and to improve our understanding of the pathophysiology of chronic liver disease, we need appropriate experimental animal models for preclinical research.

In the present study, we will functionally characterize a new large animal model for chronic liver disease, induced by irradiation of the liver (Fig. 1). We will use pigs, which are large enough to allow for the assessment of regional PET measurements and blood sampling for measurements of tracer concentration. For characterization of regional and whole liver function in this novel model, we use ^{18}F-FDGal and ^{11}C-CSar PET methods with kinetic analysis to quantify hepatic metabolic and hepatobiliary excretory function, respectively.

Finally, we will compare structural histological changes from liver biopsies against changes in PET-measured liver functions.

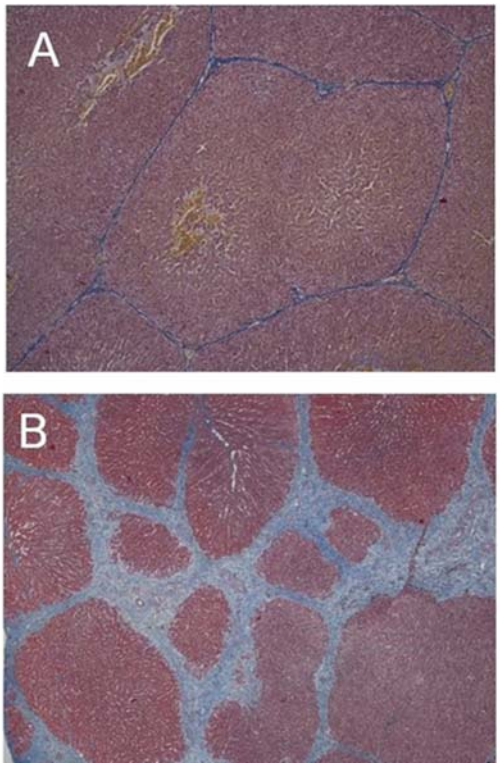
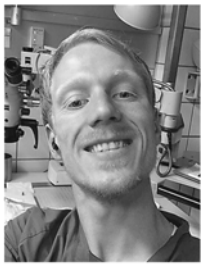


Figure 1 *Mason's trichome staining of liver biopsies from pigs after treatment with 11 Gy (A) and 14 Gy (B) radiotherapy.*

Panel A displays levels of fibrosis normal for the pig liver. In Panel B, the fibrosis grade extends to a degree that can be characterized as cirrhosis. The biopsies are from pilot experiments.

Research year project

The effect of CPT1A inhibition in renal ischemia/reperfusion organ injury.



Mads Vammen Damgaard
Research year student

Supervisors
Jørgen Frøkiær, Professor and chair, MD, DMSc., Main supervisor

Søren Nielsen Professor, MD, DMSc.

Rikke Nørregaard, Associate Professor, MSc, PhD

The aim of this research year was to investigate the potential key role of CPT1 as a novel target for protection/treatment of ischemia/reperfusion-injury in the kidney.

This research year was funded by The Danish Council for Independent Research: Medical Sciences with a 12 months scholarship.

BACKGROUND: Acute kidney injury (AKI) is associated with high mortality and a lack of effective therapeutic treatment of the most common cause i.e. ischemia/reperfusion-injury (IR-I). Hypoxia during the ischemia leads to adenosine triphosphate (ATP) depletion, apoptosis and necrosis, resulting in a marked inflammatory cascade causing further tissue damage. Inhibition of the inflammatory responses after IR-I is crucial for renal protection.

Fatty acid -oxidation is controlled by carnitine palmitoyl transferase 1 (CPT1). Etomoxir (ETO) inhibits CPT1 and block lipid metabolism, thus resulting in less lipid metabolism which have a higher O_2 consumption ratio then ATP generation from glycolysis.

We hypothesize that CPT1 blockade can enhance a metabolic shift to glycolysis, decrease the inflammatory response, induce an immune modulation, reduce mitochondrial dysfunction and hence alleviate renal IR-I.

METHODS: Male Wistar rats (n = 10 animals per group) were subjected through block randomization to either sham operation or renal ischemia/reperfusion (IR) by bilateral renal artery clamping for 40 min followed by ETO (5 mg/kg/day) or vehicle (veh) administrated at reperfusion. Clearance experiments were performed, and renal tissue was removed and prepared for qPCR, immunohistochemistry and western blot analysis at sacrifice 48 hrs after reperfusion.

	Subject	Urine output *ml/kg/day*	Urine osmol *mOsmol*	Plasma osmol *mOsmol*	$U_{Na}V$ *µmol/min/kg*	FENa *%*
Baseline	Sham	37.7 ± 3.2	1434 ± 100	0.29 ± 0.01	2.3 ± 0.2	0.29 ± 0.02
	IR	42.3 ± 3.1	1277 ± 63	0.29 ± 0.01	2.3 ± 0.1	0.29 ± 0.01
	IR + Etomoxir	40.6 ± 2.9	1330 ± 78	0.29 ± 0.01	2.4 ± 0.1	0.30 ± 0.01
Day 2	Sham	36.1 ± 2.9	1576 ± 99	0.30 ± 0.01	1.9 ± 0.3	0.28 ± 0.04
	IR	124.9 ± 6.9	577 ± 81	0.33 ± 0.01	3.9 ± 0.6	1.96 ± 0.31
	IR + Etomoxir	61.9 ± 4.3***	844 ± 87*	0.30 ± 0.01	0.9 ± 0.2***	0.27 ± 0.09

Table 1. Urine data and analysis at baseline and at 48 h. Values are means ± SEM. *P<0,05. ***P<0,001. IR compared to IR + ETO

RESULTS: IR-I resulted in polyuria, increased fractional sodium excretion *(table 1)*, plasma creatinine *(µmol/L/kg, Sham: 77 ± 3, IR: 649 ± 183, IR+ETO: 141 ± 19)* as well as BUN *(mmol/L/kg, Sham: 18 ± 1, IR: 102 ± 20, IR+ETO: 41 ± 8)*. ETO treatment prevented these increases, improved creatinine clearance *(figure 1)* as well as significantly attenuated downregulation of AQP1, Na/K-ATPase and AQP2 expression. In addition, expression of (pro)inflammatory cytokines (IL-6, IL-1, TNF, MCP-1, IL-10) and key markers (ICAM-1) were significantly reduced including NGAL and KIM-1 *(figure 1)* in response to ETO administration. All reported changes were significantly different between IR and IR+ETO treatment groups.

CONCLUSIONS: It has never before been demonstrated before, that depressing lipid metabolism and interfering with mitochondrial dysfunction under the condition of IR-I have a potent renal protecting effect. The main findings of my study are that 1) Ischemia and reperfusion injury was successfully induced in this model. 2) ETO treatment attenuated development of renal dysfunction, AQP downregulation and tissue injury after renal IR-I. 3) Decreasing the lipid metabolism reduced the inflammatory response and might provide a novel potent pathway for treatment of renal IR-I.

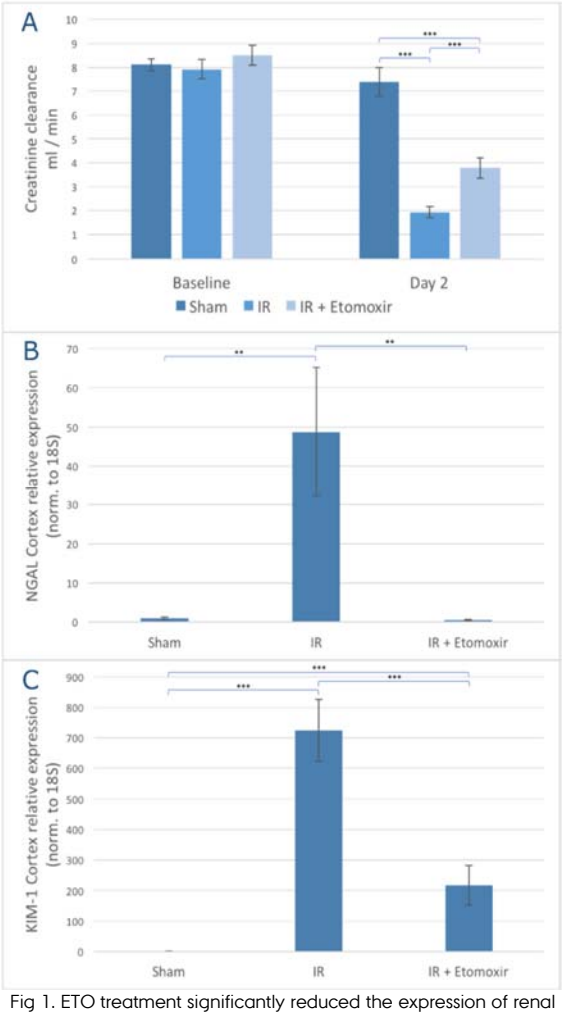


Fig 1. ETO treatment significantly reduced the expression of renal injury markers, NGAL (B) and KIM-1 (C) elevated by IR-I. ETO significantly improved the creatinine clearance (A). qPCR semi quantitative expression. Normalized to housekeeping gen 18S. Sham normalized to 1. Values are means ± SEM. **P<0,01. ***P<0,001

Research year project

Determining the timings of brain amyloid and inflammation in healthy subjects at increased risk of Alzheimer's disease

Frederik Husum Mårup
MD

Main Supervisor
David J .Brooks
Professsor

Co-Supervisors
Peter Parbo,
MD, PhD

The pathology of AD is abnormal deposition of extracellular fibrils of beta-amyloid as plaques, aggregation of intra-neuronal tau protein as tangles, and brain inflammation in the form of microglial activation. The amyloid cascade/neuroinflammation hypothesis suggests that Abeta aggregates form first and are the toxic species, activating microglia which then release neurotoxic substances such as cytokines leading to tangle formation and neuronal death. However, the timing of neuroinflammation in relation to aggregation of the amyloid and tau proteins is still unclear.

