Neurobiology Research Unit

Annual Report 2019

Department of Neurology, Neuroscience Centre
Copenhagen University Hospital, Rigshospitalet

www.nru.dk

Cover image: Our brand-new (left) 3rd generation high-resolution AnyScan SPECT-CT Mediso scanner and (right) Siemens 3 Tesla Prisma MRI.

Contents

Preface

It is a pleasure to present you with the 2019 annual report describing the activities of the Neurobiology Research Unit (NRU).

2019 turned out to be an eventful year where we installed two new scanners dedicated for brain research in the newly built North Wing. The 3T Siemens Prisma MR scanner, funded in part by the Kirsten and Freddy Johansen Foundation, arrived in October. Later, in November, our new 3rd generation high-resolution SPECT-CT Mediso scanner, funded by Rigshospitalet, arrived. The timely installations will allow for an overlap in the use of the scanners, so that we can appropriately test and prepare the new scanners to take over the clinical tasks and research projects. During 2019, we have continued to work with the architects and the construction team to prepare the North Wing 2 building for the NRU move from the Rockefeller campus and the NRU laboratories in Building 93. The demolition of the Rockefeller Building has slowly begun, in order to make space for the subsequent building of the Children's Hospital, and the expectation is that NRU will relocate to the brand-new facilities in the Fall 2020. The move will not only allow us close proximity to the scanners and to the Dept. Neurology in the future, but it will also ensure that the preclinical laboratory is conveniently situated next to the other NRU facilities.

The Lundbeck Foundation thematic alliance *BrainDrugs* formally started on July 1st and the kick-off meeting took place in August. With *BrainDrugs*, it is our ambition to set the stage for a precision medicine approach in pharmacological treatment of epilepsy and depression, for the benefit of future patients (see page 56). It is our hope that in the long run, *BrainDrugs* can serve as a model to be implemented internationally, and for other brain disorders. You can find a 2 min video introduction to the *BrainDrugs* project through the NRU webpage (www.nru.dk).

The past year has generated substantial research output from the group. Four of our PhD students have successfully defended their theses and obtained their PhD degree (page 20-23). Many NRU-affiliated researchers have presented their work at a large number of international congresses, conferences, and meetings. In total, NRU published 53 peer-reviewed scientific publications (see page 60).

I would like to take this opportunity to acknowledge and thank all of the NRU staff for their dedicated work as well as to thank our host institution, Rigshospitalet, and all our highly valued national and international collaborators and the funding agencies that support our work. These have all been essential factors to ensure that 2019 was another very successful year for NRU.

I hope that you will enjoy reading this 2019 annual report and encourage interested readers to stay tuned on our website.

On behalf of the NRU management group

Gitte Moos Knudsen
Professor, Head of Department

NRU management group consisisting of Gitte Moos Knudsen and (from left to right starting in the top row) Jens D. Mikkelsen, Vibe G. Frøkjær, Olaf B. Paulson, Claus Svarer, Patrick Fisher and Lars H. Pinborg.

Our Mission & Activities

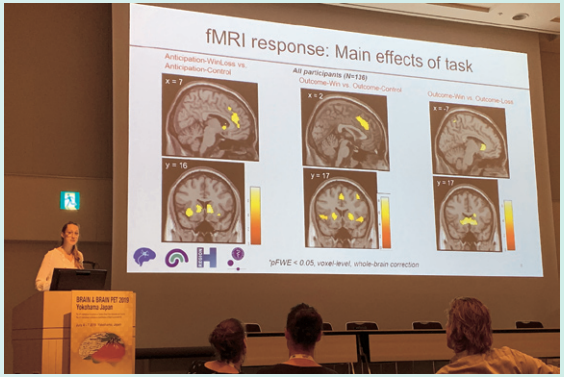
The mission of NRU is to conduct translational neuroscience research at an internationally competitive level with the aim to promote preventive, diagnostic and therapeutic advances.

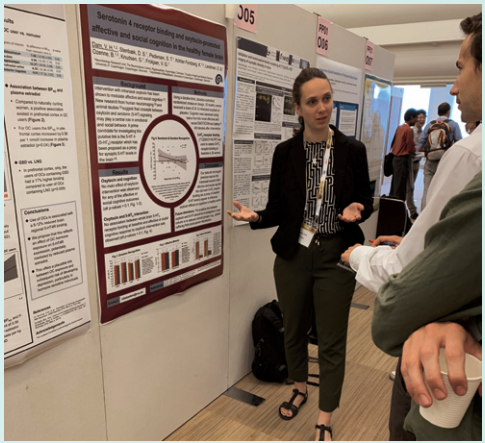
We make use of behavioural, *in vivo* molecular, structural, and functional brain imaging to uncover disease mechanisms and risk correlates, as well as to determine drug effects. We make use of animal and cell models as well as human brain tissue to investigate drug effects and diagnostic value in the clinic. We bring discoveries made in healthy volunteers and patients back to the cells and animals in the laboratory to address more basic neuroscience questions.

The activities within NRU fall in nine different categories:

1) Basic neurobiological and translational neuroscience research
2) Development and validation of new *in vivo* imaging probes
3) Neuropharmacological imaging research
4) Development and optimization of data and image analysis methods
5) Research in use of modern statistical and machine learning methods
6) Neuroimaging research studies of patients with neurological or psychiatric disorders
7) Diagnostic brain imaging of neurological patients
8) Neuropsychology research and neuropsychological testing
9) Education and training
10) Dissemination of results

We see our role at Rigshospitalet and in the Capital Region of Copenhagen as a key unit to conduct innovative diagnostic, therapeutic and preventive neuropharmacological research. This takes place in close interaction with the hospital clinics, universities and industry, enabling immediate implementation of prevention strategies, diagnostics, innovative drugs, and non-pharmacological treatments of patients with brain disorders. NRU collaborates with many other national and international research institutes (see page 12).





NRU research is often being presented at conferences and meetings world-wide, typically via poster presentations or oral talks. Here, postdocs Melanie Ganz-Benjaminsen and Martin Nørgaard (upper left), PhD-students Lene Donovan and Annette Johansen (lower left), and Vibeke Dam (lower right), as well as master student Ida Marie Brandt (upper right) share their exciting results.

Education

NRU is a major training site for pre- and post-graduate students. We aim to attract physicians and people with other relevant educations to the neuroscience field and to educate and train national and international research staff, in particular medical students, graduate students, PhD students and post docs. We organize and participate in pre- and post-graduate courses with international experts, including an international PhD-course on pharmacokinetics. We also organize regular meetings and seminars where the pre- and post-graduate students have the opportunity to present their work.

Besides supervising several Bachelor and Master students, NRU Faculty members engage in research-based teaching and education within their fields of expertise. Below are some of the major contributions to teaching and supervision in 2019.

A new Master's program in Neuroscience in Copenhagen

Beginning in 2020, the University of Copenhagen will offer about 30 bachelors with a relevant biological education enrollment in a new Master's program in Neuroscience. Professor Jens D. Mikkelsen from NRU and Institute of Neuroscience, University of Copenhagen, is the study director of this new two-year research-based education. There will be a curriculum of principles in neuroscience with a focus on describing fundamentals in cellular neuroscience, neural circuits, and higher-order cognitive functions. The NRU Faculty will provide teaching in neuropharmacology, homeostasis, and imaging in the form of lectures, exercises and journal clubs.

Master's in Neuroscience and Neuroimaging in Beijing

Lars Pinborg, NRU senior researcher and associate professor at University of Copenhagen, has again taken part in lectures at the Master's degree program 'Neuroscience and Neuroimaging' at the University of Chinese Academy of Sciences in Beijing as part of the Sino-Danish Center for Education and Research. Lars Pinborg has contributed to a course that provides an elementary overview of the structure and function of the nervous system, with special emphasis on the use of PET and SPECT tracers for the study of normal function, neurosurgical planning, and neurological and psychiatric disease.

Danish Institute of Study Abroad

Each semester, NRU senior researcher Patrick Fisher lectures across two undergraduate courses at the Danish Institute of Study Abroad: “Neuroscience of Fear” and “Neurological Disorders and Disease”.

ECNP congress in Copenhagen

NRU researchers actively participated in the 2019 European College of Neuropsychopharmacology congress, held in September in Copenhagen. NRU postdoc Sebastian Holst chaired a symposium on the glymphatic system. Professor Gitte Moos Knudsen chaired a symposium on major depressive disorder treatment and another one on psychedelics and the human brain. The latter symposium featured NRU PhD student Martin Korsbak Madsen as a speaker. NRU senior researcher Patrick Fisher was a speaker in a fourth symposium on coma and chronic disorders of consciousness.

Facilities

NRU currently has four separate locations at Rigshospitalet-Blegdamsvej and access to scanning facilities at three additional sites at the hospital. As noted earlier, NRU eagerly anticipates a move to the new North Wing of Rigshospitalet in the Fall 2020 (see photos to the right). In late 2019, two NRU scanners were installed in the North Wing: a Mediso AnyScan SPECT/CT scanner and a Siemens Prisma 3T MR-scanner (see photo to the right).

At Juliane Maries Vej 28, in the Rockefeller building (see photo on the back of the report), NRU covers 590 m^2, including 15 offices, a conference room with kitchen, a laboratory for handling human specimens, and two sound-insulated rooms with facilities for neuropsychological and -physiological testing. We also have access to shared changing facilities and meeting rooms in the building.

The NRU experimental laboratory resides in Building 93, Juliane Maries Vej 20, where we have 270 m^2 of well-equipped facilities for basic neuroscience work (*in vitro* and *in vivo* studies). Of these facilities, an office and five laboratory rooms are allocated for NRU while another eight rooms are shared with the other research groups in the building. Equipment in the laboratory includes lab benches with hoods and standard equipment, a cell culture room, microscopes, small animal storage facilities, gamma-/beta-counters, facilities for testing animal behaviour, a cell harvester, autoradiography, and much more.

The SPECT laboratory of NRU is located at the Dept. of Neurology on the 8th floor in the main complex of Rigshospitalet. The laboratory consists of a room for the 3-headed Philips IRIX SPECT scanner, a type B approved isotope laboratory, and two offices, a total of 124 m^2.

Storage and additional freezers for biobank material are located in the basement in Building 61.

NRU has a close collaboration with the PET and Cyclotron Unit at Rigshospitalet, which provides NRU access to radiochemistry production and to PET- and MR-PET scanner facilities. NRU currently uses MR-scanner facilities at the Dept. of Diagnostic Radiology, in close collaboration with the staff there.

With great interest we have followed closely the fast construction process for the North Wing 2 building, which will become the new NRU residence after Summer 2020. The two photos show the same part of the construction site in (left) March and (right) December 2019.

A very cold, rainy and windy day in October became so much more fun when our new Siemens Prisma 3T MR-scanner was delivered to the North Wing 1 building! A fantastic scanner facility has been designed in close collaboration with Siemens. We are looking very much forward to utilizing the new scanner for our future research studies.

Strategic Collaborations

Strong collaboration is fundamental for excellent brain research to happen. We have therefore for many years enjoyed working closely together with many different partners within Denmark and internationally. Listed below are some of our major strategic collaborations, which are particularly key for us. With respect to other collaborators within Dept. of Neurology, please refer to page 40.

PET and Cyclotron Unit, Rigshospitalet

We highly appreciate our long-lasting and outstanding collaboration with professor Liselotte Højgaard and her dedicated staff at the PET and Cyclotron Unit at Dept. of Clinical Physiology, Nuclear Medicine & PET.
The collaboration covers research and developmental activities and provides NRU with excellent expertise and infrastructure for radiochemistry, and PET-, and MR-PET scanner facilities. We highly appreciate this crucial collaboration and look forward to continuing the joint research activities.

Dept. of Radiology, Rigshospitalet

Over the last seven years, the Dept. of Radiology has graciously provided NRU with key access to the 3T MR-scanner facilities, available after regular working hours. We highly appreciate the collaboration with Dr. Vibeke Andrée Larsen, Chief Radiographer Bo Haugaard Jørgensen and project radiographer Christian Hammer Nielsen. We will primarily be using our newly-installed Siemens Prisma 3T MR scanner for our future research projects, but we are looking forward to a continued good collaboration with the Dept. of Radiology personnel.

Martinos Center, Massachusetts General Hospital, US

Since 2011, we have had a fruitful collaboration with the Athinoula A. Martinos Center for Biomedical Imaging in Boston, US, which has pioneered brain imaging with MRI. The collaboration has so far included retreat meetings, the successful achievement of a joint 2-year NIH grant, the NRU-anchored *NeuroPharm* Center grant (2015-22) from the Innovation Fund Denmark, and funding from Lundbeck Foundation for an international postdoc position for Hanne Demant Hansen, as well as bilateral exchange of scientists. Jan 1st, 2019, Hanne Demant Hansen initiated her 3-year stay as research fellow at Martinos, where she will be conducting her project '*Characterizing brain network effects of novel and existing drugs using hybrid PET/MR imaging''*.

University of Copenhagen

Since the establishment of Cimbi in 2006, we have had a close collaboration on PET radioligand development with Dept. of Drug Design and Pharmacology, Faculty of Health and Medical Sciences. Likewise, we also appreciate our long-standing collaboration on biostatistics with Section of Biostatistics, Faculty of Public Health, with whom we share a biostatistician postdoc, and with the Department of Psychology with whom we share an associate professor for supervision of PhD-students with a psychology background. Finally, we also highly appreciate our more recently established collaboration with Dept. of Computer Science, facilitated by a joint assisting professor position.

University of Cambridge, UK

Since 2018, we have collaborated closely with professors Trevor Robbins and Barbara Sahakian from University of Cambridge with whom we are currently running two joint research projects funded by the Lundbeck Foundation. Professors Robbins and Sahakian spend their sabbatical as NRU affiliates in 2018 and last year they also visited NRU several times to coordinate the initiation of the two projects. We appreciate the collaboration and are keen to learn the outcomes of the projects.

Mental Health Services in the Capital Region of Denmark

NRU has close collaborations with Mental Health Services in the Capital Region of Denmark, including with professor Martin Balslev Jørgensen who is directly involved in NP1 of *NeuroPharm*, with professor Lars Vedel Kessing, and professor Kamilla Miskowiak and her Neurocognition and Emotion in Affective Disorders (NEAD) group, as well as with professors Anders Fink Jensen and Birte Glenthøj. Through *BrainDrugs*, it has been possible to expand this collaborative network to also include professor Poul Videbech and Klaus Martiny.

We have initiated a new collaboration with senior consultant Clas Winding Christensen and psychologist Sarah Nielsen for inclusion of patients with obsessive-compulsive disorders (OCD) as part of our joint study on habit forming with professor Trevor Robbins and his colleagues. For our *NeuroPharm* project, we have also engaged in a close collaboration with CVD (Center for Visitation og Diagnostik), a unique new central referral site for 'treatment packages', e.g. for patients with depression or obsessive-compulsive disorder who can be treated in outpatient settings.

We highly appreciate these collaborations and look forward to strengthening our joint research activities in the future. Supporting the bridge from NRU to Clinical Psychiatry, Vibe Gedsø Frøkjær has been appointed Clinical Research Associate Professor with a part time senior consultant function at Mental Health Services in the Capital Region of Denmark.

