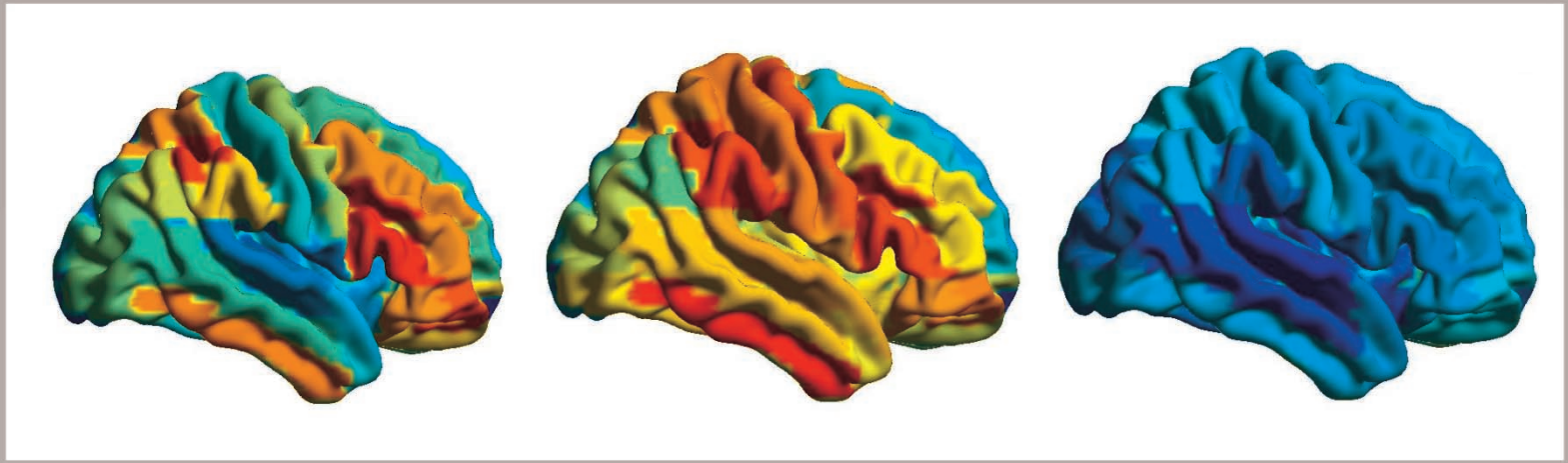
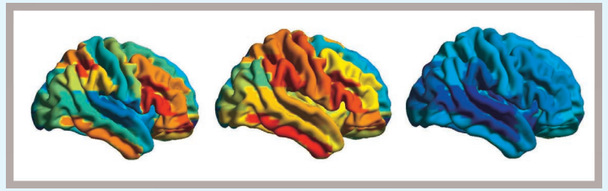
Neurobiology Research Unit

Annual Report 2022



Department of Neurology, Neuroscience Centre
Copenhagen University Hospital, Rigshospitalet

www.nru.dk



Cover page: Right hemisphere brain overlays denoting three brain states associated with acute psilocybin effects.

REGION H Rigshospitalet

KØBENHAVNS UNIVERSITET
DET SUNDHEDSVIDENSKABELIGE FAKULTET

Contents

Preface

It is a pleasure to present you with the 2022 annual report describing the activities of the Neurobiology Research Unit (NRU). The preface for the last two years focused both on the impact of the covid-19 pandemic but 2022 was almost void of the unfortunate issues generated by the pandemic. Meetings and international congresses have gradually resumed to normal, although the lessons learned over the last years have now enabled a more flexible way to meet which is also in the favour of our carbon footprint.

In 2022, we saw the largest ever number of new people at NRU. No less than 2 junior faculty members, 2 junior scientists, and 5 technical-administrative staff members and 46 pregraduate students had their first day at work at NRU, bringing the number of NRU-affiliated people to a total of 127. But in 2022 we also had to say good-bye to a dear colleague and founder of NRU, professor Olaf B. Paulson. A reception in the honour of Olaf brought many former colleagues of Olaf's to NRU, and this as well as the speeches made it a very special day. For the next two years, Olaf will continue to be at NRU as a professor emeritus.