The purpose of this project is to determine the presence and possible timing of Abeta and neuroinflammation in healthy individuals aged 60+ carrying the Alzheimer's risk gene Apoe4. These individuals have an increased risk of developing Alzheimer's disease compared to the more common Apoe3 type.

We have recruited 10 Apoe4/Apoe4 or Apoe4/Apoe3 and ten Apoe3/Apoe3 subjects. The Apoe3 subjects work as a control group. Participants have had ^{11}C-PIB and ^{11}C-PK11195 PET performed to determine whether preclinical amyloid deposition and/or inflammation can be detected and, if so, to investigate their spatial relationship. The participants have been tested with a sensitive neuropsychological battery to assess their cognitive status.

All data has been collected, and the preliminary results can be seen in figure 1.

The ^{11}C-PIB concentration is significantly higher in the Apoe4 group across all brain regions. Three individuals in the same group have abnormal ^{11}C-PIB scans, compared to none in the control group. However, these individuals show no sign of increased neuroinflammation on ^{11}C-PK11195 PET. The Apoe4 group do not show a significant increase in ^{11}C-PK11195 PET compared to controls. We are still analyzing both the relationship between cognitive status and tracer uptake as well as spatial relationship between ^{11}C-PIB and ^{11}C-PK11195 PET.

MDT - Multi disciplinary team conferences

Multidisciplinary Team (MDT) conferences from a nuclear medicine perspective

Karin Hjorthaug
Senior Consultant

MDT conferences play a crucial role in the treatment of cancer in Denmark and are considered to be a principal means of diagnostics, staging and treatment decision-making as well as being a significant element of the organisation and completion of the individual patient's progress. MDTs are recommended in all Danish Health Authority cancer pathways.

MDTs are arranged for nearly all types of cancer and for many other patient groups (cardiology, the assessment of dementia, etc).

All the relevant medical specialists are gathered together in an MDT and it is here that all aspects of information including test results for the individual patient are presented and assessed in relation to each other. Based on this background and together with the clinical guidelines, a decision regarding treatment will be taken. This joint management plan is then written into the patient's medical records and this will form the basis of all future patient progress.

Effective MDT work means that all diagnostics, treatment and progress is assessed by the relevant specialists. This is to ensure uniformity and precision regarding assessment, treatment and the follow-up of cancer patients.

MDT work is also invaluable in ensuring that cancer pathways and guarantees are complied with and that the transition between the different specialties, departments and hospitals runs smoothly.

Furthermore, MDT provides a unique forum for sharing knowledge. The collaborative teamwork provides a strong incentive for professionalism, commitment and development to be in focus for the individual MDT participant.

There is therefore no doubt that MDT ensures high quality cancer treatment in Danish hospitals. However, the introduction of MDT has also brought changes to the working day for many specialists who, in addition to their usual clinical work now also need to prepare and participate in MDT conferences – and this presents a huge problem timewise.

At the same time, there are no local guidelines for the implementation and evaluation of MDT and there is no upper management and therefore no clear placement of responsibility for the total enterprise, which is clearly a problem with something so complex as MDT.

The complexity with MDT stems partly from the need for doctors from different departments and hospitals to be able to communicate work together and follow the same rules, partly because of the need for infrastructures; conference rooms, IT facilities and enough space. These all play an important part in an effective implementation. Furthermore, the logistics surrounding MDT including the registration of patients should be organised so that everything runs smoothly.

All in all it is an enormous mechanism, requiring a great deal of attention in order for it to remain a first-rate tool under development and not a source of unused resources and an increased workload.

What is the role of the nuclear medicine doctor in this?

Doctors from the Department of Nuclear Medicine participate in approximately 20 different MDT conferences of which the majority are held weekly and just under half of them are held twice a week. This means around 25 hours of conference participation and between 10 – 12 hours of preparation time for doctors. At the same time, there are several other healthcare professional groups involved in the preparation in order to ensure that all scans and assessments are ready by the start of the conference. Preparation for conferences and participation form a large part in the everyday schedule of the department.

The role of the nuclear medicine doctor at the MDT is to present and interpret the nuclear medicine procedures and together with the other participants, compare them with the results of other procedures and patient information. This process is a prerequisite for a diagnosis made on a solid foundation.

Participation in MDTs are at the same time, particularly important for the professional development of nuclear medicine doctors and puts them in a position to precisely document the situation of a specific patient. Participation in MDTs is therefore paramount in ensuring high quality documentation of nuclear medicine procedures.

Nuclear medicine doctors also have a responsibility in regards to the overall continued development of MDTs and due to participating in many different MDTs, have a valuable foundation for assessing quality and efficiency and the ability to share knowledge and ideas which will ensure an efficient and at the same time professional MDT.

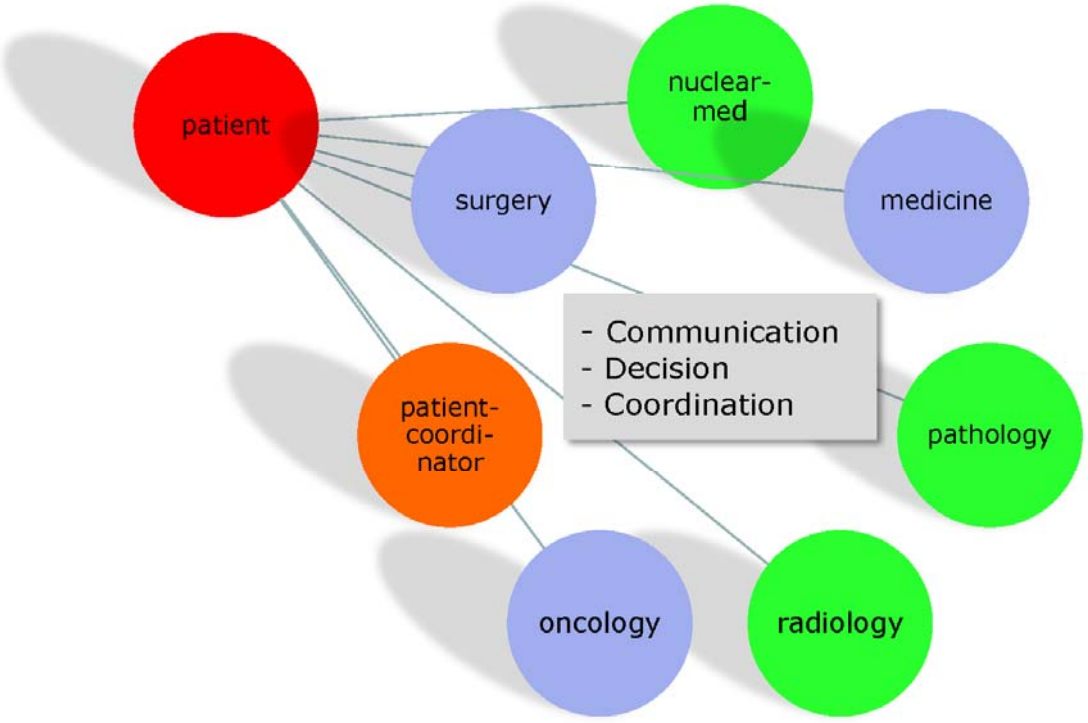
We have therefore made a commitment and together with consultant Torben Riis Rasmussen from the Department of Respiratory Medicine have produced a list of suggestions covering quality control and the development of MDT locally at Aarhus University Hospital (this was on the agenda at the Centre management meeting in November 2016).

The proposals are aimed partly at the need for management and clear responsibility as well as development and optimization of certain factors in MDT such as infrastructure, organisation, professionalism and teamwork.

MDT is a growing phenomenon, which is most certainly here to stay. This is happening at the same time as the number of patients with cancer is increasing together with the increasing complexity of the treatment of cancer and there is an enormous focus on the treatment of the individual patient.

The Department of Nuclear Medicine regards itself as an integral part of this exciting, and for the patients, very important development.

MDT – multi disciplinary team conferences



PET- Radiochemistry

PET - Radiochemistry

Dirk Andreas Bender
Chief Radiochemist, QM, PhD

In 2017 PET radiochemistry was marked by the construction of the new facilities at DNU. Again considerable resources were assigned to consultant tasks for the constructors of the new building. Even so the construction of the new building went according to schedule, a delay was experienced due to ventilation issues for operation theatres located in our buildings of the new building. Due to this delay the date for assignment of the building from constructor to the hospital is now April 4th 2018, roughly 2 months after the original schedule. Consequently, third party installations such as hotcells, cyclotron etc. are likewise delayed and it is expected that validation and qualification of new laboratories and equipment can be started before mid-august 2018. Earliest date for production start in the new facilities is therefore not before December 2018.

Cyclotron
PETtrace 800; GE Heathcare, Uppsala, Sweden.

Hotcells
Production and Development cells; ITD, Dresden, Germany.

Dispenser
Theodorico II; Comecer, Castelbolognese, Italy

The tender process for the purchase of a new cyclotron and hotcells for the new GMP production laboratory was initiated in 2016. Site visits were performed in January 2017 and tenders were awarded on June 3rd 2017. Three different suppliers were chosen for the PET chemistry related products:

Besides the installation of new equipment, the disassembly, move and reassembly of an existing hotcells, to be resurrected in the new GMP production laboratory was initiated.