Staff in 2019

NRU Faculty
Gitte Moos Knudsen, Head of NRU, professor, MD, DMSc
Claus Svarer, chief engineer, PhD
Jens D. Mikkelsen, professor, MD, DMSc
Lars H. Pinborg, associate professor, MD, DMSc
Olaf B. Paulson, professor, MD, DMSc
Patrick Fisher, group leader, PhD
Vibe G. Frøkjær, associate professor, group leader, MD, PhD

Chief technologist
Gerda Thomsen

Research administrators
Birgit Tang
Dorthe Givard
Peter S. Jensen

Junior group leaders (postdocs)
Dea S. Stenbæk, associate professor, psychologist, PhD
Hanne D. Hansen, molecular biologist, PhD
Mikael Palner, engineer, PhD

Postdocs
Brice Ozenne, biostatistician, PhD
Liv V. Hjordt, psychologist, PhD
Louise M. Jørgensen, associate professor, MD, PhD
Martin Nørgaard, engineer, PhD
Martin Schain, engineer, PhD
Melanie Ganz-Benjaminsen, computer scientist, PhD
Pontus Plavén-Sigray, clinical neuroscience, PhD
Sofi da Cunha-Bang, MD, PhD
Sebastian C. Holst, engineer, PhD
Vincent Beliveau, neuroscientist, PhD

PhD students
Agata C. Sainz, molecular biomedicine
Annette Johansen, MD
Camilla B. Larsen, MD
Cheng T. Ip, psychologist (H. Lundbeck A/S)
Giske F. Opheim, neuroscientist
Kristin Forsberg, MD (Psychiatric Center Copenhagen)
Lene L. Donovan, medicine with industrial specialization
Martin K. Madsen, MD
Nakul Raval, medical nuclide techniques
Sagar S. Aripaka, biochemistry
Sophia Armand, psychologist
Vibeke N. H. Dam, psychologist

Research assistants
Arafat Nasser, pharmacist
Emily Beaman, human biology
Gjertrud L. Laurell, nuclear medicine
Ida Marie Brandt, molecular biomedicine
Joana Menezes, molecular genetics & biomedicine
Søren V. Larsen, MD

Technical research personnel

Cecilie L. Nordberg, MRI-student assistant
Cecilie F. Skovsen, MRI-student assistant
Ditte B. Christensen, MRI-student assistant
Ditte B. Nielsen, Nurse
Gunild Vulpius, MRI-student assistant
Josephine Torp, HPLC student assistant
Kristoffer Brendstrup-Brix, MRI-student assistant
Line N. Buchwald, MRI-student assistant
Lone I. Freyr, project nurse
Lucas Korsgaard Andreasen, HPLC-student assistant
Luna S. Hansen, MRI-student assistant
Mariam Labrouzi, biomedicine
Minna Litman, research nurse
Nadia Taghavi-Larmaei, biology
Sara L. Jørgensen, MRI-student assistant
Svitlana Olsen, medical technologist
Thomas Wiklund Jørgensen, IT-support

Visiting professors

Adriaan Lammertsma, professor, VUmc, Netherlands
Barbara Sahakian, professor, Univ. Cambridge, UK
Todd Ogden, professor, Columbia University, USA
Trevor Robbins, professor, Univ. Cambridge, UK

Visiting scientists

Anna Brancato, biomedicine & neuroscience (ECNP intern)
Benno John, medical & pharm. biotech. (ERASMUS intern)
Burcu Azak Pazarlar, physiology (ERASMUS intern)
Daniel P. Casteràs, psychology (ECNP intern)
Marie Spies, MD, PhD, Medical University of Vienna, Austria
Nídia Fernandezz, biotechnology (ERASMUS scholar)

Pregraduate students

Albin Arvidsson, medicine
Ali Ilhan, engineer
Anders E. Lund, medicine
Anders S. Olsen, engineer
Andreas K. Færk, psychology
Andreea-Veronica Vascan, computer science
Ane G. Kloster, medicine
Annemette Ringsted, engineer
Annesofie Videbæk, cellular biology & physiology
Asbjørn Poulsen, medicine
Charlotte H. Nykjær, medicine
Clara Madsen, molecular biomedicine
Daniel Burmester, medicine
Dorte Bonde Zilstorff, medicine
Emilie H. Mortensen, medicine
Emily Barot, bioinformatics
Emma S. Høghsted, medicine
Frederik Gudmundsen, neurosicence & neuroimagning
Freja Jespersen, medicine
Ida V. Andersen, pharmacy
Ines Hamtache, pharmacy
Jacob V. Andersen, engineer
Jens R. Møller, medicine
Johanna Mariegaard, psychology
Katrine Kiilerich, biochemistry
Kristine Nielsen, bioinformatics
Line B. S. Knudsen, pharmacy
Louise F. Nielsen, psychology
Maja R. Marstrand-Jørgensen, medicine
Martin Prener, medicine
Mathias Glorvigen, psychology
Michael K. D. Nguyen, computer science
Niels Lorenzen, molecular biomedicine
Nikolaj R. Speth, pharmaceutical sciences
Oliver Overgaard-Hansen, psychology
Robert Sethsen Petersen, molecular medicine
Saba Ali, biomedicine
Sarah C. Pedersen, molecular & medical biology
Sebastian E. Ebert, medicine
Simone Pleinert, psychology
Sofie T. Kristensen, linguistics
Sophia K. Weber, psychology
Tina Segerberg, psychology
Tobias Fjeld, medicine
Victoria Fagerholt, molecular & medical biology

Visiting Professors

During the course of 2019, NRU has had the pleasure of hosting four highly esteemed international visiting professors. All four visiting professorships have been enabled based on either an International Neuroscience Program grant or a Visiting Professorship grant from the Lundbeck Foundation, without which it would not have been possible. We have continued our close collaboration with professors Trevor Robbins and Barbara Sahakian from University of Cambridge (Cambridge, UK) with whom we have designed and coordinated two large-scale neuroimaging studies where data acquisition will start spring 2020. Furthermore, we have welcomed Adriaan A. Lammertsma, professor of Nuclear Medicine at VU University Medical Center (Amsterdam, The Netherlands) and R. Todd Ogden, professor of Biostatistics at Columbia University (New York, NY, USA), who throughout their respective careers have made remarkable impressions on the PET field by pioneering the development of pharmacokinetic models and other methodologies advancing neuroimaging as a research tool.

During their respective visits at NRU, professors Lammertsma and Ogden are involved in many research projects, including e.g.:

- development of pharmacokinetic models describing radioligand displacement during on-going PET scans,
- estimation of PET acquisition errors and development of tools to use these errors when making statistical inference,
- estimation of the level of background signal in a PET image,
- development of statistical tools to improve the reliability of target engagement studies,
- determination of a lower limit for the injected radioactivity without sacrificing quality of the data.

Professors Lammertsma (left) and Ogden (right).

In addition to providing invaluable input to the various research projects, the visits by professors Lammertsma and Ogden enable interaction between junior researchers at NRU and these experienced researchers. That the visiting professors are very well-established in countries outside Denmark is of particular value, as these visits and interactions facilitate a deepened collaboration between the respective labs, and provide a foundation for exchanging qualified researchers, for instance via post-doc programs or PhD-students doing part of the thesis work abroad. With this, we look forward to several more visits in coming years.

Selected Staff Highlights of the Year

Symposium on Integrated Molecular Imaging Approaches to Understanding the Brain - Past, Present and Future

Honorary Symposium for Professor Gitte Moos Knudsen

Friday, February 22nd, 2019
Auditorium 2, Rigshospitalet, Copenhagen

The symposium has been generously supported by the Lundbeck Foundation.
It is open for everyone (registration not needed).

Program

13.00 Welcome

13.05 Glymphatics - Basic discoveries to next steps
Maiken Nedergaard, University of Copenhagen & University of Rochester

13.25 Molecular brain imaging with PET
Liselotte Højgaard, University of Copenhagen & Rigshospitalet

13.40 Novel tracer development for molecular brain imaging - Looking forward
Julie Price, Martinos Center, Massachusetts General Hospital, Boston

14.00 Creative surprise

14.20 Coffee break

14.45 Molecular psychiatry - Copenhagen contributions
Ida Hageman Pedersen & Martin Balslev Jørgensen, Mental Health Services in the Capital Region of Denmark & University of Copenhagen

15.00 A translational cognitive neuroscience approach to understanding OCD
Trevor Robbins, University of Cambridge

15.20 Developmental population neuroscience - Past and prologue
Terry Jernigan, University of California

15.40 Frontiers of integrated brain imaging - Methods development and perspectives
Bruce Rosen, Martinos Center, Massachusetts General Hospital, Boston

16.00 Extro

16.15 – 18.00 Reception
Hosted by Dept. of Neurology, Rigshospitalet, Copenhagen

Neurobiology Research Unit
Rigshospitalet
Copenhagen University Hospital

Rigshospitalet

On Feb 22nd 2019 NRU hosted an Honorary Symposium for professor Gitte Moos Knudsen entitled 'Integrated Molecular Imaging Approaches to Understanding the Brain - Past, Present and Future'. The symposium consisted of talks from world-class researchers from the neuroimaging field as well as a creative musical feature. Afterwards the Dept. of Neurology hosted an official reception in the hospital canteen, and the celebrations ended with a private dinner held at Domus Medica.

On May 16th 2019 it was time for another well-deserved celebration. This time we celebrated NRU chief engineer Claus Svarer's 25 years work anniversary at Rigshospitalet, an impressive milestone. The Neuroscience Center kindly sponsored the reception which was held in the NRU conference room.


Rigshospitalet

25 års jubilæum - Claus Svarer

Det er en stor glæde at kunne invitere til reception i anledning af chefingeniør, PhD Claus Svarers 25 års jubilæum

Torsdag d. 16. maj 2019 kl. 14.00
NRU, opgang 69, 3. sal, Juliane Maries Vej 28, 2100 Kbh Ø

Alle er velkomne!

Mange venlige hilsner

Gitte Moos Knudsen
Professor, leder af NRU

Receptionen er sponseret af Neurocentret

NRU PhD Degrees

Marie Deen Christensen, Medicine

Marie Deen Christensen completed her PhD at the Neurobiology Research Unit (NRU) and the Danish Headache Center (DHC) between June 2015 and May 2018 under the supervision of professors Messoud Ashina from DHC and Gitte Moos Knudsen from NRU and co-supervision by Dr. Hanne Demant Hansen from NRU and Dr. Anders Hougaard from DHC. Her PhD thesis titled "*PET investigations of brain serotonin receptor binding in migraine patients*" was submitted to the Graduate School of Health and Medical Sciences, University of Copenhagen on May 25th 2018, and presents four papers summarizing the work she performed during her appointment at NRU and DHC.

Dr. Deen's thesis supports the hypothesis that the serotonergic system plays a role in migraine pathophysiology, with migraine patients exhibiting high brain serotonin levels between attacks, which increase further during attacks. Further, the 5-HT_{1B} receptor density is altered in migraine patients and sumatriptan may act on central 5-HT_{1B} receptors. Future studies are warranted to explore the exact mechanisms by which high brain serotonin levels lead to migraine, but interventions aiming at lowering brain serotonin levels may prove efficient as a treatment of migraine in the future.

Dr. Deen successfully defended her thesis on January 4th, 2019, with professor Steen Gregers Hasselbalch from Danish Dementia Research Center, Dept. of Neurology, Rigshospitalet and University of Copenhagen as chair and professor Andrew Charles from UCLA, Los Angeles and associate professor Andrea Varone from Karolinska Institute, Stockholm as opponents.

Martin Nørgaard, Engineer

Martin Nørgaard completed his PhD at NRU between August 2016 and January 2019 under the supervision of professor Gitte Moos Knudsen and co-supervision by senior scientist Claus Svarer and assistant professor Melanie Ganz from NRU and professor Stephen C. Strother from University of Toronto. His PhD thesis titled "*Optimizing Preprocessing Pipelines in PET/MR Neuroimaging*" was submitted to the Graduate School of Health and Medical Sciences, University of Copenhagen on Jan 29th 2019.

Dr. Nørgaard's thesis focuses on preprocessing strategies in PET. In the five papers, Dr. Nørgaard evaluates current preprocessing strategies in the literature, how they affect measures of test-retest bias, variability and false-positive rates, and how they may lead to different conclusions in a double blind, randomized, placebo-controlled study. Finally, he provides a statistical framework for adequately controlling the false-positive rate when dealing with large sets of preprocessing options. The thesis demonstrates that (1) variations in choice of preprocessing strategy are an overlooked aspect in modern PET neuroscience, (2) measures of bias, within- and between-subject variability are significantly affected by preprocessing strategy, and (3) different preprocessing strategies lead to different neurobiological conclusions. His findings suggest that the preprocessing stage contributes with considerable variance into the data, with the preprocessing steps motion correction, partial volume correction and kinetic modeling being the main contributors. Cleary, knowledge about the variability of preprocessing is critical to limiting false-positive rates, which underlines the importance of selecting preprocessing strategy with great caution.

Dr. Nørgaard successfully defended his thesis on May 3rd, 2019, with professor Liselotte Højgaard from Dept. of Clinical Physiology, Rigshospitalet and University of Copenhagen as chair and professor Ronald Boellaard from VU University Medical Center, Amsterdam, NL and professor R. Todd Ogden from Columbia University, New York, USA as opponents.

Mette Thrane Foged, Medicine

Mette Thrane Foged completed her PhD at NRU and the Functional Imaging Unit, Diagnostic Department, Rigshospitalet under the supervision of associate professor Lars H. Pinborg from NRU and co-supervision by professors Sándor Beniczky, Olaf B. Paulson, Henrik B.W. Larsson, and Troels W. Kjær from Rigshospitalet and Stefan Posse from University of New Mexico, USA. Her PhD thesis titled "*Epilepsy surgery: Outcomes of the Danish evaluation program and development of new EEG based methods*" was submitted to the Graduate School of Health and Medical Sciences, University of Copenhagen on Nov 6th 2018.

The aim of Dr. Foged's thesis was to: 1) Evaluate the outcomes of the Danish epilepsy surgery program, e.g. are the patients referred according to the recommendations from the International League Against Epilepsy? Do the Danish results correspond to international standards? Is the change in cognitive function affected by the surgical approach? 2) Investigate the use of new EEG based methods with potential added value in the evaluation process aiming to identify the epileptogenic zone by a) further development of concurrent EEG and functional MRI (EEG-fMRI) and b) evaluation of the clinical utility of low-density (LD) vs. high-density (HD) electrical source imaging (ESI). The results of the Danish epilepsy surgery program were found to be comparable to international standards but international recommendations for referral of drug-resistant patients to surgical evaluation were not all fulfilled. In patients with hippocampal sclerosis, selective amygdalohippocampectomy resulted in sustained "freedom from disabling seizures" and better memory function compared with patients operated with a temporal lobe resection. EEG-fMRI results were not of use in the epilepsy surgery evaluation but showed that it is safe to perform concurrent HD EEG and high-speed fMRI which is usable in other fields. In total LD and HD ESI lead to a change in clinical decision in 34% of patients evaluated for epilepsy surgery, with changes primarily observed based on HD ESI.

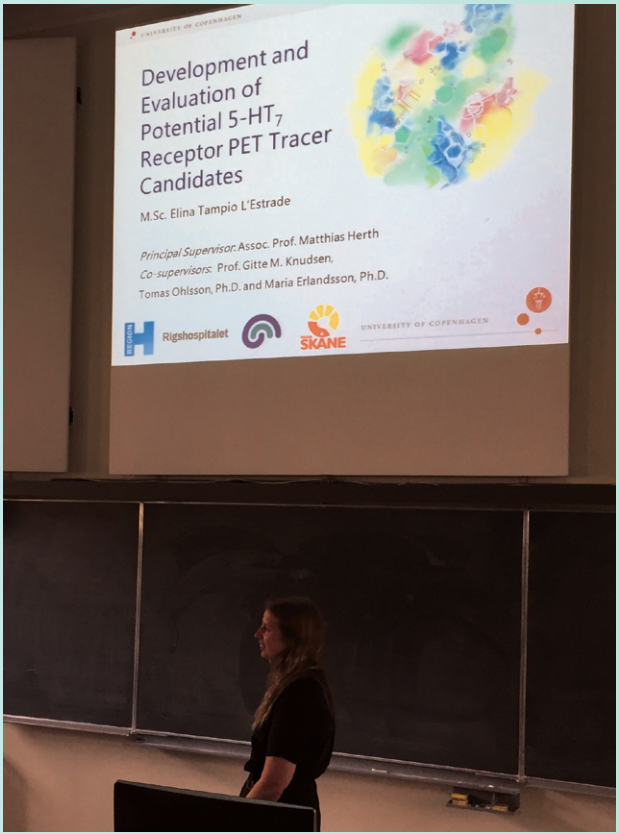
Dr. Foged successfully defended her thesis on April 26th, 2019, with professor Kirsten Møller from Dept. of Neuroanaesthesiology, Rigshospitalet and University of Copenhagen as chair and professors Andreas Schulze-Bonhage from Neurozentrum der Albert-Ludwigs-Universität, Germany and clinical lecturer Antonio Valentin from Neuroscience Academy Centre, Kings College London, United Kingdom as opponents.

Elina Tampio L'Estrade, Radiochemist

On March 8th 2019, Elina Tampio L'Estrade submitted her PhD thesis entitled "*Development and Evaluation of Potential 5-HT$_7$ Receptor PET Tracer Candidates*" to the Graduate School of Health and Medical Sciences, University of Copenhagen. During her PhD Dr. L'Estrade was supervised by associate professor Matthias M. Herth from Dept. of Drug Design and Pharmacology, University of Copenhagen and co-supervised by professor Gitte Moos Knudsen from NRU and Dr. Tomas Ohlsson and Dr. Maria Erlandsson from Radiation Physics, Nuclear Medicine Physics Unit, Skånes University Hospital.

The aim of Dr. L'Estrade's thesis was to develop a PET tracer selective for the serotonin 7 receptor (5-HT$_7$R) which is the most recently discovered subfamily of the serotonergic receptor system. Fifteen potential 5-HT$_7$R PET tracer candidates were designed, synthesized and characterized, which led to the identification of three of them as the most promising ones to image the 5-HT$_7$R *in vivo*, namely [18F]ENL10, [11C]Cimbi-701 and [18F]ENL30.

Dr. L'Estrade successfully defended her thesis on May 6th, 2019, with associate professor Anne-Marie Heegaard from Dept. of Drug Design and Pharmacology, University of Copenhagen as chair and associate professor Stina Syvänen from Dept. of Public Health and Caring Sciences, Uppsala University, Sweden and professor Tobias L. Ross from Dept. of Nuclear Medicine, Hannover Medical School, Germany as opponents.



ECNP Presidency

The European College of Neuropsychopharmacology (ECNP) is an independent scientific association dedicated to the science and treatment of disorders of the brain. It is the largest non-institutional supporter of applied and translational neuroscience research and education in Europe.

In September 2019, professor Gitte Moos Knudsen was officially inaugurated as president of ECNP. The inauguration took place at the 32nd ECNP annual congress, which was held in Copenhagen with attendance of close to 6,000 neuroscience researchers and clinical practitioners. Gitte Moos Knudsen will serve as ECNP president for the next three years.

Left: Professor Gitte Moos Knudsen giving a speech at the ECNP general assembly at the 32nd ECNP annual congress in Copenhagen after officially having taken over as ECNP president. Right: The ECNP Executive Committee which consists of six officers – the president, vice- president, president-elect, past-president, secretary and treasurer – and a maximum of six councillors. Members sit for three-year terms, and can be re-elected a maximum of four times.

New Associate Professors

In the fall, three NRU staff members were assigned as associate professors at the University of Copenhagen. This is a welcomed contribution to our senior scientist staff and will facilitate additional training and supervision of future Master's- and PhD-students.

Louise Møller Jørgensen

NRU postdoc Louise Møller Jørgensen was appointed *Clinical Associate Professor with function as innovation ambassador* at Institute of Clinical Medicine, University of Copenhagen. In her new role she will be serving in SUND's *Innovation Working Group*, which aims to advance innovations and entrepreneurship in the clinics.

Dr. Møller Jørgensen came to NRU in early 2013 and completed her PhD here from 2014 to 2017, after which she held a shared position as postdoc and staff specialist at NRU and the spine unit at Rigshospitalet-Glostrup. She is a neuroscientist and neurosurgeon by training with a special interest in electroceutical therapy, such as neurostimulators. Her research focus is to answer the basic questions of how electroceuticals work in the body. To do so, she has recently, together with two co-inventors, developed a recently patented device (an fMRI compatible electrical stimulator), which allows feedback from brain imaging of the effects of electroceutical therapy using functional magnetic resonance imaging. She has applied the device in her research exploring the effects of deep brain stimulation on monoaminergic neurotransmission, neurocircuits, cerebral blood flow and metabolism. In 2019 Dr. Møller Jørgensen obtained funding from the Novo Nordisk Foundation Proof of Concept Programme to improve the prototype and advance toward regulatory approval.

Vibe G. Frøkjær

NRU senior researcher and independent Group Leader of the Imaging Psychiatry and Psychoneuroendocrinology (IPSY) group, Vibe Gedsø Frøkjær was appointed as Clinical Research Associate Professor at University of Copenhagen with a related function as half-time Senior Consultant in Psychiatry.

Dr. Frøkjær is a medical doctor with clinical experience in neurology and psychiatry. Her research line aims at uncovering neurobiological correlates to vulnerability for developing neuropsychiatric disease, which ideally hold a preventive potential. She has been affiliated with NRU since the mid 2000's and lately has been focusing her research on molecular imaging of serotonergic neurotransmission in the context of steroid hormone biology, and genetic and personality risk factors for neuropsychiatric disease. Her work on risk- and robustness mechanisms for depression now can move into translation to relevant high-risk groups for depression, which includes evaluation of a preventive strategy for postpartum depression. She currently holds PI grants from Independent Research Fund Denmark, i.e. Project 1 and Sapere Aude grants, and RH-infrastructure plus other smaller grants. Dr. Frøkjær serves as work package leader in *NeuroPharm* (see page 50) as well as work package leader and steering group member in *BrainDrugs* (see page 56).

Dea S. Stenbæk

NRU Junior Group Leader Dea Siggaard Stenbæk was appointed research Associate Professor at the Institute of Psychology at University of Copenhagen. This appointment is expected to strengthen the collaboration between NRU and the Institute.

Dr. Stenbæk is a psychologist by training and has been with NRU for more than a decade. Her overall research focus has been on pharmacological manipulations of the serotonin system in both healthy research participants and patients, using most recently psilocybin with the aim of investigating brain mechanisms of novel treatments for neuropsychiatric disorders with an affective component. To understand how serotonin is involved in affective processing in the healthy brain, Dr. Stenbæk has also studied associations of various 5-HT receptors using PET imaging, i.e., 5-HT_{2A}R, 5-HT_4R, 5-HTT and 5-HT_{1B}R with personality and affective cognition.

Preclinical Neurobiology

Experimental neurobiological research is conducted at the Neurobiology Research Unit where several researchers are working on research projects to study mechanisms *in vitro* and *in vivo*.

Radioligand Development

In the radioligand development group we combine biology, chemistry, radiochemistry and neuroimaging to develop PET radioligands. PET imaging allows us to quantify the receptors in the living brain of animals or humans; novel and sensitive radioligands can even measure changes in endogenous neurotransmitter levels in the brain.

Our group have been focusing on developing radioligands for the 5-HT_{2A} and 5-HT_7 receptors for many years. For the 5-HT_{2A} receptor we developed the agonist radioligand [^{11}C]Cimbi-36 and in the final evaluation stage of this radioligand we performed whole-body scans in healthy volunteers (**Figure 1**) to determine the distribution of the tracer outside of the brain [25]. Within Cimbi, the development of novel radioligands for the 5-HT_{2A} receptor - the target of, e.g., psilocybin and LSD psychedelic actions - has led to the establishment of a small Danish pharmaceutical company, Lophora. One of Lophoras founders is our close collaborator professor Jesper Langgaard Kristensen from the Dept. of Drug Design and Pharmacology at the University of Copenhagen.

Another of our close collaborators at Dept. of Drug Design and Pharmacology, Dr. Matthias Herth, has a strong interest in developing new techniques for imaging targets in the brain. Using a two-step process called “pre-targeted imaging” (**Figure 2**), Dr. Herth is developing novel and superior methods for imaging protein aggregates in the brain such as amyloid-beta or alpha-synuclein. This year, we published the first preclinical evaluation of this technique [43].

Developing a 5-HT_7 receptor radioligand is still in its early phases with chemical synthesis of new compounds, *in vitro* evaluation of target affinities and preclinical testing of radioligands in rats, pigs and non-human primates. We published [19,48] the evaluation of [^{18}F]ENL09, [^{18}F]ENL10 and [^{18}F]2FP3. Despite great effort, we are still short of a good tracer for this receptor as none of the tested ligands were good enough for further progress into the clinic.

Hanne D. Hansen &
Mikael Palner
Junior Group Leaders

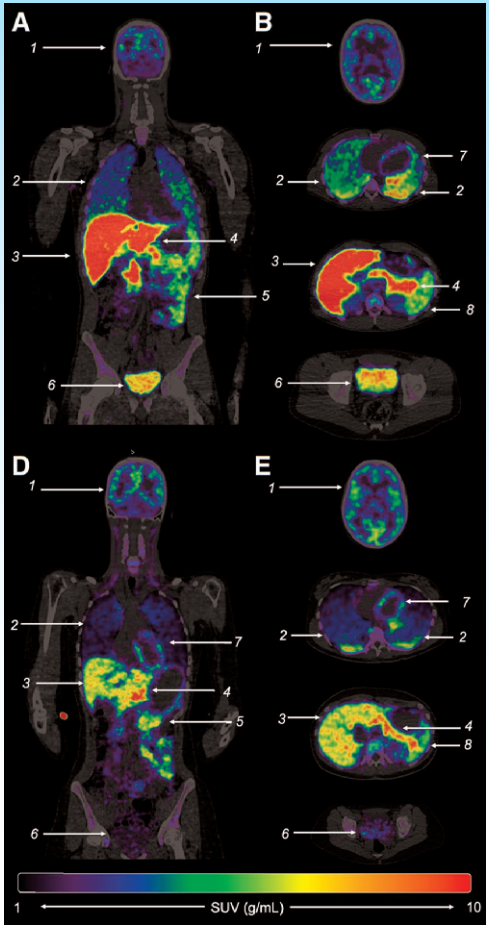


Figure 1: Coronal and horizontal PET/CT fused images of ^{11}C-Cimbi-36 (A, B) and ^{11}C-Cimbi-36_5 (D, E) 40 min into the scan. Brain (1), lungs (2), liver (3), pancreas (4), small intestines (5), urinary bladder (6), heart wall (7), spleen (8). Modified from [25], Copyright © 2019 The Authors.

The collaboration with the Dept. of Drug Design and Pharmacology sometimes allows us to test new radioligands for targets that we normally do not focus on. This was the case with a compound called DS2 which binds to the delta-subunit containing GABA receptors [32]. Our results showed that [^{11}C]DS20Me is a promising lead in the development of a tracer for this target.

There has also been a great focus on new tracers for alphasynuclein, with the launch of the PET-alphaSY European PhD training network (www.alphasy.eu) as well as preclinical evaluation of [^{11}C]UCB-J in both rats and pigs.

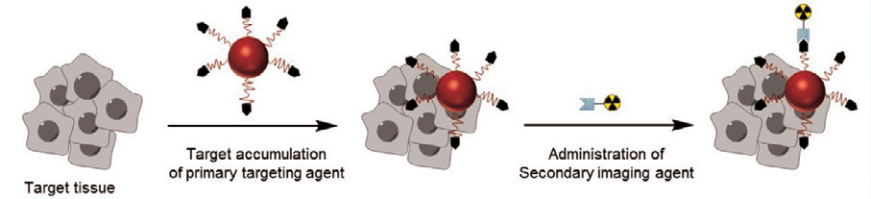


Figure 2: Schematic illustration of a pretargeting strategy for nuclear imaging. A primary targeting agent functionalized with reactive tags is first administered and allowed to accumulate in the target tissue. In the second phase, the secondary imaging agent is administered. The latter will bind/interact with the compatible reactive tags of the primary targeting agent, which allows for imaging of the targeting agent accumulated in the target tissue. From [43], Copyright © 2019 The Authors.

Translational Neuroimaging and Behavior

The research focus is to gain a functional and mechanistic understanding of clinical imaging results and to validate novel PET tracers. We use genetic tools to target selective brain circuits and correlate activation of these neuronal pathways to imaging outcomes and behaviour.

In 2019 we have measured Clozapine N-oxide induced neuroreceptor occupancy and changes in neurochemicals in frontal cortex and striatum, measured with magnetic resonance spectroscopy (MRS) (**Figure 3**) [3].

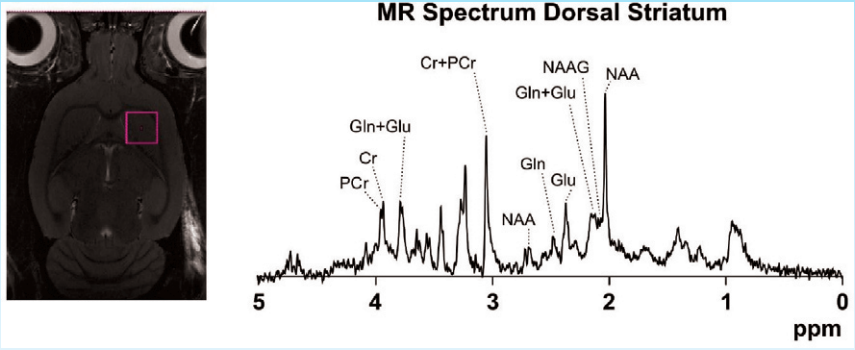


Figure 3: Neurometabolite concentrations (in ppm) as measured in vivo using MR spectroscopy from a cubic voxel 27µL in dorsal striatum. Modified from [3], CC-BY, version 4.0.

Detection of Synaptic Plasticity in the Brain

Structural plasticity is adaptive changes in the wiring of neuronal connections. The formation of new synapses is important when new neuronal connections are formed. This occurs in the normal brain under development and is also considered to occur in response to neuronal damage and other pathological processes seen in CNS disease. With the recent development of radioligands for imaging of the synaptic vesicle glycoprotein 2A (SV2A) it has now become possible to image this presynaptic protein, but it remains to be understood how the SV2A density reflects synaptic plasticity. At NRU, we make use of the tight integration between preclinical and clinical studies to investigate these critical functions.

Jens D. Mikkelsen
Laboratory Leader

Translational Pharmacology of the α7 Nicotinic Acetylcholine Receptor

The α7 nicotinic acetylcholine receptor (α7 nAChR) has been extensively studied as a drug target for treatment of cognitive impairment in Alzheimer's disease and schizophrenia but whereas agonists have shown some promise in rodent studies, randomized clinical trials have been disappointing. One explanation for this could be that the structure of the human α7 nAChR is different from rodents; for example, in contrast to animals most humans express the hybrid gene *CHRFAM7A*. Therefore, we used human induced pluripotent stem cell (hiPSC) derived neurons to establish a humanized α7 nAChR model. We established a cryobank of

neural stem cells that could reproducibly be matured into neural cultures expressing neuronal markers and genes *CHRNA7* and *CHRFAM7A*, encoding the α7 nAChR subunits and the duplication. The neurons responded to NMDA, GABA, and acetylcholine and exhibited synchronized spontaneous calcium oscillations. Notably, the cells did not respond to PNU-282987 and other α7 nAChR partial agonists alone. However, application of a range of α7 nAChR positive allosteric modulators (PNU-120595, TQS, JNJ-39393406 and AF58801) together with PNU-282987 demonstrated the presence of functional α7 nAChR in matured hiPSC-derived neurons. Pharmacological α7 nAChR activation also resulted in intracellular signaling as measured by ERK 1/2 phosphorylation and c-Fos protein expression. Moreover, PNU-120596 increased the frequency of the spontaneous calcium oscillations, demonstrating implication of α7 nAChR in human synaptic activity. Overall, we show that hiPSC derived neurons are an advanced *in vitro* model for studying human α7 nAChR receptor pharmacology and the involvement of this receptor in cellular processes as intracellular signaling and synaptic transmission [30].

Neuropsychology

The psychology group constitutes an NRU core facility that supports the interdisciplinary scientific approach undertaken at NRU to study human risk and resilience factors. We focus particularly on psychological factors related to the brain serotonin system, serotonergic pharmacology and clinical disorders.

In 2019, the psychology group took part in, and continues to take part in, investigating effects of the psychedelic drug psilocybin in healthy volunteers [33] and neuroinflammation in patients with mild traumatic brain injury [13]. As psilocybin acts on the 5-HT_{2A} receptor and is associated with long-term changes in personality trait Openness, we investigated whether unstimulated 5-HT_{2A} receptor levels are associated with individual differences in this trait in a large PET study of healthy individuals [45] but did not find evidence in favour of such association (**Figure 4**). We

Dea S. Stenbæk
Junior Group Leader

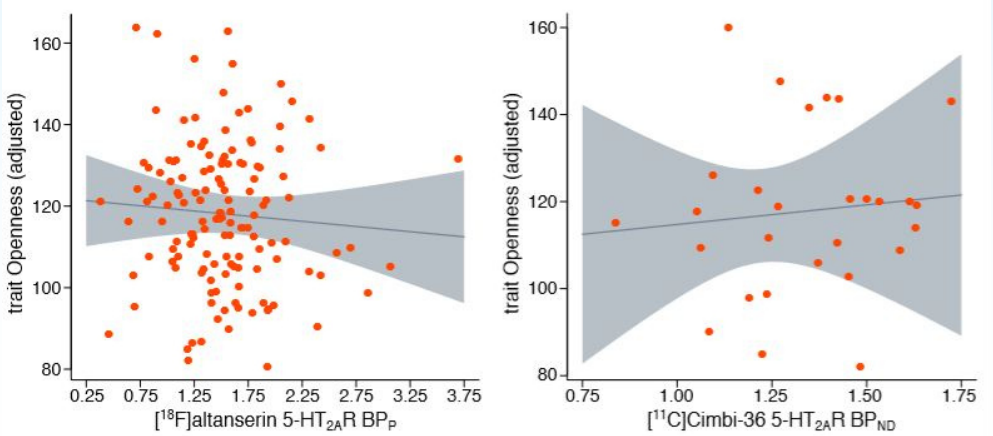


Figure 4: Two scatterplots of neocortex 5-HT_{2A}R binding imaged with [^{18}F]altanserin (n = 139) and [^{11}C]Cimbi-36 (n = 28), respectively, against trait Openness scores. Orange dots represent individual measurement points and lines and shading for each line represent slope estimates and 95% confidence intervals. Data shown are adjusted for age and sex. From [45], Copyright © 2019 Wiley Periodicals, Inc.