Installation/Re-installation of this equipment is planned from mid-April 2018. As four different suppliers deliver and install equipment at the same time, a rather challenging and time consuming process is expected during coordination of the installations and during the installations.

In terms of tracer productions, PET tracers were supplied again every working day, meaning no downtime was observed. The center's 7 PET radiochemists, 3 PET radiochemistry technologists and 4 other technologists, taking care of the FDG morning production, performed almost 1400 PET tracer productions, dedicated for use in patients and healthy control subjects. The radiotracer portfolio of tracers produced within delivery permits or marketing authorization was unchanged 42 in 2017. From this radiotracer portfolio 22 different tracers were used in 2017. All productions resulted in 15103 single doses an increase of almost 10% compared to the 13846 doses supplied in 2016. Main reason for this increase in delivered doses is an increased number of Rb-82 perfusion studies and increased number of FDG studies as a result of the new scanner installation at the department's site at Skejby Hospital. In this context, it should be noted that the number of productions was almost constant in 2017 and 2016.

In terms of doses, FDG was also in 2017 with 10736 doses (69.5%) the dominating PET tracer. Besides the generator based Rb-82 (2490 doses, 16.1%), all other tracer productions varied from few produced doses to several 100. An interesting trend was again observed for the C-11 labelled radiotracers. Whereas in 2016 mainly C-11 PIB and C-11 PK11195 was produced, a shift towards the norepinephrine transporter ligand C-11 MeNER and the metabolic substrate C-11 acetate were applied most.

For the Ga-68 labelled tracers the demand for Ga-68 PSMA was still increasing in 2017. For Ga-68 DOTATOC, the center's other Ga-68 tracer, an unfortunate development was observed. The private company AAA achieved marketing authorization for a kit based production method (Somakit-TOC™) in 2017. As a consequence the department was forced by the authorities to use this marketed alternative. This "simplified preparation method" resulted in an increased number of production failures and herewith cancellation of patient examinations, so far not seen in the department.

For the Ga-68 labelled tracers the demand for Ga-68 PSMA was still increasing in 2017. For Ga-68 DOTATOC, the center's other Ga-68 tracer, an unfortunate development was observed. The private company AAA achieved marketing authorization for a kit based production method (Somakit-TOC™) in 2017. As a consequence the department was forced by the authorities to use this marketed alternative. This "simplified preparation method" resulted in an increased number of production failures and herewith cancellation of patient examinations, so far not seen in the department.

In 2017 three new tracers were included into the pipeline for tracer development for human use:

The dopamine transporter ligand F-18 PE2I, C-11 UCB-J for imaging the Synaptic Vesicle Glycoprotein 2A in the Brain and F-18 PSMA-1007 for prostate cancer imaging.

F-18 PE2I PET imaging is intended to replace to the costly SPECT scanning procedure applying the commercial available DaTscan™ and herewith help to compensate for budget reductions.

C-11 UCB-J, developed at Yale University, is probably the most promising PET tracer for PET neuroimaging in years and several projects aiming to image synapses in neurological disease stated are already lining up.

F-18 PSMA-1007 is meant to be a replacement for the above mentioned Ga-68 PSMA. Besides the considerable higher resolution due to the better PET properties of F-18, the availability of the generator based Ga-68 PSMA is a considerable limitation for covering the demand of PSMA examinations. Based on the bad experiences with Somakit-TOC™, it is under consideration to apply for a national marketing authorization for F -18 PSMA-1007 to avoid the forced implementation of marketed Ga-68 PSMA alternatives.

It is the aim to have these entire three tracers available for studies in humans in 2018.

In 2017 the department continued to supply radiotracers out- of house to up to 8 different user sides. The total number of radiotracer deliveries was 1082 and herewith roughly increased by 10%. The main out of house users sites were as well in 2017 Aalborg University Hospital, Aarhus University Hospital Department for Nuclear Medicine at Skejby, Aarhus University Hospital Department for Oncology at Skejby and the Regional Hospital in Herning with each more than 200 deliveries per year. The total number of delivered doses was in 2017 9562 doses. PET departments at Odense University Hospital and Herlev Hospital received their respective production license for F-18 FDOPA in 2017, resulting in a drastic decrease of deliveries of this tracer in 2017. On the other hand an increased demand for F-18 NaF from several sites was observed in 2017.

Main challenge for 2018 will the establishment of the department's new facilities within the New Aarhus University Hospital in Skejby and to obtain production license for this new production site in combination with continuation of productions activities at the existing production site at Aarhus C. It is the aim to have production license for the new facility and start production of F-18 tracers by end of 2018. Upon availability of production and PET scanning capacity at Skejby, relocation of the existing two cyclotrons and hotcell equipment will be started. However, it is not likely that relocation will be finished before 2020.

In terms of research activities the PET centers radiochemistry continues it program for the development of new labelling techniques and tracer development. These research activities are both performed in department internal collaborations, AUH internal collaborations, joint projects with Aarhus University departments and other universities both in Denmark and Europe, here besides others partner in EU FP 7 initiative targeting tracers for alpha synuclein aggregates. Besides scientific collaborations, collaborations with industry (currently Novo Nordisk, Lundbeck, Ferring and Ipsen/Octreopham) continued as well in 2017.

Within teaching obligations, the PhD course, "Introduction to GMP", introduced in 2016, was held again in 2017. Again this course was a success and will be available again in September 2018.

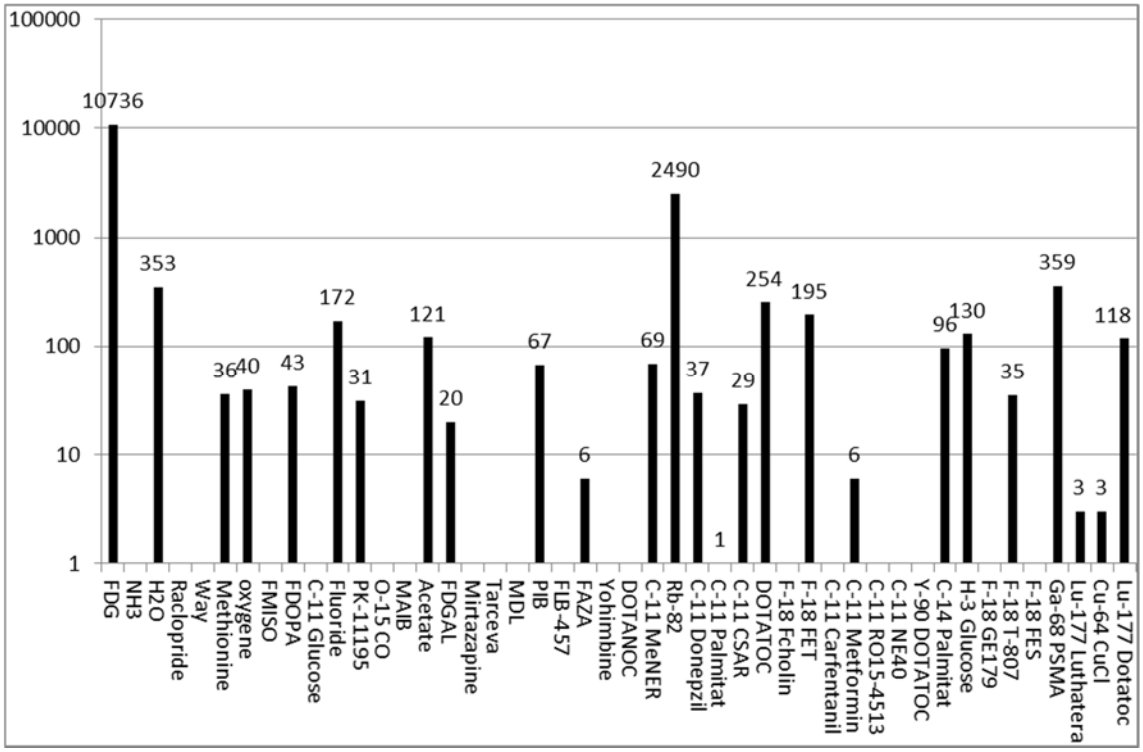


Figure 1: Portfolio of radiotracers produced for human use, both under marketing authorization and within compassionate delivery permits (GMP tracers) in 2016 including number of doses.