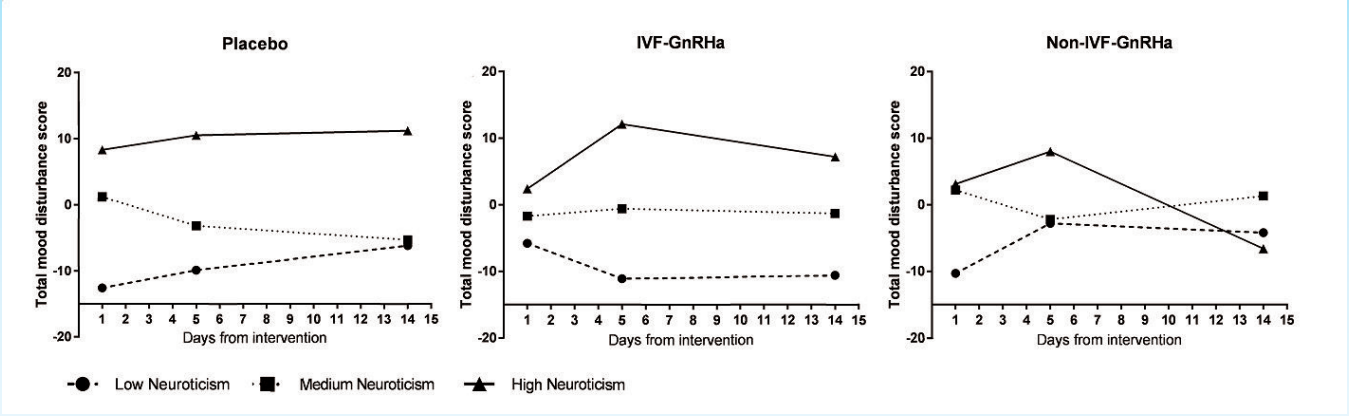


Figure 5: Illustration of mood development during 14 days of intervention for the three study groups across three categories of trait Neuroticism: Low, medium and high. The numbers of days are shown on the x-axis and total mood disturbances scores are shown on the y-axis. GnRHa=gonadotropin-releasing hormone agonist, IVF=in vitro fertilization. From [44], Copyright © 2019 Published by Elsevier Ltd.

also investigated personality trait Neuroticism as a vulnerability marker related to mood changes in healthy women undergoing pharmacological hormone manipulation [44]. We found that trait Neuroticism significantly modulated daily mood responses to pharmacological hormone manipulation, but not placebo (**Figure 5**). In another study [21], we investigated a related trait, known as sensory processing sensitivity (SPS), and showed that individuals with seasonal affective disorder have higher trait SPS in both remitted and symptomatic phase compared to matched healthy controls and that higher trait SPS is associated with greater depression severity in winter.

We have continued data collection and initiated several studies in collaboration with the Cambridge Cognition Group, UK, the Heart Centre at Rigshospitalet, the Copenhagen Business School, and Psychiatric Centre Copenhagen. One psychology master thesis project was successfully completed and we were again fortunate to accommodate several talented students from University of Copenhagen and University of Southern Denmark.

Data Analysis

Optimizations of data analysis pipelines using multivariate and machine learning methods have been a focus area for the data analysis group in the past years.

Claus Svarer
Chief engineer

Preprocessing Strategies in PET

In 2019, we published three papers dealing with different aspects of preprocessing strategies in PET. First, we reviewed the approaches used in 105 original research articles published by 21 different PET centres, using the PET tracer [^{11}C]DASB for quantification of cerebral serotonin transporter binding. We highlighted and quantified the impact of the remarkable variety of ways in which researchers are currently conducting their studies (**Figure 6**). Our review provided evidence that the foundation for a given choice of a preprocessing pipeline seems to be an overlooked aspect in modern PET neuroscience [37]. As a follow-up to this review, we systematically examined 384 different pipeline strategies in data from 30 healthy participants scanned twice using the radioligand [^{11}C]DASB. Five commonly used

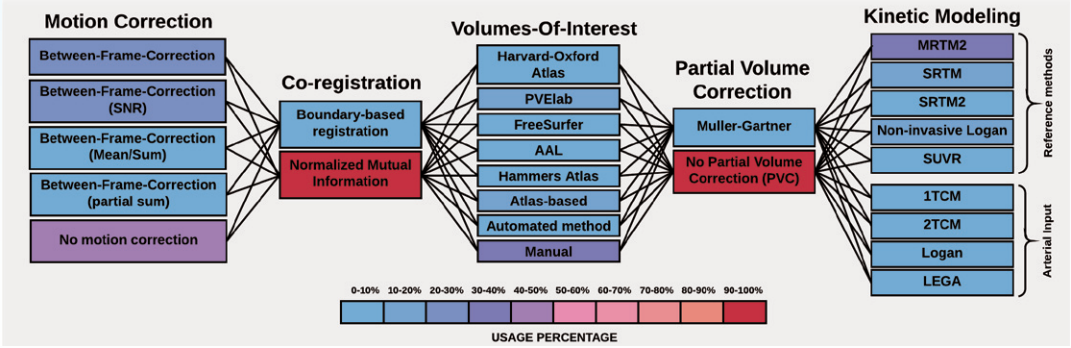


Figure 6: Schematic overview of the various preprocessing steps used in analyzing dynamic [^{11}C]DASB data. This ranges from different motion correction techniques, co-registration, volume-of-interest definitions, partial volume correction, and kinetic modeling. The colors indicate the percentage, in which a given step has been applied in the 105 [^{11}C]DASB PET studies. From [37], Copyright © 2019 The Authors.

preprocessing steps with two to four options were investigated: (1) motion correction, (2) co-registration, (3) delineation of volumes of interest, (4) partial volume correction, and (5) kinetic modeling. The results showed that statistical measures of bias, within- and between-subject variability were all markedly affected by the preprocessing strategy [38]. Finally, we also assessed the impact of preprocessing choices when the data is subsequently used for prediction [P1]. We demonstrated a framework for extending the non-parametric testing of statistical significance in predictive modeling by including a plausible set of preprocessing strategies to measure the predictive power (**Figure 7**). Our approach adopts permutation tests to estimate how likely we are to obtain a given predictive performance in an independent sample, depending on the preprocessing strategy used to generate the data.

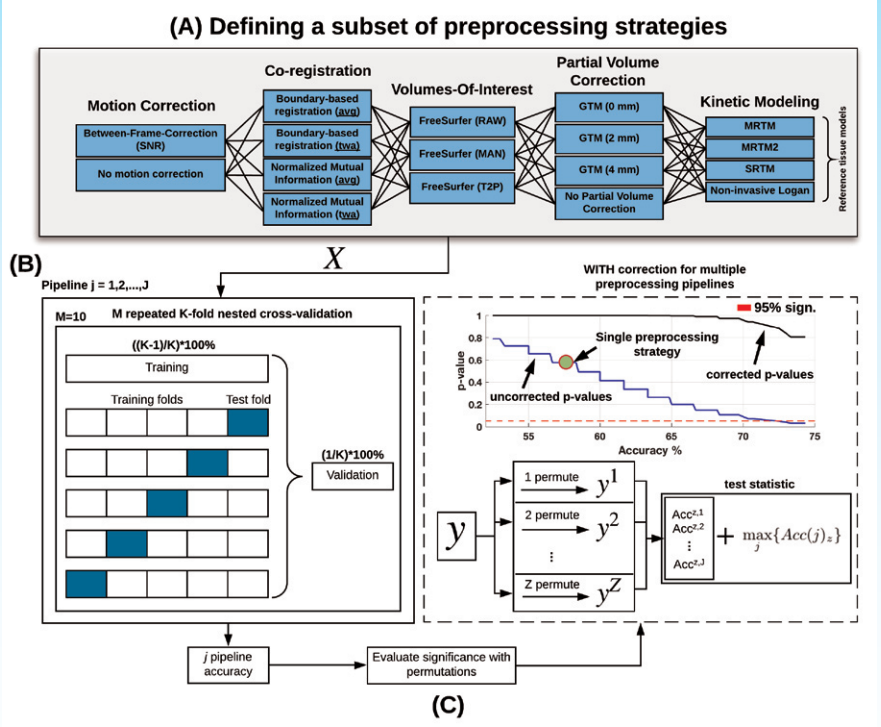


Figure 7: (A) Definition of a subset of preprocessing strategies j = 1, ..., J: This includes preprocessing steps such as motion correction, co-registration, delineation of volumes of interest, partial volume correction, and kinetic modeling. (B) Model selection and cross-validation: For each pipeline j, select a classification model (e.g. Linear Discriminant), and a K-fold nested cross-validation scheme with M repetitions. (C) Evaluate the significance with permutations: Randomly permute the class labels y, and re-run (B) for each pipeline j to obtain a classification accuracy for the z = 1, .., Z permutation. For each permutation z select the maximum accuracy across all preprocessing pipelines J and for Z permutations generate a null-distribution of maximum accuracies. Use the null-distribution of the max-accuracies to obtain the p-value for each pipeline at a significance level alpha. NOTE: uncorrected p-values refer to original accuracies according to their permuted null-distribution at a significance level alpha. From [P1], Copyright © 2019 The Authors.

Sleep-related Pharmacotherapies and Pharmacogenetics

NRU postdoc Sebastian Holst has, as part of his Marie Sklodowska-Curie Individual Fellowship, over the past two years used MRI to investigate a novel mechanism of human sleep known as glymphatic flow. We are currently preparing the results and interpretations from this study, but already last year we published two reviews summarizing current pharmacotherapies and pharmacogenetics related to sleep-wake regulation and disorders of the sleep-wake continuum [B1,B2]. Pharmacological treatments often are the first-line clinical option to improve disturbed sleep and wake states, but not all patients respond to pharmacotherapy in a uniform and beneficial fashion, partly due to genetic differences. The improved understanding of the neurochemical mechanisms regulating sleep and wakefulness and the mode of action of sleep-wake therapeutics has provided a conceptual framework, to search for functional genetic variants modifying individual drug response phenotypes.

Individualized Quantification of the Benefit from Reperfusion Therapy using Stroke Predictive Models

Thrombolysis is the treatment of choice for acute stroke. However, because it also increases the risk of intracranial hemorrhage, strict eligibility criteria for thrombolysis are needed. Current criteria (e.g. time of symptom onset <4.5 hours) are unsatisfactory as they ignore the individual stroke characteristics or are sometimes not available (e.g. wake-up stroke). In [39], we investigated the use of diffusion-weighted imaging (DWI) and perfusion-weighted imaging (PWI) to obtain an individualized quantification of the potential benefit of reperfusion therapy. We considered various predictive models (e.g. logistic regression and adaptive boosting) and processing strategies, and assessed their ability to correctly identify the final infarct based on the acute PWI-DWI values. We also proposed a visual representation of the brain combining the current infarct, the predicted risk of infarct, the predictive lesion volume if reperfusion and if no reperfusion (**Figure 8**). Together, they provide guidance to the clinician to understand how the patient would benefit from a thrombolysis.

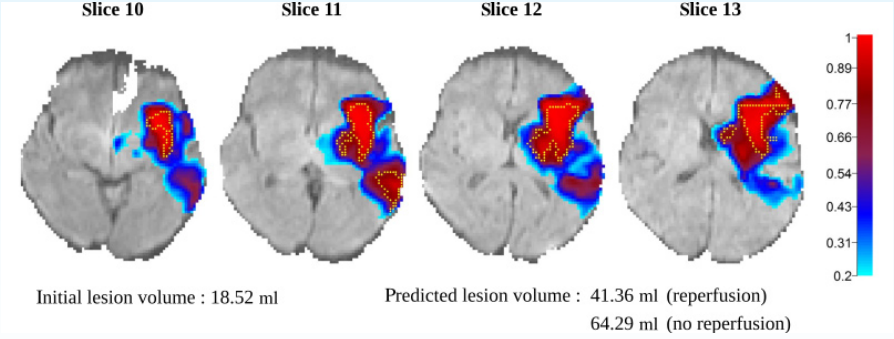


Figure 8: Acute risk of infarction estimated by the predictive model: red corresponding to high risk and blue to low risk. This risk is the probability of infarction at each voxel predicted by the statistical model (only risks above 0.2 are displayed). The acute lesion is outlined in yellow. The volume of the acute lesion, the predicted volume of the final lesion in case of reperfusion and non-reperfusion are reported below the slices. Modified from [39], Copyright © 2019 Federation of European Neuroscience Societies.


PEAKPERFORMANCE

Clinical Psychiatry

We use imaging to map brain architecture in risk and resilience to mental disorders to provide a rationale for targeted prevention and treatment. We hold expertise in frontier molecular brain imaging of key features of the serotonin signaling system [7], which is profoundly involved in mood disorders, schizophrenia, neurodegenerative disorders and their treatments. In particular, we are interested in serotonin brain biology as a driver of healthy adaptation to e.g. stressors, genetic make-up, personality [14], sex-steroid hormone milieu [17, 35, 45, 46], and healthy navigation in social relations.

Vibe G. Frøkjær
Group Leader

Sex-Steroid Hormones

The dynamic interplay between brain biology and sex-steroid hormone systems represents a potent driver of risk and resilience for neuropsychiatric disorders, which we aim to understand better in order to illuminate targetable risk and disease mechanisms. We have previously shown how sex-hormone manipulations may trigger depressive symptoms in some women; this involves changes in serotonergic signaling, functional brain connectivity, and emotion and reward processing. We propose that sensitivity to hormone transitions, such as across pregnancy and the postpartum period, may represent a clinically relevant and distinct subgroup within the broad diagnostic category of depression. To enable future precision medicine approaches to targeted prevention and treatment we need to find ways to identify hormone sensitive women at high risk for e.g. perinatal depression. Together with Elisabeth Binder´s lab at Max-Planck Institute in München, we have worked with candidate molecular markers of such risk and provided the first direct human evidence of the role of molecular oestrogen sensitivity demonstrated at the level of gene transcription by bridging observations from their clinical data and our sex hormone manipulation model [36]. Likewise, we have demonstrated that the susceptibility to sex hormone triggered mood reactions depends, at least partially, on women's general tendency to experience distress in terms of personality trait Neuroticism [44]. Such personality measures may thus also represent relevant stratification markers for directing preventive strategies e.g. in reproductive care.

In a study on women of fertile age we found that lower serum levels of allopregnanolone, a metabolite of the sex hormone progesterone, were associated with higher serotonin transporter (SERT) binding in the prefrontal cortex. Also, allopregnanolone levels were found to be negatively associated with measures of alertness, although this finding was not mediated by prefrontal

cortex SERT binding (**Figure 9**). These findings suggest a link between the typical psychological well-being experienced in the follicular phase when allopregnanolone levels are low and higher SERT in the prefrontal cortex, a region for higher cognitive functions and top-down regulation of emotions.

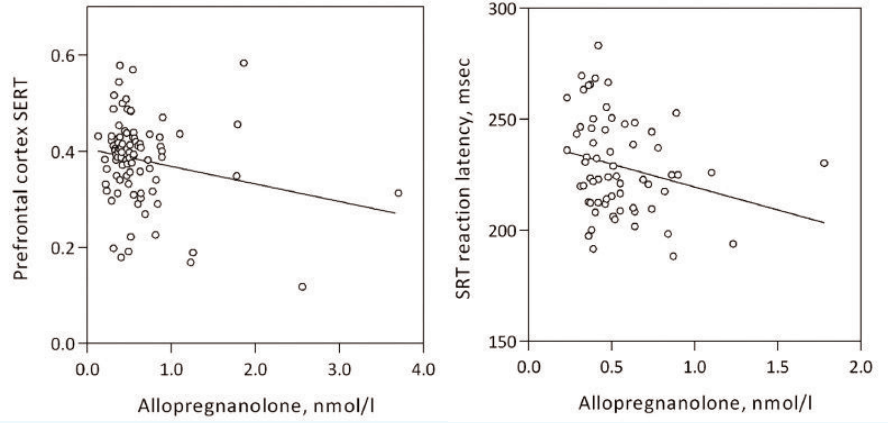


Figure 9: Linear association between serum allo-pregnanolone level in women of fertile age and (left) prefrontal cortex SERT binding and (right) mean reaction latency in the simple reaction test. Left: slope = -0.038, SD = 0.017, beta = -0.248, p = 0.024. Right: Spearman's rho = -0.267, p = 0.033. From [46], Copyright © 2019 the authors.

In ongoing studies, Sapere Aude recipient Vibe Frøkjær and her group pursue opportunities to protect mother and infant mental health across pregnancy and the postpartum in high risk groups.