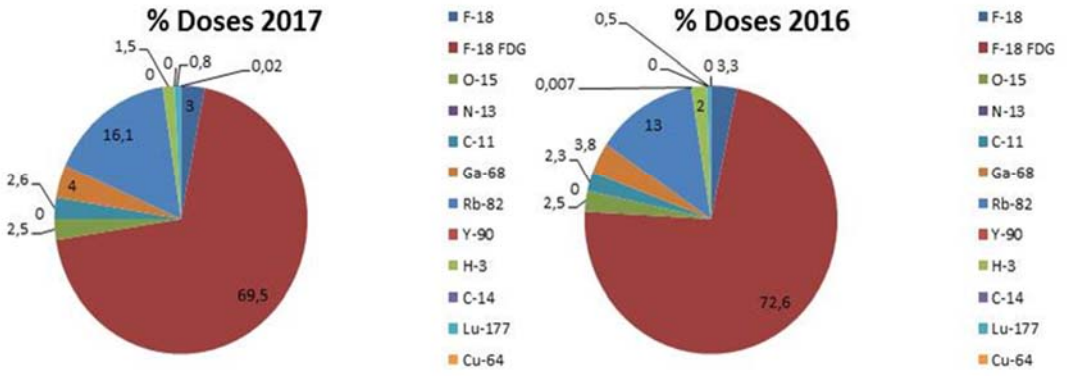


Figure 2: GMP productions: Distribution per radioisotope for 2015 and 2016

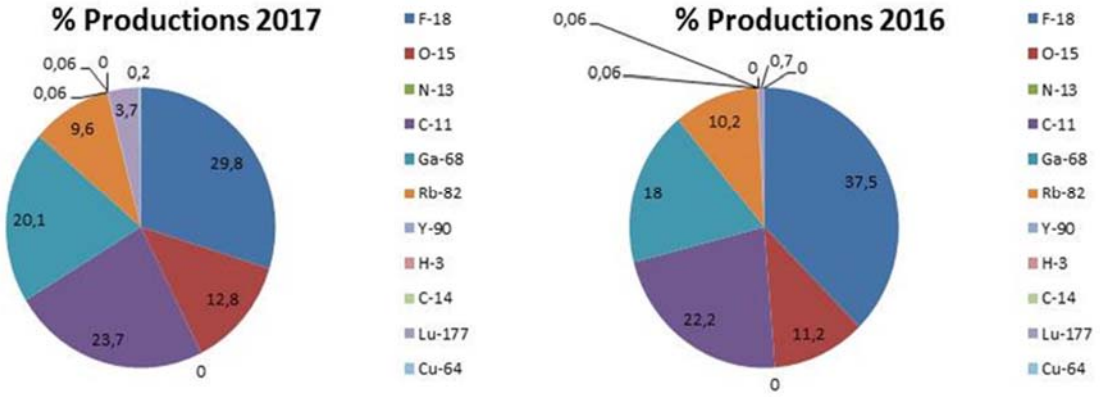


Figure 3: GMP produced doses: Distribution per radioisotope for 2015 and 2016

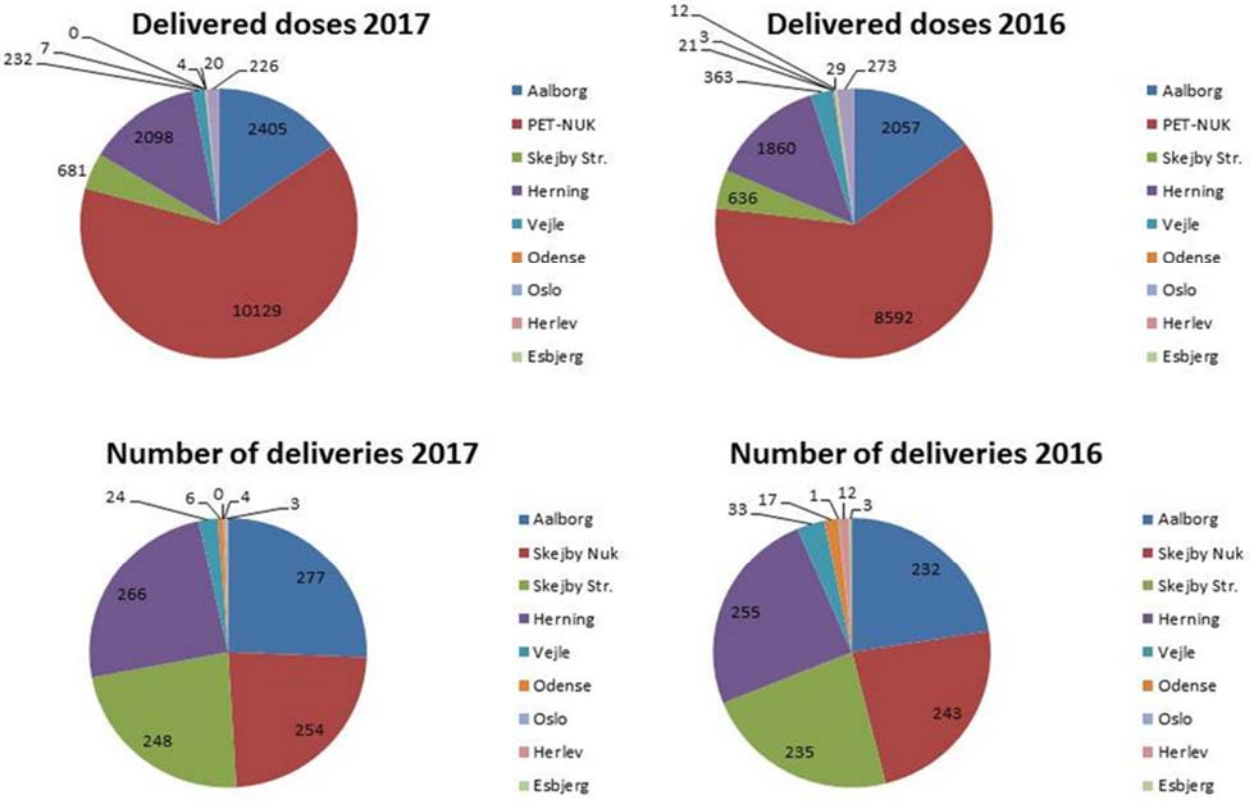
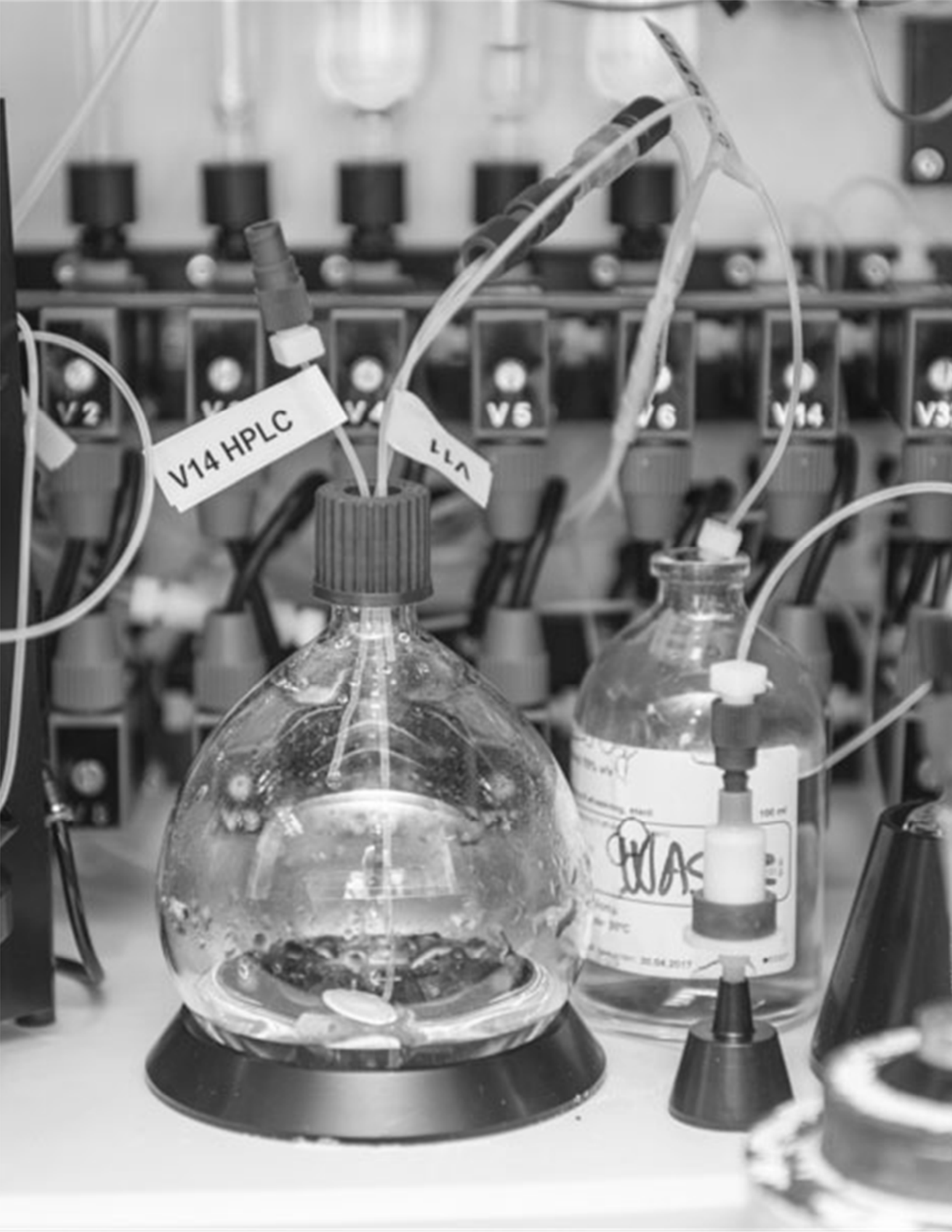


Figure 4: Doses delivered and number of deliveries for out of house users for 2015 and 2016


V14 HPLC
V2
V5
V6
V14
V3

MSc in Neuroscience and Neuroimaging

MSc in Neuroscience and Neuroimaging

Arne Møller
Senior Consultant.
Associate professor

Søren Baarsgaard Hansen
Physician, PhD

The *Sino-Danish Center* for Education and Research (SDC) is a collaboration concerning education and research between the eight Danish universities, Ministry of Science, Innovation and Higher Education, the Chinese University of the Chinese Academy of Sciences (UCAS) and the Chinese research institute Chinese Academy of Sciences (CAS). The main focus so far has been the establishment of masters programs within seven interdisciplinary areas considered to have large potential for collaboration between the two countries.

The approximately 150 students per year as well as the teachers are recruited from both China and Denmark. All classes take place at one of the UCAS campuses in Beijing, and from 2017 at the new Yanqihu Campus located approximately 60 km north of the city center close to the Great Wall. At this location the future home of SDC, The House of the Danish Industry Foundation, was officially inaugurated on the 25th of September 2017 with many participants from both countries, including His Royal Highness the Crown Prince and the Danish Minister of Higher Education and Science, Søren Pind.

Since the start-up and arrival of the first students in September 2012, Arne Møller and Søren Baarsgaard Hansen have contributed to the Neuroscience and Neuroimaging program as course organizer, teacher, masters and PhD thesis supervisor. The courses cover a variety of topics within biology, medicine, physics, and engineering. The study is concluded with a one year masters thesis project performed in one of the laboratories at UCAS, but with a participating supervisor from both countries.

Søren is course coordinator and teaching radionuclide imaging and PET at the introductory medical imaging course as well as the more advanced neuroimaging course. Also he has been supervisor of a master thesis project entitled: "Atlas based software applications for automatic analysis of PET/CT data from dementia patients".

Arne is coordinating and teaching at the course dealing with Neurology, Neurotransmission, Psychiatry and Neuropsychology. He has been supervising three master students and currently supervising three PhD students within the program:

- Carsten Gleesborg, Aarhus University – CAS Beijing
- Visse Moestrup, Aarhus University – CAS Shanghai
- Windy Dai 戴玮讷, CAS Beijing, Aarhus and Aalborg Universities.

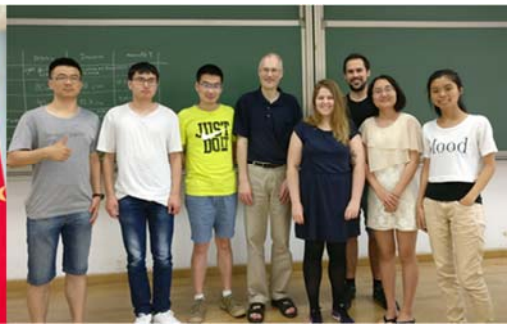
Latest publications within the framework:

Lim NK-H, Moestrup V, Zhang X, Wang W-A, Møller A, Huang F-D: An Improved Method for Collection of Cerebrospinal Fluid from Anesthetized Mice: *(2018) J Vis Exp, e56774, doi:10.3791/56774* http://www.jove.com/video/56774

Wang Y, Zou L, Xie W, Yang Z, Zhu, Cheung EFC, Sørensen TA, Møller A, Chan RCK: Altered functional connectivity of the default mode network in patients with schizo-obsessive comorbidity: A comparison between schizophrenia and obsessive-compulsive disorder. *(2018) Schizophr Bull, doi: 10.1093/schbul/sbx194*

Zou LQ, Zhou HY, Zhuang Y, Hartevelt TJ, Lui SSY, Cheung EFC, Møller A, Kringelbach ML, Chan RCK: Neural responses during the anticipation and receipt of olfactory reward and punishment in human.(*2018) Neuropsychologia; doi.org/10.1016/ j.neuropsychologia.2018.02.003*

Wang Y, Zou L, Xie W, Yang Z, Zhu, Cheung EFC, Sørensen TA, Møller A, Chan RCK: Altered grey matter volume and cortical thickness in patients with schizo-obsessive comorbidity. (*2018) Psy Res Neuroimaging doi: 10.1016/ j.pscychresns. 2018.03.009*



Training and teaching

Training and teaching are highly prioritized by our department. The department offers teaching on the pre- and postgraduate levels to the many different groups including medical doctors from many specialties, medical students, PhD students, medical laboratory technologists, molecular medicine students, medical secretaries, radiologists, physicists and chemists. In addition, many university students from science and psychology do their bachelor or master thesis at our department.

Camilla Molich Hoff
Senior Registrar, PhD

Medical doctors/specialists

Training of medical students/doctors and specialists must be and is naturally integrated into the department's daily clinical program. In 2016, the department was commended by the National Board of Health for its educational/training program.

Medical students are introduced to the department and the work of a specialist in clinical physiology and nuclear medicine through lectures in medical school and visits, both short and long visits can be arranged at the department. Recently a team of medical students has been trained to participate in nuclear cardiology procedures with great benefit for both students and doctors at the department.

Work-based training of junior doctors in specialist medical education is a natural part of the daily routine. Junior doctors document a great proportion of the procedures performed daily and their work is supervised by a specialist or a junior doctor who is nearing the end of their training, often resulting in instant feedback, fast work progression, excellent discussions and confusion at a higher level! In 2017, there were four junior doctors who were in the early stages of training and four who were nearing the end of their specialist training. Medical doctors in specialist training in other specialties, especially urology, internal medicine and endocrinology visit the department on focused educational stays.

To follow progression and optimize training for the individual doctors in all aspects (medical expert, communicator, collaborator, academic, leader, professional and health care advocate) of the medical training program, the department has scheduled meetings for all specialists and main supervisors. Within the department, three specialists are certified as feedback providers after the mandatory 360-feedback evaluation all young doctors have during their training.

The junior doctors are involved in administrative tasks at the department, they are an active part of weekly presentations of clinical cases, facilitated and supplemented by specialists both in nuclear medicine and guests from collaborating departments at educational sessions approximately once a month.

As part of the medical specialist training program, the department houses the renal physiology and pathophysiology course and also the Extended course in radiation, medical isotopes and radiation protection, offered as part of the PhD programme at The Graduate School, Aarhus University. This is a qualifying course leading to certification by the Danish authorities to handle radioactive isotopes. The courses are in collaboration with the department's physicists, chemists and medical doctors/specialists. The department also houses part of a 3-day course for doctors in early training describing the theoretical background for basic nuclear medicine examinations.

In addition to courses and educational stays, the department's physicists/chemists/medical technicians and doctors participate in many educational lectures at internal conferences, at collaborating departments and as invited speakers at national and international meetings and courses.

Moving on into 2018, one of the main focus areas in training and teaching will be evolving functional work flows including educational strategies for the merged department! The ideas were touched on in the 3-hour meeting in 2017, where worries and ideas were discussed, and an ongoing working group of all junior doctors and more formal junior doctor internal conferences have already been established.

Peter Frølich Staanum
Medical Physicist, PhD

Medical physicists

In 2017 the isotope course for medical laboratory technologists was held at the department with 19 participants from 9 different departments in Denmark. The majority of the lectures and the laboratory exercises was given by medical physicists from the department.

Other teaching activities include lectures in PET physics at the University College of Northern Denmark as part of the degree programme in Radiography, lectures on Radioisotope imaging and PET/CT/MRI image fusion in the postgraduate radiotherapy education for nurses at Aarhus University Hospital and lectures on Radionuclide Imaging at the MS program in engineering as well as the Scandinavian School of Cardiovascular Technology at Aarhus University. Lectures were also given abroad: Radionuclide imaging and PET instrumentation was taught at the Sino-Danish Center for Education and Research, Beijing.

In 2017 two PhD students, Medical Physicist Lars Jødal and MD Mads Ryø Jochumsen, were supervised by medical physicists from the department. Furthermore the departments' physicists hosted five physicists from other hospitals and departments who visited the department as part of their postgraduate education as medical physicists and finally Paw Simesen, Randers, was supervised in his postgraduate education as a medical physicist in nuclear medicine.

Anders Floor Frellsen
Chemist, PhD

Radiochemists

Chemists at the department are trained in specialized work techniques for handling radioisotopes by apprenticeship. The chief chemist arranges an individualized package of courses for new chemists at the department regarding radiopharmacy, radiochemistry, and radioprotection – *e.g.* participation in the European Radiopharmacy Course at Eidgenössische Technische Hochschule (ETH) Zürich. If no previous radioprotection training has been performed the locally taught Isotope course for medical laboratory technologists is also part of the training of chemist at the department.

Christian S.A. Juhl
Medical Laboratory Technologist and Responsible for Training

Medical Laboratory Technologists

The department plays an important role in the training of medical laboratory technologists. The students come from VIA University College, Aarhus at different stages in their training. In 2017, there were 29 students who undertook a placement in the department. The placements lasted between 3 and 15 weeks. Of these 29 students, 20 completed their training here followed by a clinical exam and 2 students carried out and completed their training by writing their dissertation here.

In 2017, training underwent a comprehensive overhaul. One of the effects of this will be a longer clinical training period for the students, containing more learning goals. Training is now more concentrated on the patient, the development of generic skills and a closer relationship between theory and practice. These changes were started in the autumn of 2016 and are expected to be fully implemented by 2018.

Over the last four years, the number of ECT points for medical laboratory technologists and radiography students has doubled. This has been due to a larger intake of students from VIA University College, Aarhus, and fewer training departments in the Central Denmark Region as well as a new and exciting collaboration with the radiography course at University College Lillebaelt, Odense (UCL) and University College of Northern Denmark, Aalborg (UCN). In 2017, there were 19 radiography students on a clinical placement at the department.

In connection with the department's contribution to the training of future medical laboratory technologists and radiographers, Christian Juhl is the medical laboratory technologist who is responsible for the administrative and training assignment. Annette Dysterdich and clinical supervisor Rikke Bertelsen are responsible for the teaching assignments. Furthermore, the department has three external examiners in the Danish National Censor Corps.

Participation in the advancement of the profession as a whole as well as other health science professions is actively encouraged through collaboration with other educational institutions.