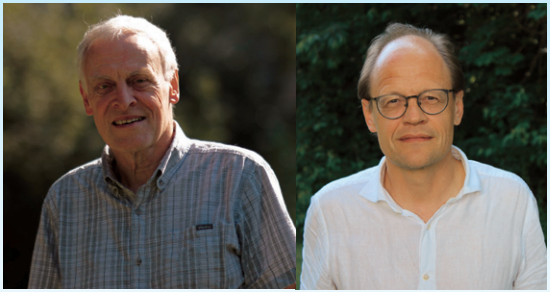
Aggression

Aggressive behavior is an enormous societal challenge. We pursue an interest in the neural mechanisms involved in aggression which may inform anti-aggressive treatments strategies and prevention of violence. We have shown that men with higher impulsive aggression trait scores respond to fearful faces with higher amygdala reactivity, relative to individuals with low scores, which suggest that impulsive aggression is associated with amygdyla overreactivity to submissive cues [6].

Interpreting and responding to facial expressions is critical for appropriate social interactions and behavioral decisions within complex social environments. We examined whether criminally violent offenders show altered brain responses to a threatening faces fMRI paradigm compared to healthy controls. We found that the amygdala, a core threat-processing brain region, was more responsive in criminally violent offender [6]. Further, that amygdala response was positively related to a composite measure of impulsive aggression. These findings indicate that criminally violent offenders have altered threat-processing neural circuits, which possibly mediates a proneness to impulsive and aggressive behavior. These findings highlight neural mechanisms that may be targeted in treatment strategies for clinically aggressive or antisocial behavior.

Clinical Neurology

Epilepsy



Olaf B. Paulson & Lars H. Pinborg
Group Leaders

Patients with medically intractable epilepsy and with a focal start in the brain are possible candidates for epilepsy surgery. In Denmark, epilepsy surgery is centralized at Rigshospitalet, and annually, approximately 100 patients are evaluated here and at the Epilepsy Hospital Filadelfia in Dianalund.

At NRU we work together with several national and international groups to identify new targets for anti-epileptic drug (AED) treatment or alternative strategies to AED treatment such as gene therapy. Together with professor Merab Kokaya from Lund University we showed that application of neuropeptide Y to tissue resected during epilepsy surgery and kept alive *in vitro* for 48 hours exerted a significant inhibitory effect on epileptiform activity [53]. As part of a PhD study with professor Lars Juhl Jensen from the University of Copenhagen, we used transcriptome analysis in tissue resected during epilepsy surgery to provide a robust list of candidate genes involved in temporal lobe epilepsy such genes involved in the immune system and druggable voltage gated potassium [26].

The object of several studies with professor Sandor Beniczky from the Danish Epilepsy Centre in Dianalund was to improve methods for localizing the epileptogenic zone before epilepsy surgery. We showed that the diagnostic yield of EEG is higher at a recording duration of 4 days using 25 electrodes compared to 90 mins using 256 electrodes (**Figure 10**) [2]. In 141 consecutive patients from the Danish epilepsy surgery program, EEG and MEG were recorded simultaneously. Electromagnetic source imaging localized epileptiform discharges in 94 patients (67%), and most of the epileptiform discharge clusters (72%) were identified by both modalities, but interestingly 15% only by EEG, and 14% only by MEG [11].

Living a future life without AEDs is an important motive for patients evaluated for epilepsy surgery. In a clinical study with professor Anne Sabers from Rigshospitalet, we demonstrated that despite being seizure free for more than 3 years after epilepsy surgery, the majority of our patients still take anti-epileptic drugs mainly related to their fear of relapse [15].

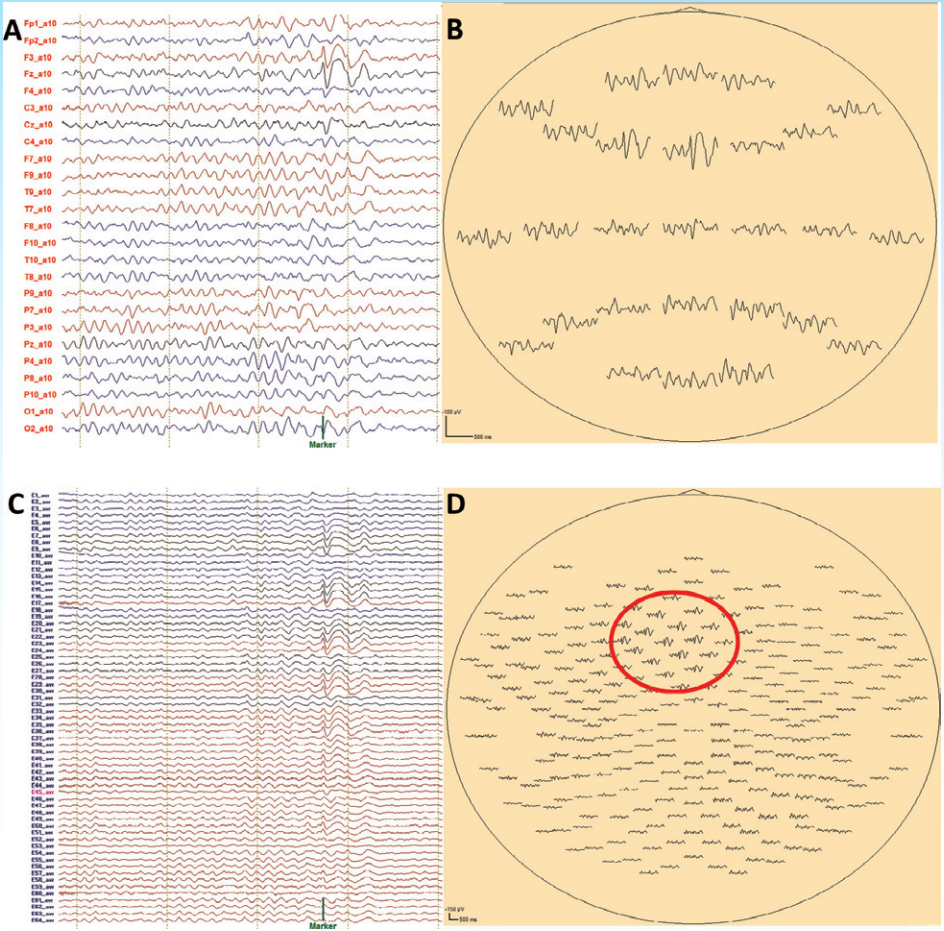


Figure 10: Low-density (LD) and high-density (HD) EEG arrays in a patient with right parietal focus. A and B: LD array. C and D: HD array. Spikes are at the green vertical marker in A and C, and highlighted by the red circle in D. From [2], Copyright © 2019 International Federation of Clinical Neurophysiology.

Mild traumatic brain injury

We here tested the hypothesis that neuroinflammation is present in mild traumatic brain injury and persists in patients that develop post-concussion symptoms (**Figure 11**). We used [^{123}I]CLINDE SPECT binding to TSPO as a biomarker of regional neuroinflammation in the brain. Compared to healthy subjects, the binding to TSPO in all 14 patients was increased 1-2 weeks after mild traumatic injury (range 2%-19%). After 3-4 months, TSPO was increased in all seven patients with persistent post-concussion symptoms (range 13%-27%) and in most patients with a good recovery (range -9%-17%) [13].

Cardiac surgery

In close collaboration with the cardiac anesthesiologists and surgeons at Rigshospitalet, we have collaborated in the perfusion pressure cerebral infarcts trial of patients undergoing cardiac surgery with cardiopulmonary bypass. The patients were allocated to a mean arterial pressure of either 70-80 mm Hg (high-target) or 40-50 mm Hg (low-target). We previously reported that new cerebral infracts were slightly, non-significantly lower in the low-target group. Here we observed that domain-specific patterns of postoperative cognitive dysfunction (POCD) were comparable between groups [51]. Further no significant association was found between intraoperative regional cerebral oxygen saturation as measured by near-infrared spectroscopy and POCD [23].

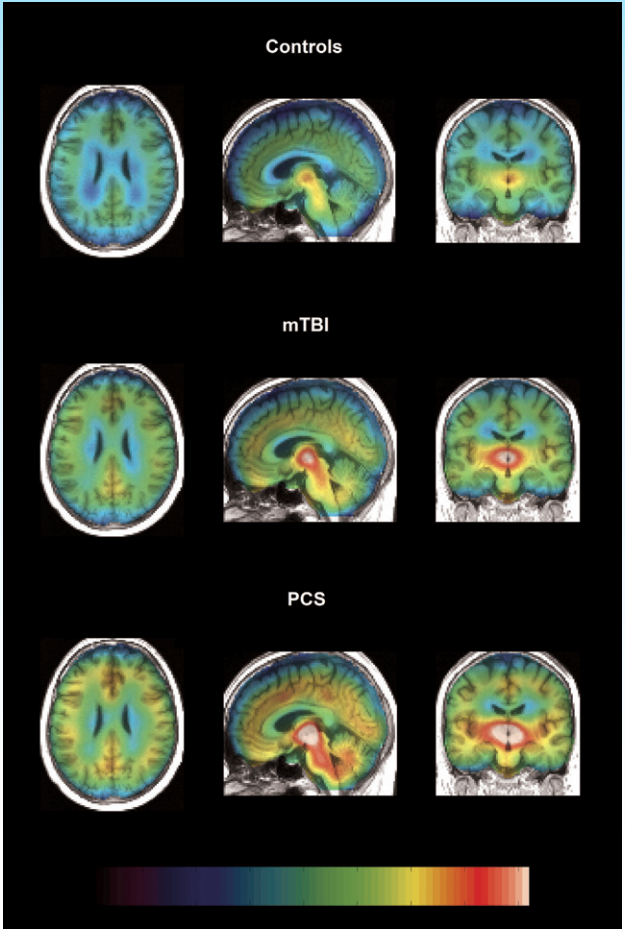


Figure 11: Combined normalized [^{123}I]CLINDE SPECT images of all high-affinity binder participants: 12 healthy controls, seven patients scanned at 1-2 weeks post-injury [mild traumatic brain injury (mTBI)] and six patients with three or more persistent symptoms scanned at 3-4 months post-injury [post-concussion symptoms (PCS)]. SPECT images were normalized by using the mean activity from 30-90 min after tracer injection divided by the area under the curve for the plasma input function from 0-90 min and combined in standard space by averaging images groupwise. From [13], Copyright © 2019 EAN.

Glucocorticoid treatment in childhood

In close collaboration with the Department of Paediatrics at Rigshospitalet and the Danish Research Centre for Magnetic Resonance at Hvidovre Hospital, we have investigated the potential side effect of glucocorticoid treatment. Glucocorticoids are widely used in the treatment of several pediatric diseases with undisputed disease-related benefits, but glucocorticoids also have some side effects. Previously, we observed smaller total brain volumes in children with glucocorticoid treatment. We now disclosed reduced subcortical grey matter volumes and lower right hippocampal mean diffusivity later in life [22].

Migraine

In close collaboration with the Human Migraine Research Unit at the Danish Headache Centre, Rigshospitalet, we have conducted a series of research projects that aimed to elucidate the effect of vasoactive migraine-inducing substances. An important novel finding obtained with 3T MR was that both sildenafil and calcitonin gene-related peptide dilate intradural arteries, supporting the notion that all known pharmacological migraine triggers dilate cephalic vessels [4]. In another study it was further investigated whether higher 7T magnetic field would lower variance, but the results showed that the dilation was comparable between 3T and 7T. Thus, the findings suggest no gain from the increase in voxel resolution but cemented dilatory findings [5]. Furthermore, we have conducted a series of research projects that aimed to elucidate the effect of the serotonin system in migraine [9,10]. These are described later in the report (see page 46).

Consciousness in the Neurocritical Patient (CONNECT-ME)

In this project, under the leadership of associate professor Daniel Kondziella, the wish is to establish a cutting-edge tertiary care clinical service for unresponsive patients in the intensive care unit and lay the foundation for a fruitful multidisciplinary research environment for the study of consciousness in acute brain injury. Of note, CONNECT-ME will not only enhance our understanding of consciousness disorders in acute brain injury but it will also raise awareness for these patients who, for obvious reasons, have lacked a voice so far. Pupillary dilatation occurs with many kinds of mental or emotional processes, following sympathetic activation or parasympathetic inhibition. These reactions are controlled by subcortical and cortical structures that are directly or indirectly connected to the brainstem pupillary innervation system, as reviewed in [40]. In preparation for the bedside evaluation of the neurocritical patient, we have investigated automated pupillometry and when combined with mental arithmetic, this appears to be a promising paradigm for the detection of covert consciousness in people with brain injury [49]. We investigated the pupillary light reflex in stroke patients and found that cortical infarcts of the prefrontal eye field or insula did not impair the pupillary light reflex in humans [50]. We found, however, subtle changes when the pupils dilate back to baseline, probably due to autonomic dysfunction.

The NRU Neuroimaging Laboratory

New brain research dedicated Siemens Prisma 3T MRI

As mentioned in the Preface, NRU acquired in 2019 a Siemens 3T Prisma MRI (see photo below). The scanner was delivered in October 2019 to the new North Wing construction at Rigshospitalet. This state-of-the-art MRI will facilitate high-quality structural and functional MRI. We have fMRI capabilities including noise-canceling headphones for auditory stimuli, a 40" high-definition MRI-compatible screen for visual display and hand-contoured response equipment for measuring behavioral responses. Our collaboration with Siemens has coupled these hardware tools with top-of-the-line functional sequences to delineate key aspects of brain function and connectivity.

Patrick Fisher
MR Group Leader

Siemens MRI Applications Specialist Karen Kettless has been integral in establishing foundational structural and functional sequences. Her sequence optimization expertise has facilitated the adaptation of the cutting-edge MREG sequence, troubleshooting functional imaging challenges, and expansion of spectroscopy imaging capabilities.

Functional MRI (fMRI) can be used to assay features of brain function and connectivity that map onto 1) relevant behavioral and molecular phenotypes and 2) intervention

strategies in healthy and clinical populations. For many projects, 2019 saw the completion of numerous projects applying fMRI and represented a period of transition to the laborious process of analyzing and evaluating these data with an eye toward numerous publications in 2020.

New molecular imaging SPECT-CT system

The SPECT scanner facility will soon re-open in a new location, at the ground floor close to the main entrance of the North Wing of Rigshospitalet. Here, a brand-new 3rd generation high-resolution AnyScan SPECT-CT Mediso scanner was installed in the Fall of 2019 (see cover image). The staff has been trained in operating the new scanner which has unprecedented spatial resolution and high sensitivity. Preliminary phantom studies (see photos on next page) show really good results and expectations are high for the new scanner, both clinically and research-wise.

Gerda Thomsen
SPECT Laboratory Leader

Clinical work

Patients with neurological disorders are referred to the NRU SPECT-laboratory for diagnostic SPECT investigations from Dept. of Neurology, Rigshospitalet, Dianalund and other hospitals in Denmark. The diagnostic investigations include:

- **Regional cerebral blood flow with the SPECT ligand [^{99m}Tc]HMPAO**

  This examination is mostly used as a technique for localizing the epileptic focus in patients with drug-resistant epilepsy that are candidates for epilepsy surgery. We are the only laboratory in Denmark to conduct ictal-interictal SPECT imaging with co-registration to MRI (SISCOM). This requires personnel specifically trained to inject as soon as the epileptic activity commences.

- **Striatal dopamine transporter imaging with the SPECT ligand [^{123}I]FP-CIT**

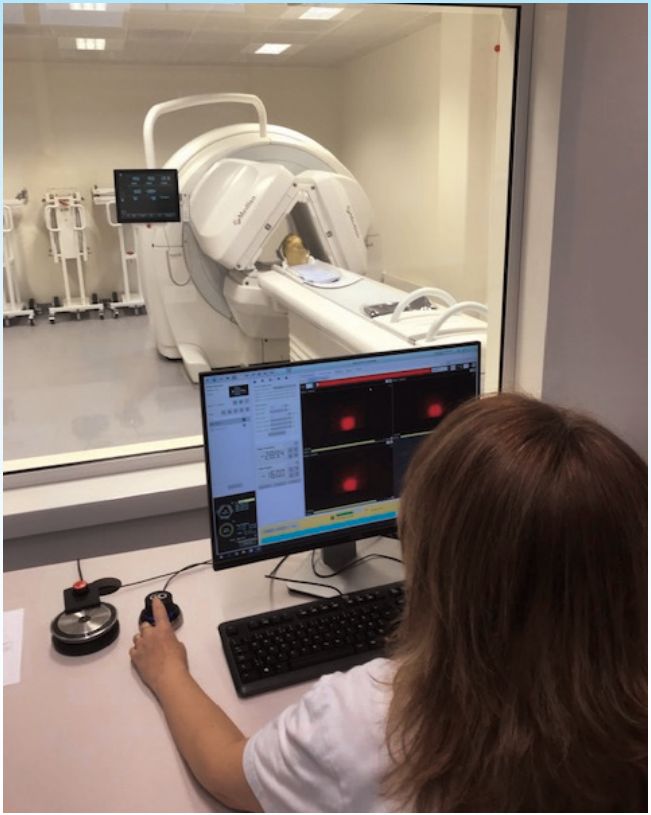
  This is a robust technique for early detection of dopaminergic deficits and is helpful when considering differential diagnoses in patients with movements disorder and/or dementias. The diagnostic report comes with a reference to a healthy age-matched population and is evaluated and commented by a neurologist specialized in reading the DAT-SPECT scan data.