Courses are also held for qualified technologists as well as the yearly isotope course.

Karin Fenger
Head Medical Secretary

Medical Secretaries

Each year 25-40 medical secretary students complete their training in Aarhus University Hospital. In the Department of Nuclear Medicine & PET Centre Stine Mark Nielsen Gunni is responsible for the training of medical secretary students. Together with the department's other medical secretaries she ensures that the students receive the appropriate training throughout their stay. Students also participate in the clinic.

Training is well established and well integrated throughout the department with focus on learning and feedback as well as the ongoing implementation of different systems, logbooks and supervisor interviews. The politically determined and mandatory goals of the training program are also taken into account.

In 2017, there were three medical secretary students on an 8-month stay in the department.

Medical and Molecular Medicine Students

Jørgen Frøkiær
Professor, Head of Department, MD, DMSc

The undergraduate clinical teaching is undertaken by the department's Clinical Associate Professors Lars C Gormsen, Kirsten Bouchelouche and Per Borghammer. The medical education at the Faculty of Health, Aarhus University is organized in thematic blocks when students enter the master programme. The programme consists of six blocks each taking up one semester including areas such as cardiovascular medicine, neuro and inflammation among others. Together with colleagues from adjacent disciplines we provide a variety of lectures in general nuclear medicine and molecular imaging in all these blocks in the format of both ordinary lectures and cross-disciplinary symposia. This interaction is very important and it results in recruitment of students who show a special interest in our department and in nuclear medicine, and decides to spend additional time at our department for their volunteer student rotation.

Similarly, we also provide teaching for the molecular medicine students. Molecular Medicine is a joint programme provided by the faculty of Science and Technology and the Faculty of Health, and students will meet teachers from both fields including teachers from The Department of Nuclear Medicine and PET-Centre. On the Molecular Medicine Bachelor's degree programme the students study anatomy, physiology, and genetics of the human body in combination with attending science courses in e.g. molecular biology and biochemistry. Teaching on the Molecular Medicine programme includes practical exercises in the laboratory, theoretical lectures as well as problem solving in smaller groups. Thus, the students' understanding of the principles and perspectives of molecular imaging is optimal. In particular, our department is relevant in diseases like diabetes, cardio-vascular diseases, cancer, diseases of the brain and nervous system and arthritis affect a large proportion of the population. The Master's degree programme includes teaching in the molecular mechanisms that have an impact on the development of these diseases; as well as teaching in their diagnosis, treatment and possible prevention physiology, and genetics of the human body in combination with attending science courses in e.g. molecular biology and biochemistry. Teaching on the Molecular Medicine programme includes practical exercises in the laboratory, theoretical lectures as well as problem solving in smaller groups. Thus, the students' understanding of the principles and perspectives of molecular imaging is optimal. In particular, our department is relevant in diseases like diabetes, cardio-vascular diseases, cancer, diseases of the brain and nervous system and arthritis affect a large proportion of the population. The Master's degree programme includes teaching in the molecular mechanisms that have an impact on the development of these diseases; as well as teaching in their diagnosis, treatment and possible prevention.

Studies and patient investigations

Total activity	2017
Number of examinations	23860
Total value of examinations	kr. 96.557.825,00

Referring hospital	2017
Aarhus University Hospital	17260
Regional Hospital Horsens	1476
Regional Hospital Randers	1650
General Practice	1635
Regional Hospital of Viborg, Skive and Silkeborg	1292
Regional Hospital of West Jutland	327
Private Hospitals	9
The North Denmark Region	145
Region of Southern Denmark	28
Capital Region of Denmark	11
Psychiatry Central Denmark Region	27

Radiotherapy planning	2017
Radiotherapy planning delineation, PET/CT	556

PET research scanning	2017
Human research scanning, PET/CT	794

CT examinations	2017
In total	*3069*
CT WholeBody PET/CT	3068
CT WholeBody på SPECT/CT	1

Blood and lymph system	2017
In total	*264*
Bone marrow scintigraphy	4
Spleen scintigraphy, Tc-99-erythrocyte, heated	3
Sentinel node scintigraphy, tumour drainage, c. mammae	4
Sentinel node scintigraphy, tumour drainage, c. vulva	22
Sentinel node scintigraphy, tumour drainage, c. penis	39
Sentinel node scintigraphy, tumour drainage, MM	192

CNS og peripheral nervous system	2017
In total	*1042*
Regional cerebral receptor, C-11-XX	0
Regional cerebral receptor, C-11-PIB	31
Regional cerebrale blood flow, pharm. prov., O-15-H2O	36
Regional cerebrale blood flow, physiol. prov., O-15-H2O	15
Regional cerebrale metabolism, F-18-FDG	541
Cisternography, In-111-DTPA	2
Regional cerebral receptor, F-18-FET	90
Regional Dopamine Transporter Receptor Imaging, I-123-FP-CIT (DAT-Scan)	327

Bone and Joint	2017
In total	*688*
Bone Scintigraphy, multi phased	22
Bone Scintigraphy, regional, static	0
Bone Scintigraphy, whole body, static	45
Bone Scintigraphy, SPECT	621

Other diagnostic procedures	2017
In total	*5937*
White blood cell scintigraphy, In-111-leuco	5
PET infection scanning, F-18-FDG	452
Neuro endocrine receptor scanning, F-18-DOPA	11
Tumourscintigraphy, In-111-Octreotide	0
Tumourscintigraphy, I-123-jodid	0
Tumourscintigraphy, I-131-jodid	196
Whole body scintigraphy following Lu-177-therapy	121
PET tumour scanning, F-18-FDG	4359
PET tumour scanning, F-18-Cholin	0
PET tumour scanning, GA-68-DOTANOC	0
PET tumour scanning, GA-68-DOTATOC	251
PET tumour scanning, GA-68-PSMA	357
PET tumour scanning following Y-90-SIRT therapy	13
Tumourscintigraphy, I-123-MIBG	22
Tumourscintigraphy following Lu-177 therapy	121
Intraarteriel tumour-/shunt scintigraphy, Tc-99m	16
Tumourscintigraphy following Y-90-SIRT therapy	13

Gastrin intestinal tract, liver, biliary tract and pancreas	2017
In total	*216*
Meckels diverticulum scintigraphy, Tc-99m-pertechnetat	4
Gastric emptying scintigraphy, solid food, Tc-99m	52
Liver metabolisme, F-18-FDGal	7
Gall bladder scintigraphy, Tc-99m-Mebrofenin	32
Biliary tract scintigraphy, Tc-99m-Mebrofenin	31
Bile acid turnover, Se-75-SeHCAT	89
Bleeding scintigraphy, abdomen, Tc-99-erythrocyte	1

Heart and cardiovascular system	2017
In total	*4795*
hyperinsulinemic euglycemic clamp	79
ECG, physiol.stress, Tc-99m-MIBI	11
ECG, pharm. stress,Tc-99m-MIBI	1253
Isotope cardiography, LVEF, Tc-99m-HSA	854
Myocardiel perfusion, Rb-82, pharm. stress	1162
Myocardiel perfusion, Rb- 82, rest	1166
Myocardiel metabolisme, F-18-FDG	79
Myocardiel perfusion scintigraphy, Tc-99m-MIBI, pharm. stress, adenosine	77
Myocardiel perfusion scintigraphy, Tc-99m-MIBI, physiol. stress	22
Myocardiel perfusion scintigraphy, Tc-99m-MIBI, pharm. stress, dipyr	0
Myocardiel perfusion scintigraphy, Tc-99m-MIBI, pharm. stress, dobu	14
Myocardiel perfusion scintigraphy, Tc-99m-MIBI,rest	74
Myocardiel sympaticus activity, I-123-MIBG	4