- **[^{123}I]CLINDE SPECT for imaging of neuroinflammation**

  This technique is currently offered primarily as a research tool but also used in special patient cases for imaging of neuroinflammation in terms of the Translocator Protein. This protein is mainly found on the outer mitochondrial membrane and is upregulated when glial cells are activated.

Research projects

The SPECT-laboratory is also engaged in several ongoing research projects. We have performed [^{123}I]CLINDE-SPECT investigations in our recently published study on the role of neuroinflammation in patients with brain concussion [13] and in another ongoing study on neuroinflammation in patients with multiple sclerosis. Furthermore, we have performed several SPECT investigations as part of a collaboration project led by professor Anders Fink Jensen from the Psychiatric Centre Copenhagen, investigating if glucagon-like peptide-1 (GLP-1) receptor agonist stimulation reduces alcohol intake in people with alcohol dependence.



Cimbi Database and Biobank

At NRU, we have for more than a decade systematically investigated the 5-HT neurotransmitter system in humans by acquiring high-resolution brain imaging data (PET, MRI, rsMRI, and fMRI) from several hundreds of carefully screened and well-characterized healthy individuals and patients with various neuropsychiatric disorders. We have imaged the system to the extent that this is possible today, i.e. the serotonin transporter and the 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A}, and 5-HT_4 receptors. Thereby, we have been able to build a large cohort database (the **Cimbi Database**) that contains a wide range of imaging associated data including demographic, neuropsychological, biochemical, genetic and imaging data.

Peter Steen Jensen
Database Manager

Arafat Nasser
Biobank Manager

The **Cimbi biobank** is the associated collection of biological specimens from the cohort, including saliva, blood, and in some instances, urine and hair samples, which allow for additional biochemical and genetic analyses. In 2019, Arafat Nasser took over the responsibility for the biobank.

The Cimbi database and biobank represent a unique and valuable research instrument serving the purpose of storing the wealth of acquired data in a highly structured and safe manner as well as providing a quality-controlled resource for future hypothesis-generating and hypothesis-driven studies. From an international perspective, the comprehensive nature and the sample sizes are exceptional. In 2019 a total of 17 official requests for data were approved. Further, the database provided aggregated data that were used in a total of 19 publications in 2019.

Innovation Fund Denmark

NeuroPharm

Center for Experimental Medicine Neuropharmacology

The Center for Experimental Medicine Neuropharmacology (*NeuroPharm*) is funded by the Innovation Fund Denmark and resides at NRU. National partners include the pharmaceutical company H. Lundbeck A/S and four academic partners: one from University of Copenhagen and three from university hospitals in the Capital Region of Denmark, while international partners include Massachusetts General Hospital/Harvard and the British-based small-medium sized enterprise, Invicro LLC. Additionally, Imperial College London and the two large pharmaceutical drug companies Pfizer Inc. in USA and Takeda in Japan are involved as affiliated partners.

The short-term goal of *NeuroPharm* is to answer pertinent and basic questions regarding human brain disease mechanisms and predict brain responses to categories of neuromodulatory interventions as well as treatment efficacy.

The research in *NeuroPharm* is divided into four work packages (NP1-4) which are described in detail below.

Vibe G. Frøkjær
NP1 WP-leader

NP1: Treatment outcome in Major Depressive Disorder

The goal of this work package is to identify neurobiological and other predictors of response to pharmacological treatment of depression. The research will illuminate basic mechanisms of action of pharmacological treatment of Major Depressive Disorder (MDD) and will, in the long term, provide a rationale for tailored treatment choice for MDD patients based on predictors such as quantitative measures of brain function, rather than - as is the case today - rely exclusively on clinical assessment.

We have enrolled a total of 100 MDD patients and examined how different markers (neuropsychology, MRI, PET, EEG) relate to the outcome of a standard antidepressant treatment, i.e., escitalopram, adjusted contingent on effects and side effects. Patients have been followed across a period of 12 weeks from treatment start. Neuroimaging was repeated at week 8 in a subgroup of 40 patients with variable antidepressant response. We work now to prepare NP1 results and interpretations, which will be published through 2020.

Patrick Fisher
NP2 WP-leader

NP2: 5-HT_{2A}R modulation effects on neurobiology, cognition and mood

The goal of NP2 is to apply an experimental medicine strategy coupled with human functional neuroimaging to elucidate the effects of 5-HT_{2A} receptor (5-HT_{2A}R) modulation on brain function and mood in healthy individuals. We are comparing psilocybin (5-HT_{2A}R agonist) and ketanserin (5-HT_{2A}R antagonist) effects on brain function to identify neural mechanisms mediating the clinical effects of psilocybin and, more broadly, to establish this comparative strategy as a pathway for delineating pharmacological effects on the brain in humans.

Data collection for the first and second subproject is completed. These projects focus on 1) 5-HT_{2A}R occupancy in with [^{11}C]Cimbi-36 in healthy volunteers and 2) lasting changes in 5-HT_{2A}R and personality following a single psilocybin administration in psychedelic naïve healthy volunteers. The third and final subproject evaluates psilocybin and ketanserin effects on brain connectivity and blood flow measured with MRI. Data collection for this subproject is on-going with 14 out of 30 datasets collected through 2019. We aim to finish data collection in early 2020.

In recent years, numerous small clinical studies have provided compelling initial evidence that psilocybin provides therapeutic benefits to a range of neuropsychiatric illnesses, including depression, addiction and anxiety. Psilocybin is a serotonin psychedelic, the psychoactive constituent in *magic mushrooms*, and has perceptual effects that depend on 5-HT_{2A}R signaling. To further its clinical application, detailing the pharmacokinetic profile of psilocybin in the human brain is critical. In 2019, we applied our unique expertise in imaging the living human brain serotonin system and published the first ever study demonstrating psilocybin occupancy of 5-HT_{2A}R [33]. Eight healthy individuals completed [^{11}C]Cimbi-36 PET scans before and immediately following psilocybin administration. We measured the change in [^{11}C]Cimbi-36 PET signal to determine the fraction of 5-HT_{2A}R occupied by psilocybin during the psychedelic experience and whether this occupancy related to psilocybin dose, concentration in blood and perceptual effects. [^{11}C]Cimbi-36 is a 5-HT_{2A}R agonist PET radioligand developed and validated through our strong and close collaboration with Department of Drug Design and Pharmacology at University of Copenhagen and Department of Clinical Physiology, Nuclear Medicine and PET at Rigshospitalet. We observed that we could effectively measure psilocybin 5-HT_{2A}R occupancy with [^{11}C]Cimbi-36 PET and that the amount of 5-HT_{2A}R occupancy strongly correlated with psilocybin dose, drug levels in blood and perceptual effects (**Figure 12**). The close association with psilocybin dose and drug levels enables clinicians to more effectively calibrate dosing in patients. The association with perceptual effects converges with the central role of 5-HT_{2A}R signaling in mediating those perceptual effects. Our study represents the first ever brain imaging study in humans with a serotonin psychedelic in Denmark. As

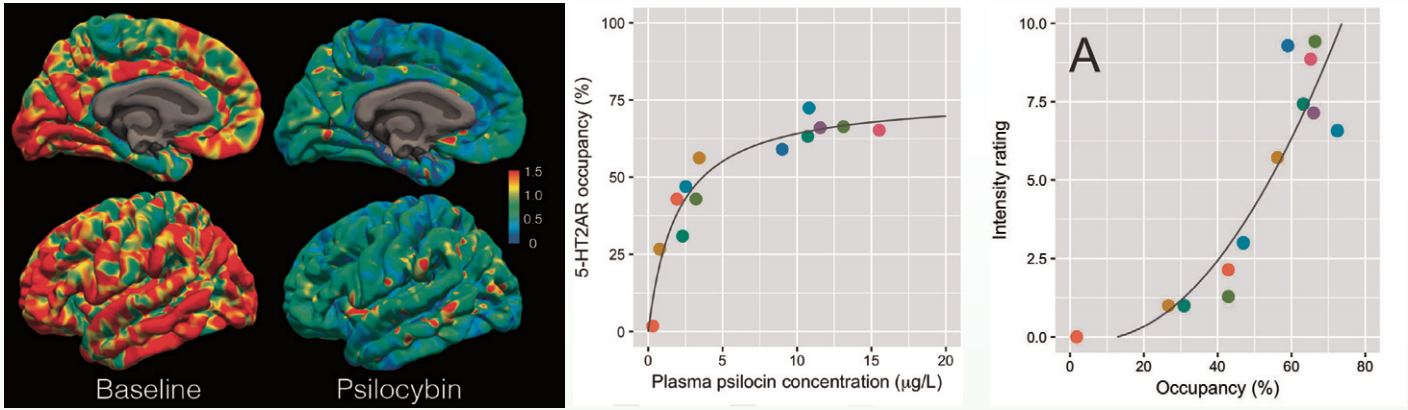


Figure 12: (Left panel) Psilocybin occupancy of 5-HT$_{2A}$R. [^{11}C]Cimbi-36 BP$_{ND}$ map of the cortical surface of the left hemisphere of Subject 5 at baseline and at the first post-psilocybin intervention scan. Color bar in units BP$_{ND}$. (Middle panel) Relationship between mean within-scan plasma psilocin levels and neocortical 5-HT$_{2A}$R occupancy. Estimated EC50 [95% CI]: 1.95 [1.16; 3.15] µg/L and Occ$_{max}$ [95% CI]: 76.6 [67.3; 88.0]%. (Right panel) Relationship between subjective intensity ratings of the psychedelic experience at the time of the PET scan and neocortical 5-HT$_{2A}$R occupancy. The fitted line was obtained using a quadratic function. From [33], Copyright © American College of Neuropsychopharmacology 2019.

the first such study to establish receptor occupancy in the living human brain, this study demonstrates how the interdisciplinary and collaborative research promoted at NRU can lead the development and application of cutting-edge tools ([^{11}C]Cimbi-36 PET) and novel therapeutics (psilocybin) to detail clinically relevant brain mechanisms.

In addition to our first publication [33], we have participated in numerous events disseminating NP2-related findings. Prof. Knudsen chaired a symposium at the 2019 European College of Neuropsychopharmacology annual meeting, held in Copenhage. NP2 PhD student Martin K. Madsen presented our findings at this symposium to a packed auditorium of 500 people. Dr. Madsen also appeared on the national morning program, *Go'morgen Danmark*, to discuss psychedelic research. NP2 WP-leader Dr. Patrick Fisher participated in a panel discussion about psychedelics with Michael Pollan, author of the best-selling book about psychedelics "*How to Change Your Mind*". Finally, our NP2 neuropsychologist Dr. Dea Stenbæk participated in the radio program "*24 spørgsmål til professoren*" to discuss psychedelic research with best-selling author Lone Frank.

Hanne D. Hansen
NP3 WP-leader

NP3: Novel neuroimaging methods for an experimental medicine approach

The most prescribed anti-migraine drugs, the triptans, act as partial agonists on the 5-HT_{1B} receptor (5-HT_{1B}R) and it has long been speculated that serotonergic dysfunction is causally involved in the emergence of migraine attacks. In close collaboration with the Human Migraine Research Unit, led by professor Messoud Ashina at the Danish Headache Center, we have conducted a series of research projects that aim to elucidate the effect of the serotonin system in migraine.

It has long been debated whether sumatriptan can cross the blood-brain barrier and bind to the central 5-HT_{1B}Rs. In our most recent experiments [9, 10], we found that a single dose of sumatriptan results in a mean 5-HT_{1B}R occupancy of 16 %. This either indicates that sumatriptan indeed binds to the central receptors or that the migraine attack is associated with a release of endogenous serotonin (**Figure 13**).

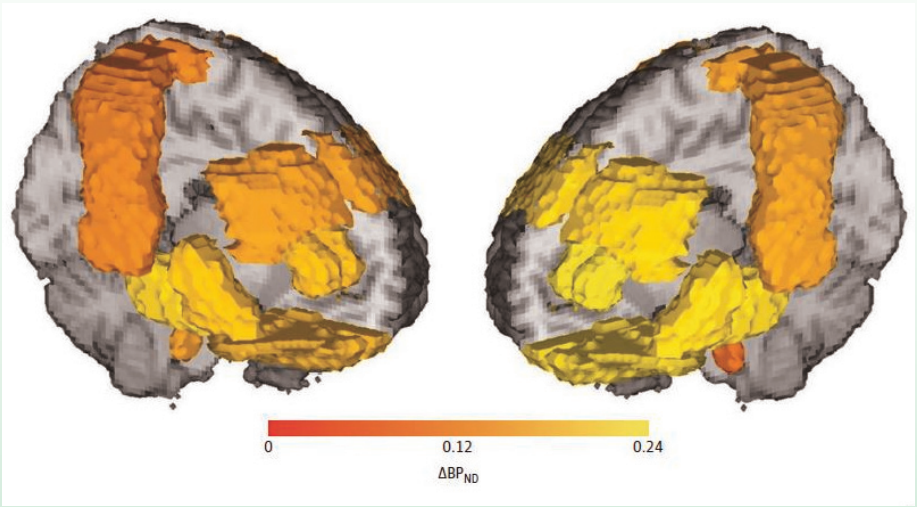
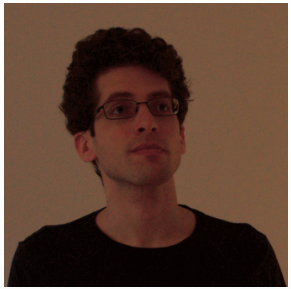


Figure 13: Group-based mean difference in nondisplaceable binding potential (BP_{ND}) for the region of interest analyzed. The color bar represents change in BP_{ND} between (left) interictal and ictal and between (right) ictal and postictal after sumatriptan. From [10], Copyright © 2019 American Medical Association.



Brice Ozenne
NP4 WP-leader

NP4: Bioinformatics, statistical and predictive models

NP4 aims at addressing the need for flexible statistical methods to analyse the data produced by the other work packages (NP1-3). We are particularly interested in Latent Variable Models (LVMs), a multivariate technique using latent variables, to model the relationship between indirect measurements of quantities of interest, e.g. of the brain serotonin level and the depression status of the patient. In this framework, we pursue our developments on efficient adjustments for multiple comparisons as well as corrections for the small sample bias of the maximum likelihood estimator. The software we developed is now being used in the analysis of the data collected in NP1, e.g., to assess the association between 5-HT_{2A}R binding and treatment response.

Assessing the ability of the cerebral serotonin level to predict patient response to antidepressant therapy is also a key element of *NeuroPharm*. We have investigated the influence of the data processing pipeline on the predictive performance (**Figure 14**) and proposed a procedure for quantifying the uncertainty of the performance for various processing strategies. We also work with NP2 to validate a statistical procedure able to identify relevant brain regions and test group differences in the selected brain regions using the same dataset.