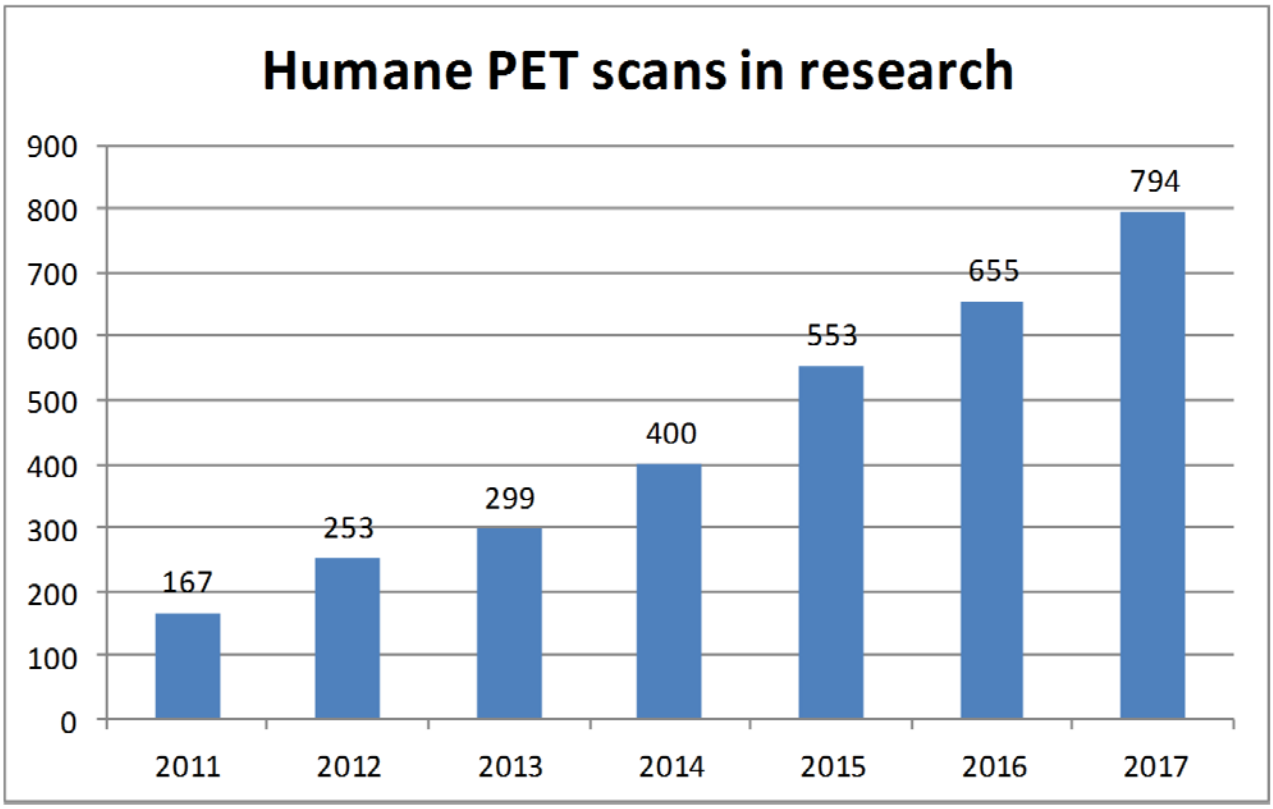
Respiratory organs	2017
In total	*1066*
Lung perfusion scintigraphy, regional, Tc-99m-MAA	199
Lung perfusion scintigraphy, Tc-99m-MAA	0
Lung ventilation scintigraphy, regional, Tc-99m-MAA	39
Lung ventilation scintigraphy, Tc-99m-MAA	0
Lung function test, spirometry	224
Lung perfusion scintigraphy, SPECT, Tc-99m-MAA	303
Lung ventilation scintigraphy, SPECT, Tc-99m-technegas	301

Peripheral vessels	2017
In total	*657*
Systolic blood pressure, fingers	1
Skin perfusion pressure measurement	16
Systolic blood pressure, ancle and toes	640

Endocrine organs	2017
In total	*2075*
Thyroid scintigraphy, Tc-99-Pertechnatet	1530
Iodine uptake test, I-131-Iodide	241
Parathyreoid scintigraphy, Tc-99m-MIBI	304
Adrenocortical scintigraphy, I-131-norcholesterol	0

Kidneys and urinary tract	2017
In total	*3001*
Renography, Tc-99m-MAG3, diuresis	579
Renography, Tc-99m-MAG3	98
Renography, Tc-99m-DTPA, ACE-inhibitor	95
Renography, Tc-99m-DTPA	18
Renal scintigraphy, Tc-99m-DMSA	122
Glomerular filtration, Cr-51-EDTA, multi samples	321
Glomerular filtration, Cr-51-EDTA, single sample	1715
Micturition cystourethrography scintigraphy, Tc99m-MAG3	53

Radioisotope therapy	2017
In total	***494***
Isotope therapy with Lu-177-DOTA-TOC	123
Isotope therapy with Y-90-DOTATOC	1
Isotope therapy with I-131-MIBG	0
Isotope treatment with I-131, benign	237
Isotope treatment with I-131, malignant	121
Selective internal radiotherapy with Y-90-SIRTEX	12
Isotope therapy with Ra-223	34


Humane PET scans in research
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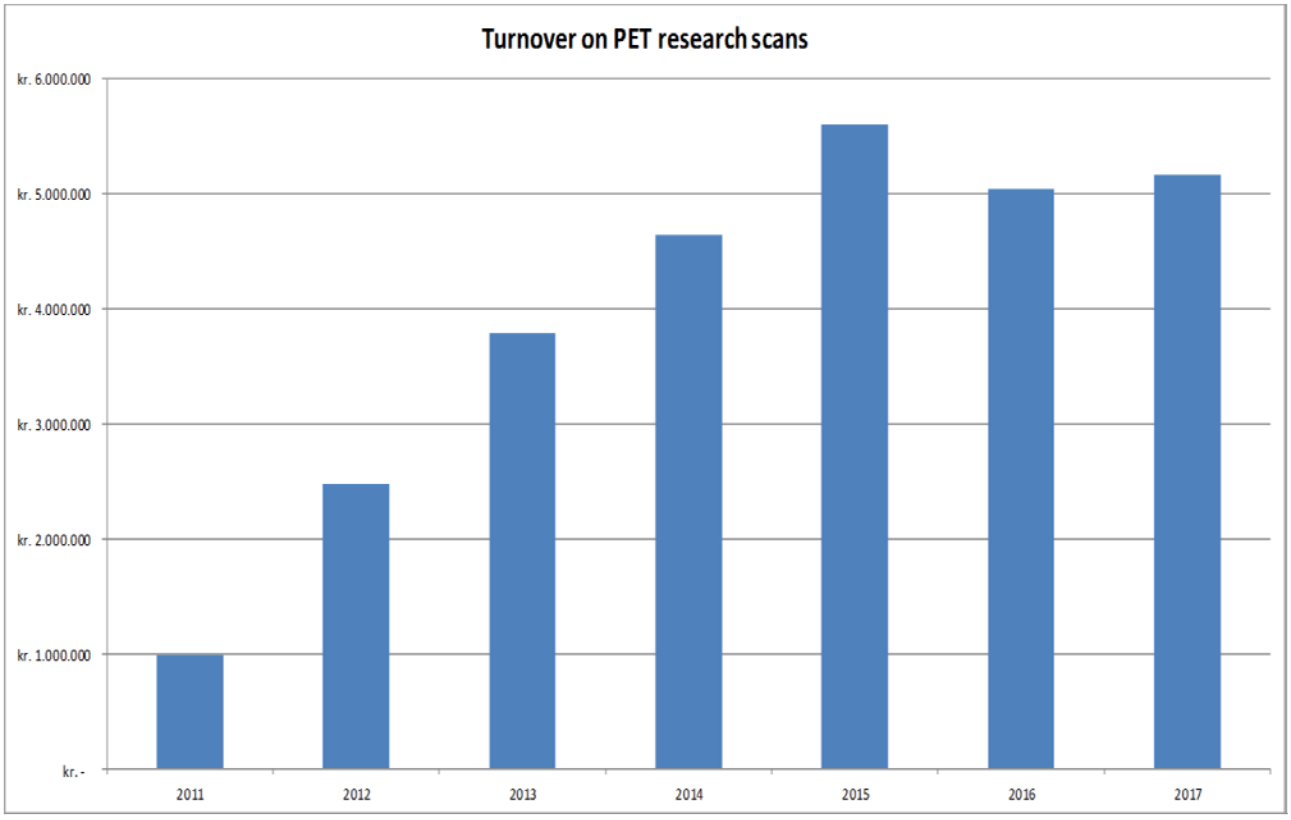
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Funding

The Department of Nuclear Medicine & PET-Centre wishes to thank the Foundations and Institutions listed below for their financial support:

A. P. Møller Foundation for the Advancement of Medical Science

Aarhus University

Aarhus University Hospital

Aarhus University, Graduate School of Health

Agnes and Poul Friis Foundation (Agnes og Poul Friis Fond)

Dagmar Marshalls Foundation (Dagmar Marshalls Fond)

Danish Cancer Society (Kræftens Bekæmpelse, Knæk Cancer)

Danish Council for Independent Research, Technology and Production Sciences

Danish Parkinson Association (Parkinsonforeningen)

Harboe Foundation (Harboefonden)

Health Research Fund of Central Denmark Region
(Region Midtjyllands Sundhedsvidenskabelige Forskningsfond)

International Parkinson and Movement Disorder Society

Knud and Edith Eriksens Foundation (Knud og Edith Eriksens Mindefond)

Lundbeck Foundation (Lundbeckfonden)

New Carlsberg Foundation (Ny Carlsbergfondet)

Olav Thon Foundation (Olav Thon Stiftelsen)