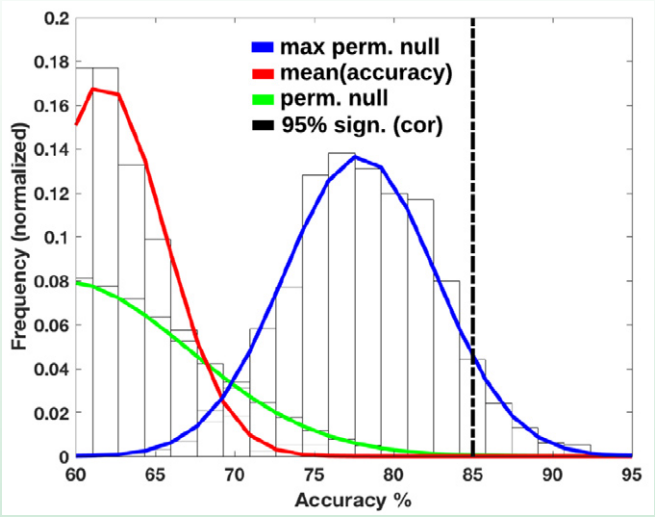


Figure 14: Comparison between the estimated distribution of the accuracy of the biomarker of interest (in red), the one of a non-informative biomarker for a pre-processing pipeline (in green) and for, when selecting among several pipelines, the pipeline giving the best accuracy (in blue). This figure shows that it is critical to account for pre-processing choices when evaluating the predictive performance of a biomarker, e.g., selecting the pre-processing pipeline for its predictive performance may positively bias the estimation of the predictive performance of a biomarker. Modified figure from [P1], Copyright © Springer Nature Switzerland AG 2019.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BrainDrugs

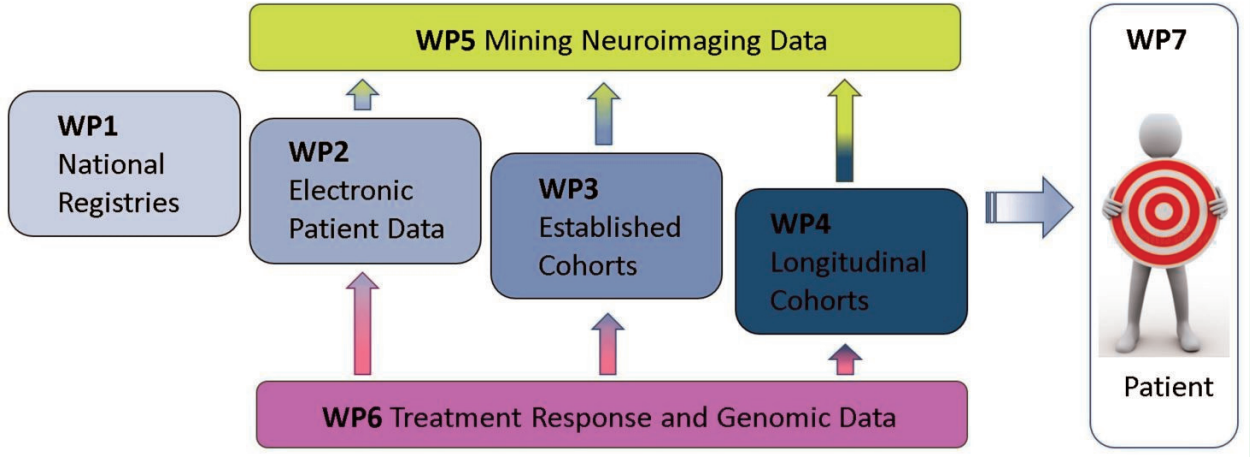
July 1st, 2019, we officially inaugurated the strategic alliance *BrainDrugs*, which is our large-scale precision medicine project in epilepsy and depression (https://nru.dk/index.php/braindrugs). The alliance is a 5-year project funded by 40 mio DKK from the Lundbeck Foundation aiming at establishing which key features predict drug response in patients with epilepsy or depression. The alliance builds on strong cross-disciplinary research environments within universities and hospitals in Denmark and is supported by two European partners from Lausanne University Hospital, Switzerland and VU University Medical Center in Amsterdam, the Netherlands. The involved Danish institutions span several different departments at Copenhagen University Hospital, Rigshospitalet, University of Copenhagen, Aarhus University Hospital, and Aarhus University, as well as the Filadelfia Epilepsy Hospital and three different mental health centers from the Capital Region of Denmark; Psychiatric Center Copenhagen, Psychiatric Center Glostrup, and Mental Health Center Sct. Hans.

The background for the *BrainDrugs* project is that there is currently an enormous unmet need for the development of effective precision medicine approaches for brain disorders. More precise treatment strategies are needed to replace the present "one-size-fits-all" and subsequent "trial-and-error" approach currently applied in our patients. An important step to achieve this goal is to uncover endophenotypes and biomarkers that can critically help to stratify patient cohorts.

To enable stratification of patients based on their underlying pathogenetic and pathophysiological brain disturbances will provide "enriched" patient populations that are more likely to benefit from specific interventions. Stratification will also be enormously beneficial for interpretation of clinical trials that aim to test new compounds and is essential to allow for an optimised treatment of patients with brain disorders. Another important challenge is to determine the target engagement of pharmacological interventions, and to predict occupancy based on, e.g., plasma drug concentrations.

With *BrainDrugs*, we have chosen to study epilepsy and depression because they are frequent and devastating brain disorders with significant comorbidity. Further, both conditions are treated with pharmacological interventions that often fail to succeed, including failure due to intolerable adverse effects. Epilepsy often co-occurs with mood disorders and there is reason to believe that the comorbidity is underrecognized in both patient groups. Comorbidity is also associated with less favourable outcome of drug treatment. That is, there is a huge unmet medical need to better diagnose and treat these two serious brain disorders.

We will make use of Danish registries to identify associations between intake of brain targeting drugs and clinical outcomes in order to uncover which patient features define a successful antidepressive or antiepileptic drug treatment. To investigate if we can



identify patient subgroups, we will conduct advanced text-mining analyses that extract specific clinical features from electronic patient records. Through existing deep phenotyping or genetic databases with biobanks, those features will be related to, e.g., genetic and neuroimaging data to define biologically valid patient subgroups suffering from depression and epilepsy. To increase power to detect biomarkers and treatment response, we will establish new cohorts of patients with epilepsy and depression that we follow longitudinally. *BrainDrugs* will consist of seven coherent work packages, as depicted in the figure above.

It is our ambition to set the stage for a precision medicine approach in pharmacological treatment of epilepsy and depression, for the benefit of future patients. To succeed in our mission, we have devised a strategy for implementation of research outcomes in the clinic. It is our hope that in the long run, *BrainDrugs* can serve as a model to be implemented internationally, and for other brain disorders.

Positions of Trust

Gitte Moos Knudsen:

President of European College of Neuropsychopharmacology (ECNP) since 2019, chair of the Scientific Advisory Board for The Human Brain Project since 2017, and chairman of the Professors' Association at Rigshospitalet from 2017. Member of the Brain Prize Council since 2017, board member of the Elsass Foundation since 2015, and member of the Scientific Advisory Board of the Kristian G. Jebsen Foundation since 2014. Field Editor at the International Journal of Neuropsychopharmacology.

Olaf B. Paulson:

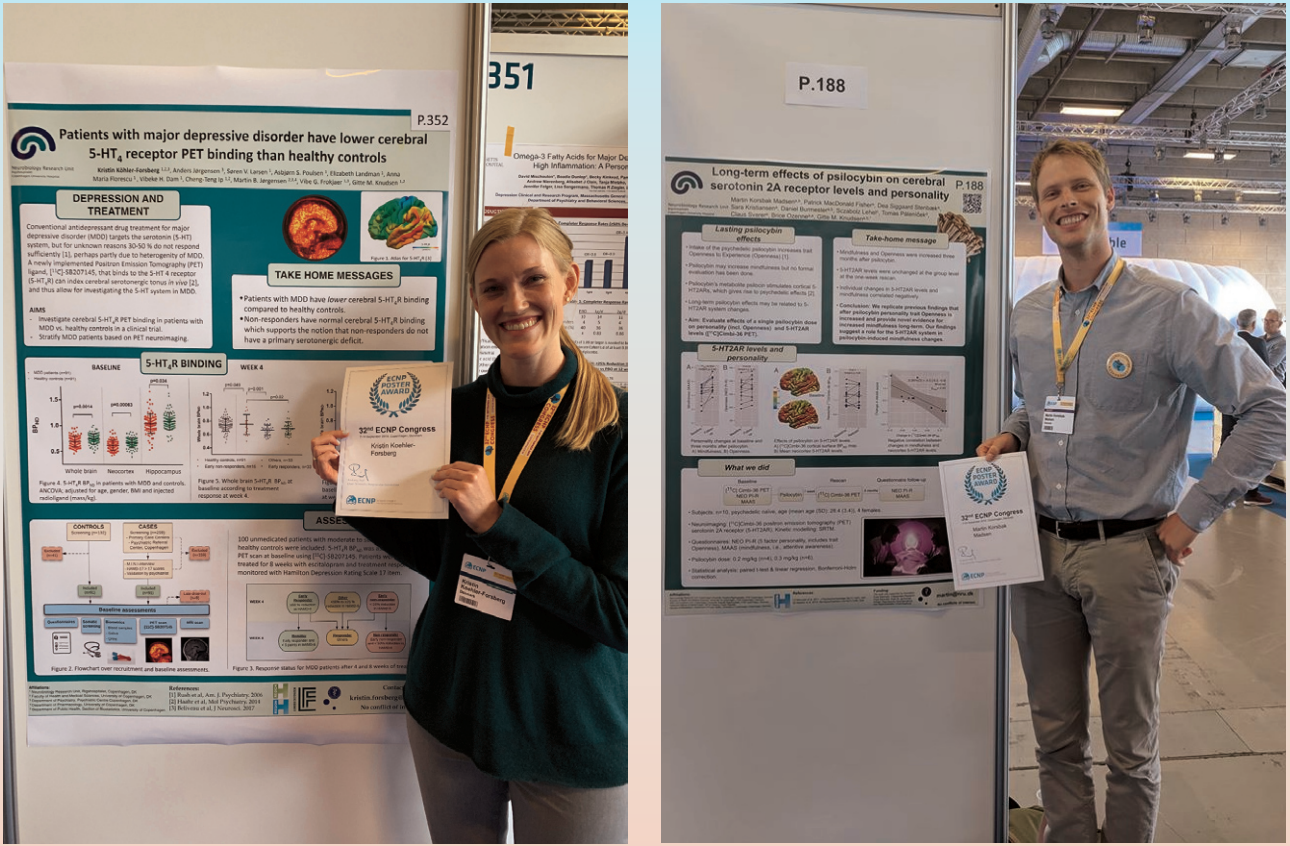
Member of the Research Ethical Committee for Science and Health at the University of Copenhagen since 2019 and of the Research Ethical Committee of the Capital Region of Denmark since 2015. Member of the International Advisory Board of the Wallenberg Centres of Molecular Medicine, Lund University, Sweden, since 2015. Auditor for Danish Society for Neuroscience since 2010. Referee for several international journals.

Jens D. Mikkelsen:

Member of the Independent Research Fund Denmark | Medical Sciences, member of the chairman committee for external evaluations of medical educations in Denmark, and member of the Academy for Technical Sciences.

Vibe G. Frøkjær:

Appointed Danish representative in the management committee for the EU-based Riseup-Post Partum Depression (PPD) COST Action since 2019, and appointed member of the Neuroimaging Network of ECNP since 2017. Board member of Danish Society for Affective Disorders. Coordinating research associate professor for PhD students in Psychiatry enrolled at University of Copenhagen.



PhD-students Kristin Forsberg and Martin Korsbak Madsen each received a poster award for their respective posters at the 2019 ECNP congress. Great examples of the high-quality research performed at NRU.

Publications 2019

Our most important form of dissemination is through publications in high impact peer-reviewed journals. We also communicate our results at national and international meetings and thereby establish and maintain national and international recognition. We edit and contribute chapters to Danish medical textbooks within brain-related topics. Broader public dissemination is also prioritized. We contribute with articles in popular journals, give public lectures, and participate in interviews for newspapers, TV and radio.

NRU has in 2019 published a total of 4 PhD dissertations, 16 Master's or Bachelor theses, and 53 scientific peer-reviewed papers.

PhD dissertations

- Marie Deen Christensen. PET investigations of brain serotonin receptor binding in migraine patients. University of Copenhagen, Faculty of Health and Medical Sciences. Defended Jan 4, 2019
- Mette Thrane Foged. Epilepsy surgery: Outcomes of the Danish evaluation program and development of new EEG based methods. University of Copenhagen, Faculty of Health and Medical Sciences. Defended Apr 26, 2019
- Martin Nørgaard. Optimizing Preprocessing Pipelines in PET/MR Neuroimaging. University of Copenhagen, Faculty of Health and Medical Sciences. Defended May 3, 2019
- Elina Tampio L 'Estrade. Development and Evaluation of Potential 5-HT7 Receptor PET Tracer Candidates. University of Copenhagen, Faculty of Health and Medical Sciences. Defended May 6, 2019

Theses and reports

The following list of NRU-affiliated students have successfully defended their theses or research year reports during 2019:

- Ali Ilhan, "Likelihood Estimation of Drug Occupancy using PET – Generalization to Multiple Doses", Master's thesis in Biomedical Engineering, DTU & University of Copenhagen
- Andreas Kirknæs Færk, "A correlational study of the relationship between perceived stress and verbal affective memory", Master's thesis in Psychology, University of Copenhagen
- Annemette Ringsted, "Chemogenetic Activation of Neurons in Anterior Cingulate Cortex and Striatum Enhance Rearing in Rats", Master's thesis in Engineering in Biotechnology, DTU
- Dorte Bonde Zilstorff, "Effects of adrenergic antagonists on recovery sleep", Master's thesis in Medicine, University of Copenhagen

- Emily Barot, “Optimisation of voxelwise and surface-based preprocessing pipelines for PET data”, Master’s thesis in Bioinformatics, University of Copenhagen
- Emily Beaman, “Effect of beta-blockers on the risk of Alzheimer's disease: A nation-wide cohort study”, Master’s thesis in Human Biology, University of Copenhagen
- Ida Marie Brandt, “Functional magnetic resonance imaging of reward processing in patients with major depressive disorder”, Master’s thesis in Molecular Biomedicine, University of Copenhagen
- Kristine Nielsen, “Evaluating measures of intra cranial volume in same-subject multiple MR images over time”, Master’s thesis in Bioinformatics, University of Copenhagen
- Maja Rou Marstrand-Jørgensen, “Resting-state default mode network functional connectivity is negatively associated with personality trait Openness to Experience”, Master’s thesis in Medicine, University of Copenhagen
- Niels Lorenzen, “Dynamic vs. static functional connectivity in resting-state fMRI”, Bachelor thesis in Molecular Biomedicine, University of Copenhagen
- Nikolaj Speth, “The 5-HT2a/5-HT2c pharmacology of psilocybin in relation to microdosing”, Master’s thesis in Pharmaceutical Sciences, University of Copenhagen
- Roberth Sethsen Petersen, “Synaptic vesicle glycoprotein 2A (SV2A) radioligand binding in the developing rat brain”, Master’s thesis in Molecular Medicine, Aarhus University
- Saba Ali & Mariam Labrouzi, “Synaptic vesicle glycoprotein 2A (SV2A) as a measure of synaptic plasticity in animal models of depression”, Master’s thesis in Biomedicine, Roskilde University
- Sofie Theilmann Kristensen, “Validation of the memory test MEMPAIR – A psycholinguistic study assessing semantic priming and behavioral response to affective information”, Master’s thesis in Linguistics, University of Copenhagen
- Sophia Armand, “Post-Traumatic Stress Disorder in Cardiac Arrest Survivors and Their Close Relatives - An Empirical Thesis in Psychotraumatology”, Master’s thesis in Psychology, University of Copenhagen
- Søren Vinther Larsen, “Use of oral contraceptives is associated with altered serotonergic brain architecture: A molecular brain imaging study in healthy women”, Master’s thesis in Medicine, University of Copenhagen

Book chapters

B1. Holst SC, Werth E, Landolt HP. Pharmacotherapy of Sleep-Wake Disorders. Praxis (Bern 1994). 2019 Jan;108(2):131-138. doi: 10.1024/1661-8157/a003189.

B2. Landolt HP, Holst SC, Valomon A. Clinical and Experimental Human Sleep-Wake Pharmacogenetics. Handb Exp Pharmacol. 2019;253:207-241. doi: 10.1007/164_2018_175.