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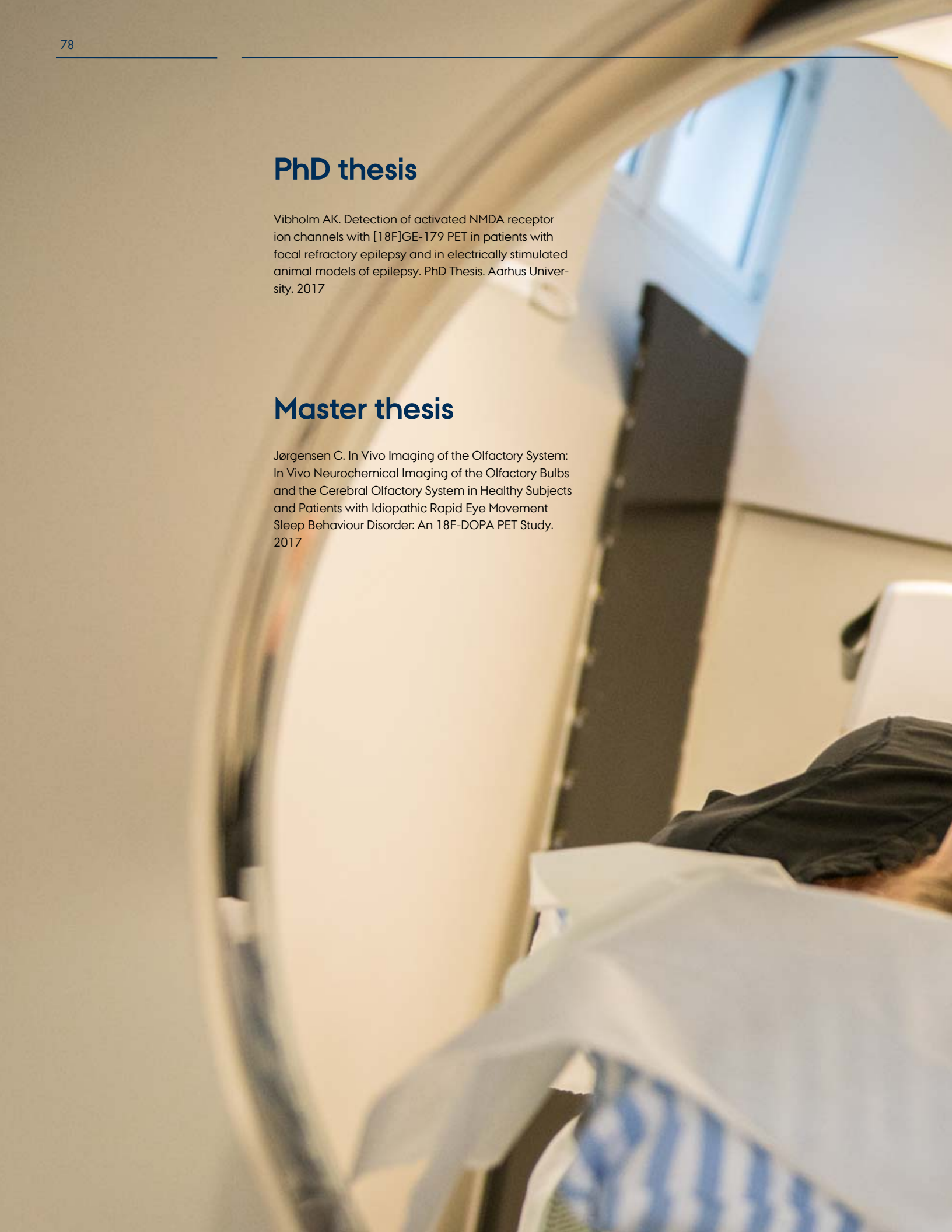

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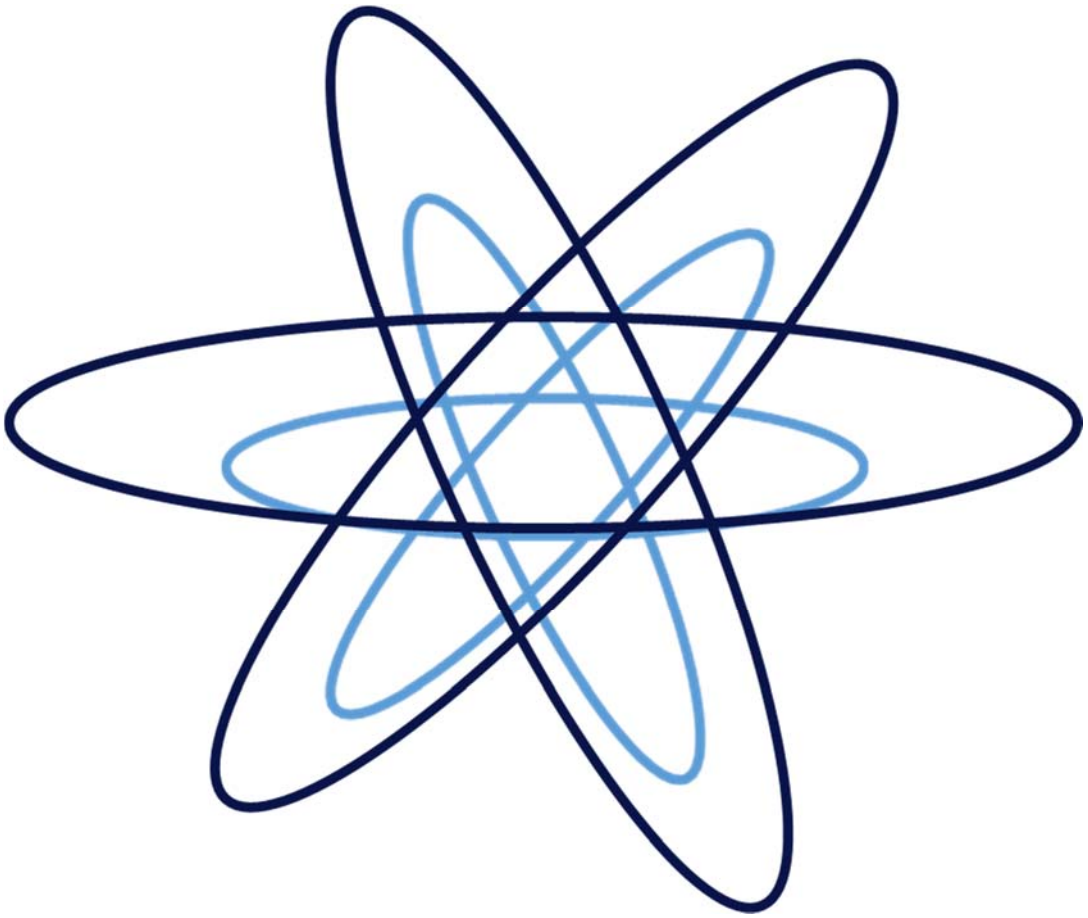
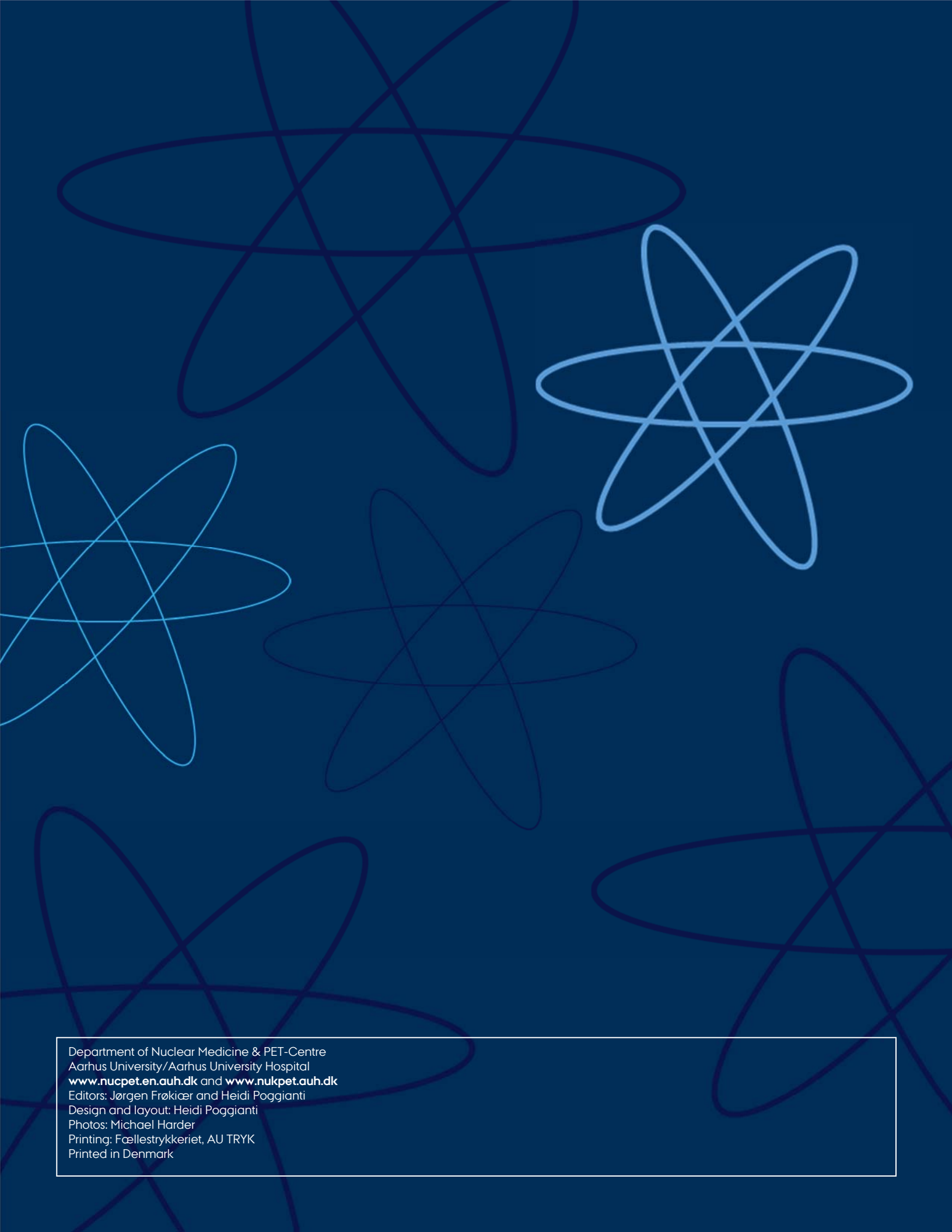


Staff on the stairway to the new Aaarhus University Hospital section leading to our new consolidated department, where we are heading in 2018.



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Editors: Jørgen Frøkiær and Heidi Poggianti
Design and layout: Heidi Poggianti
Photos: Michael Harder
Printing: Fællestrykkeriet, AU TRYK
Printed in Denmark