Peer-reviewed conference proceedings

P1. Nørgaard M, Ozenne B, Svarer C, Frokjaer VG, Schain M, Strother SC, Ganz M. Preprocessing, Prediction, and Significance: Framework and Application to Brain Imaging. Springer Nature Switzerland AG 2019 D. Shen et al. (Eds.): MICCAI 2019, Lecture Notes in Computer Science 11767, pp. 196-204, 2019

Multicenter studies without co-authorships

- Perani D, Iaccarino L, Jacobs AH; IMBI Brain Imaging Working Group. Application of advanced brain positron emission tomography-based molecular imaging for a biological framework in neurodegenerative proteinopathies. Alzheimers Dement (Amst). 2019 Apr 16;11:327-332
- Perani D, Iaccarino L, Lammertsma AA, Windhorst AD, Edison P, Boellaard R, Hansson O, Nordberg A, Jacobs AH; IMBI Project. A new perspective for advanced positron emission tomography-based molecular imaging in neurodegenerative proteinopathies. Alzheimers Dement. 2019 Aug;15(8):1081-1103

Papers in peer-reviewed journals

1. Agren T, Millroth P, Andersson P, Ridzén M, Björkstrand J. Detailed analysis of skin conductance responses during a gambling task: Decision, anticipation, and outcomes. Psychophysiology. 2019 Jun;56(6):e13338

2. Bach Justesen A, Foged MT, Fabricius M, Skaarup C, Hamrouni N, Martens T, Paulson OB, Pinborg LH, Beniczky S. Diagnostic yield of high-density versus low-density EEG: The effect of spatial sampling, timing and duration of recording. Clin Neurophysiol. 2019 Nov;130(11):2060-206

3. Bærentzen S, Casado-Sainz A, Lange D, Shalgunov V, Tejada IM, Xiong M, L'Estrade ET, Edgar FG, Lee H, Herth MM, Palner M. The Chemogenetic Receptor Ligand Clozapine N-Oxide Induces in vivo Neuroreceptor Occupancy and Reduces Striatal Glutamate Levels. Front Neurosci. 2019 Apr 3;13:187

4. Christensen CE, Amin FM, Younis S, Lindberg U, de Koning P, Petersen ET, Paulson OB, Larsson HBW, Ashina M. Sildenafil and calcitonin gene-related peptide dilate intradural arteries: A 3T MR angiography study in healthy volunteers. Cephalalgia. 2019 Feb;39(2):264-273

5. Christensen CE, Younis S, Lindberg U, Boer VO, de Koning P, Petersen ET, Paulson OB, Larsson HBW, Amin FM, Ashina M. Ultra-high field MR angiography in human migraine models: a 3.0T/7.0T comparison study. J Headache Pain. 2019 May 6;20(1):48

6. da Cunha-Bang S, Fisher PM, Hjordt LV, Holst K, Knudsen GM. Amygdala reactivity to fearful faces correlates positively with impulsive aggression. Soc Neurosci. 2019 Apr;14(2):162-172

7. da Cunha-Bang S, Ettrup A, Mc Mahon B, Skibsted AP, Schain M, Lehel S, Dyssegaard A, Jørgensen LM, Møller K, Gillings N, Svarer C, Knudsen GM. Measuring endogenous changes in serotonergic neurotransmission with [11C]Cimbi-36 positron emission tomography in humans. Transl Psychiatry. 2019 Apr 11;9(1):134

8. Dam VH, Thystrup CK, Jensen PS, Bland AR, Mortensen EL, Elliott R, Sahakian BJ, Knudsen GM, Frokjaer VG, Stenbæk DS. Psychometric Properties and Validation of the EMOTICOM Test Battery in a Healthy Danish Population. Front Psychol. 2019 Dec 3;10:2660

9. Deen M, Hougaard A, Hansen HD, Svarer C, Eiberg H, Lehel S, Knudsen GM, Ashina M. Migraine is associated with high brain 5-HT levels as indexed by 5-HT4 receptor binding. Cephalalgia. 2019 Apr;39(4):526-532

10. Deen M, Hougaard A, Hansen HD, Schain M, Dyssegaard A, Knudsen GM, Ashina M. Association Between Sumatriptan Treatment During a Migraine Attack and Central 5-HT1B Receptor Binding. JAMA Neurol. 2019 Jul 1;76(7):834-840

11. Duez L, Tankisi H, Hansen PO, Sidenius P, Sabers A, Pinborg LH, Fabricius M, Rásonyi G, Rubboli G, Pedersen B, Leffers AM, Uldall P, Jespersen B, Brennum J, Henriksen OM, Fuglsang-Frederiksen A, Beniczky S. Electromagnetic source imaging in presurgical workup of patients with epilepsy: A prospective study. Neurology. 2019 Feb 5;92(6):e576-e586

12. Dyrvig M, Mikkelsen JD, Lichota J. DNA methylation regulates CHRNA7 transcription and can be modulated by valproate. Neurosci Lett. 2019 Jun 21;704:145-152

13. Ebert SE, Jensen P, Ozenne B, Armand S, Svarer C, Stenbaek DS, Moeller K, Dyssegaard A, Thomsen G, Steinmetz J, Forchhammer BH, Knudsen GM, Pinborg LH. Molecular imaging of neuroinflammation in patients after mild traumatic brain injury: a longitudinal 123 I-CLINDE SPECT study. Eur J Neurol. 2019 Dec;26(12):1426-1432

14. Erritzoe D, Smith J, Fisher PM, Carhart-Harris R, Frokjaer VG, Knudsen GM. Recreational use of psychedelics is associated with elevated personality trait openness: Exploration of associations with brain serotonin markers. J Psychopharmacol. 2019 Sep;33(9):1068-1075

15. Foged MT, Stefánsdóttir A, Brændgaard M, Holm E, Pinborg LH, Sabers A. Why are antiepileptic drugs continued after successful epilepsy surgery in adults? Epilepsy Behav. 2019 Nov;100(Pt A):106452

16. Frederiksen KS, Madsen K, Andersen BB, Beyer N, Garde E, Høgh P, Waldemar G, Hasselbalch SG, Law I. Moderate- to high-intensity exercise does not modify cortical ß-amyloid in Alzheimer's disease. Alzheimers Dement (N Y). 2019 Jun 7;5:208-215

17. Galea LAM, Frokjaer VG. Perinatal Depression: Embracing Variability toward Better Treatment and Outcomes. Neuron. 2019 Apr 3;102(1):13-16

18. Griem-Krey N, Klein AB, Herth M, Wellendorph P. Autoradiography as a Simple and Powerful Method for Visualization and Characterization of Pharmacological Targets. J Vis Exp. 2019 Mar 12;(145)

19. Hansen HD, Constantinescu CC, Barret O, Herth MM, Magnussen JH, Lehel S, Dyssegaard A, Colomb J, Billard T, Zimmer L, Tamagnan G, Knudsen GM. Evaluation of [18 F]2FP3 in pigs and non-human primates. J Labelled Comp Radiopharm. 2019 Jan;62(1):34-42

20. Heurling K, Smith R, Strandberg OT, Schain M, Ohlsson T, Hansson O, Schöll M. Regional times to equilibria and their impact on semi-quantification of [18F]AV-1451 uptake. J Cereb Blood Flow Metab. 2019 Nov;39(11):2223-2232

21. Hjordt LV, Stenbæk DS. Sensory processing sensitivity and its association with seasonal affective disorder. Psychiatry Research. 2019 Feb;272:359-364

22. Holm SK, Madsen KS, Vestergaard M, Born AP, Paulson OB, Siebner HR, Uldall P, Baaré WFC. Previous glucocorticoid treatment in childhood and adolescence is associated with long-term differences in subcortical grey matter volume and microstructure. Neuroimage Clin. Neuroimage Clin. 2019;23:101825

23. Holmgaard F, Vedel AG, Rasmussen LS, Paulson OB, Nilsson JC, Ravn HB. The association between postoperative cognitive dysfunction and cerebral oximetry during cardiac surgery: a secondary analysis of a randomised trial. Br J Anaesth. 2019 Aug;123(2):196-205

24. Jensen CG, Krogh SC, Westphael G, Hjordt LV. Mindfulness is positively related to socioeconomic job status and income and independently predicts mental distress in a long-term perspective: Danish validation studies of the Five-Factor Mindfulness Questionnaire. Psychol Assess. 2019 Jan;31(1):e1-e20

25. Johansen A, Holm S, Dall B, Keller S, Kristensen JL, Knudsen GM, Hansen HD. Human biodistribution and radiation dosimetry of the 5-HT2A receptor agonist Cimbi-36 labeled with carbon-11 in two positions. EJNMMI Res. 2019 Jul 31;9(1):71

26. Kjær C, Barzaghi G, Bak LK, Goetze JP, Yde CW, Woldbye D, Pinborg LH, Jensen LJ. Transcriptome analysis in patients with temporal lobe epilepsy. Brain. 2019 Oct 1;142(10):e55

27. Kuypers KP, Ng L, Erritzoe D, Knudsen GM, Nichols CD, Nichols DE, Pani L, Soula A, Nutt D. Microdosing psychedelics: More

questions than answers? An overview and suggestions for future research. J Psychopharmacol. 2019 Sep;33(9):1039-1057

28. Lansner J, Jensen CG, Petersen A, Fisher PM, Frokjaer VG, Vangkilde S, Knudsen GM. Three weeks of SSRI administration enhances the visual perceptual threshold - a randomized placebo-controlled study. Psychopharmacology (Berl). 2019 Jun;236(6):1759-1769

29. Larsen LK, Frøkjaer VG, Nielsen JS, Skrobik Y, Winkler Y, Møller K, Petersen M, Egerod I. Delirium assessment in neuro-critically ill patients: A validation study. Acta Anaesthesiol Scand. 2019 Mar;63(3):352-359

30. Larsen HM, Hansen SK, Mikkelsen JD, Hyttel P, Stummann TC. Alpha7 nicotinic acetylcholine receptors and neural network synaptic transmission in human induced pluripotent stem cell-derived neurons. Stem Cell Res. 2019 Dec;41:101642

31. López-Picón FR, Kirjavainen AK, Forsback S, Takkinen JS, Peters D, Haaparanta-Solin M, Solin O. In vivo characterization of a novel norepinephrine transporter PET tracer [18F]NS12137 in adult and immature Sprague-Dawley rats. Theranostics. 2019 Jan 1;9(1):11-19

32. L'Estrade ET, Hansen HD, Falk-Petersen C, Haugaard A, Griem-Krey N, Jung S, Lüddens H, Schirmeister T, Erlandsson M, Ohlsson T, Knudsen GM, Herth MM, Wellendorph P, Frølund B. Synthesis and Pharmacological Evaluation of [11C]4-Methoxy-N-[2-(thiophen-2-yl)imidazo[1,2-a]pyridin-3-yl]benzamide as a Brain Penetrant PET Ligand Selective for the δ-Subunit-Containing γ-Aminobutyric Acid Type A Receptors. ACS Omega. 2019 May 22;4(5):8846-8851

33. Madsen MK, Fisher PM, Burmester D, Dyssegaard A, Stenbæk DS, Kristiansen S, Johansen SS, Lehel S, Linnet K, Svarer C, Erritzoe D, Ozenne B, Knudsen GM. Psychedelic effects of psilocybin correlate with serotonin 2A receptor occupancy and plasma psilocin levels. Neuropsychopharmacology. 2019 Jun;44(7):1328-1334

34. Magnusson PO, Boer VO, Marsman A, Paulson OB, Hanson LG, Petersen ET. Gamma-aminobutyric acid edited echo-planar spectroscopic imaging (EPSI) with MEGA-sLASER at 7T. Magn Reson Med. 2019 Feb;81(2):773-780

35. Mehta D, Rex-Haffner M, Søndergaard HB, Pinborg A, Binder EB, Frokjaer VG. Genome-wide gene expression in a pharmacological hormonal transition model and its relation to depressive symptoms. Acta Psychiatr Scand. 2019 Jul;140(1):77-84

36. Mehta D, Rex-Haffner M, Søndergaard HB, Pinborg A, Binder EB, Frokjaer VG. Evidence for oestrogen sensitivity in perinatal depression: pharmacological sex hormone manipulation study. Br J Psychiatry. 2019 Sep;215(3):519-527

37. Nørgaard M, Ganz M, Svarer C, Feng L, Ichise M, Lanzenberger R, Lubberink M, Parsey RV, Politis M, Rabiner EA, Slifstein M, Sossi

V, Suhara T, Talbot PS, Turkheimer F, Strother SC, Knudsen GM. Cerebral serotonin transporter measurements with [11C]DASB: A review on acquisition and preprocessing across 21 PET centres. J Cereb Blood Flow Metab. 2019 Feb;39(2):210-222

38. Nørgaard M, Ganz M, Svarer C, Frokjaer VG, Greve DN, Strother SC, Knudsen GM. Optimization of preprocessing strategies in Positron Emission Tomography (PET) neuroimaging: A [11C]DASB PET study. NeuroImage. 2019 Jun 1;199:466-479

39. Ozenne B, Tae-Hee C, Mikkelsen IK, Hermier M, Thomalla G, Pedraza S, Roy P, Berthezène Y, Nighoghossian N, Østergaard L, Baron JC, Maucort-Boulch D. Individualized Quantification of the Benefit from Reperfusion Therapy using Stroke Predictive Models. Eur J Neurosci. 2019 Oct;50(8):3251-3260

40. Peinkhofer C#, Knudsen GM, Moretti R, Kondziella D#. Cortical modulation of pupillary function: systematic review. PeerJ. 2019 May 7;7:e6882.

41. Prabhakaran J, DeLorenzo C, Zanderigo F, Knudsen GM, Gilling N, Pratap M, Jorgensen MJ, Daunais J, Kaplan JR, Parsey RV, Mann JJ, Kumar D. In vivo PET Imaging of [11C]CIMBI-5, a 5-HT2AR Agonist Radiotracer in Nonhuman Primates. J Pharm Pharm Sci. 2019;22(1):352-364

42. Sigurdsson ST, Bie P, Nielsen AH, Strandgaard S, Paulson OB. No effect of the angiotensin receptor blocker candesartan on cerebrovascular autoregulation in rats during very high and low sodium intake. J Renin Angiotensin Aldosterone Syst. 2019 Jul-Sep; 20(3): 1470320319874615

43. Stéen EJL, Jørgensen JT, Petersen IN, Nørregaard K, Lehel S, Shalgunov V, Birke A, Edem PE, L'Estrade ET, Hansen HD, Villadsen J, Erlandsson M, Ohlsson T, Yazdani A, Valliant JF, Kristensen JL, Barz M, Knudsen GM, Kjær A, Herth MM. Improved radiosynthesis and preliminary in vivo evaluation of the 11C-labeled tetrazine [11C]AE-1 for pretargeted PET imaging. Bioorg Med Chem Lett. 2019 Apr 15;29(8):986-990

44. Stenbæk DS, Budtz-Jørgensen E, Pinborg A, Jensen PS, Frokjaer VG. Neuroticism modulates mood responses to pharmacological sex hormone manipulation in healthy women. Psychoneuroendocrinology. 2019 Jan;99:251-256

45. Stenbaek DS, Kristiansen S, Burmester D, Madsen MK, Frokjaer VG, Knudsen GM, Fisher PM. Trait Openness and serotonin 2A receptors in healthy volunteers: A positron emission tomography study. Hum Brain Mapp. 2019 May;40(7):2117-2124

46. Sundström Poromaa I, Comasco E, Bäckström T, Bixo M, Jensen P, Frokjaer VG. Negative Association Between Allopregnanolone and Cerebral Serotonin Transporter Binding in Healthy Women of Fertile Age. Front Psychol. 2019 Jan 11;9:2767

47. Svensson JE, Schain M, Plavén-Sigray P, Cervenka S, Tiger M, Nord M, Halldin C, Farde L, Lundberg J. Validity and reliability of extrastriatal [11C]raclopride binding quantification in the living human brain. Neuroimage. 2019 Aug 29;202:116143

48. Tampio L'Estrade E, Xiong M, Shalgunov V, Edgar FG, Volk B, Baerentzen SL, Palner M, Erlandsson M, Ohlsson T, Knudsen GM, Herth MM. Development and Evaluation of Two Potential 5-HT7 Receptor PET Tracers: [18F]ENL09 and [18F]ENL10. ACS Chem Neurosci. 2019 Sep 18;10(9):3961-3968

49. Tozlu C, Ozenne B, Tae-Hee C, Nighoghossian N, Mikkelsen IK, Derex L, Hermier M, Pedraza S, Fiehler J, Østergaard L, Berthezène Y, Baron JC, Maucort-Boulch D. Comparison of classification methods for tissue outcome after ischaemic stroke. Eur J Neurosci. 2019 Nov;50(10):3590-3598

50. Vassilieva A, Olsen MH, Peinkhofer C, Knudsen GM, Kondziella D. Automated pupillometry to detect command following in neurological patients: a proof-of-concept study. PeerJ. 2019 May 13;7:e6929

51. Vedel AG, Holmgaard F, Siersma V, Langkilde A, Paulson OB, Ravn HB, Nilsson JC, Rasmussen LS. Domain-specific cognitive dysfunction after cardiac surgery. A secondary analysis of a randomized trial. Acta Anaesthesiol Scand. 2019 Jul;63(6):730-738

52. Veronese M, Moro L, Arcolin M, Dipasquale O, Rizzo G, Expert P, Khan W, Fisher PM, Svarer C, Bertoldo A, Howes O, Turkheimer FE. Covariance statistics and network analysis of brain PET imaging studies. Sci Rep. 2019 Feb 21;9(1):2496. doi: 10.1038/s41598-019-39005-8

53. Wickham J, Ledri M, Bengzon J, Jespersen B, Pinborg LH, Englund E, Woldbye DPD, Andersson M, Kokaia M. Inhibition of epileptiform activity by neuropeptide Y in brain tissue from drug-resistant temporal lobe epilepsy patients. Sci Rep. 2019 Dec 18;9(1):19393.

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