Some of the larger projects that were funded during 2022 were: '*Unlocking the doors of perception: Impact of music on acute and lasting effects of psilocybin in depressed patients*' (Dr. Stenbæk, DFF-Sapere Aude), '*Concentration-effect relationship of agonistic and antagonistic serotonin 2A receptor occupancy using LSD and ketanserin*' (Postdoc grant for Friederike Holze, Swiss National Science Foundation), and '*From psychedelics to novel therapeutics: Positive allosteric modulators of the BDNF receptor TrkBI*' (PI Dr. Jensen, Univ. Copenhagen, The Lundbeck Foundation). Many other smaller grants were successfully achieved, and all of these are very helpful for us achieving our mission.

NRU continued to generate a substantial research output in 2022. Three PhD students successfully defended their theses and obtained their PhD degree. Many NRU-affiliated researchers presented their work at international congresses, conferences, and meetings. In total, NRU published 88 peer-reviewed scientific publications.

I would like to take this opportunity to acknowledge and thank all 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 2022 was another very successful year for NRU.

I hope you will enjoy reading this 2022 annual report and encourage interested readers to stay tuned on https://nru.dk.

On behalf of the NRU management group

Gitte Moos Knudsen
Professor, Head of Department

NRU management group consisting of Gitte Moos Knudsen (in the middle, photo credit to Royal Academy of Sciences and Letters 2022) and (clockwise from upper right) Olaf B. Paulson, Claus Svarer, Jens H. Mikkelsen, Dea S. Stenbæk, Patrick M. Fisher, Lars H. Pinborg, and Vibe G. Frøkjær.

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 or resilience 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 basic neuroscience questions.

The activities within NRU fall in ten 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 and data sharing
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 Denmark 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.

Facilities

NRU facilities cover more than 1,400 m^2 and are spread over several locations at Rigshospitalet (RH), but mainly located at fifth and sixth floors of the North Wing building, sections 8057 and 8067.

At fifth floor, we span 822 m^2, including 15 offices with space for 57 desks, a conference room with kitchen, a regular meeting/conversation room, a science lounge, two smaller quiet rooms for video calls, a laboratory for handling human specimens, a storage room, two sound-proof rooms with facilities for neuropsychological and -physiological testing, a calm sleep/intervention room, and an EEG-room (see photo to the right) equipped with high density EEG equipment as well as an adjacent observation room. Furthermore, a server room and two printer rooms which house all the equipment needed to run our own IT-infrastructure.

At sixth floor, the NRU experimental laboratory has 167 m^2 of well-equipped facilities for basic neuroscience work (only *in vitro* studies). We have four brand new GMO-1 approved laboratories (see photo to the right), one of which is also approved as an isotope lab with an S1 permission, a storage room equipped with two -80 degrees freezers, a dedicated 4-degree room, i.e., a huge build-in fridge, as well as an office equipped with two desks. Equipment in the laboratories include several lab benches with hoods and standard equipment, gamma- or beta-counters, a cell culture room, cell harvester, autoradiography, and much more.

At seventh floor, in the Neuromuscular Research Unit, we have access to a shared microscope room and in the basement, we share a large (62 m^2) freezer-core facility for biobank material together with good colleagues from the Danish Dementia Research Centre and the Memory and Neuromuscular clinics. In the basement we have access to shared shower/changing facilities.

In building 93, RH section 9302, we have two dedicated laboratories for our *in vivo* studies, including small animal storage facilities and facilities for testing animal behaviour. These rooms cover 46 m^2 and both are approved as isotope labs with an S1 permission. Furthermore, we have access to a storage room equipped with three -80 degrees freezers, shared with the other research groups in the building.

NRU has a close collaboration with the PET and Cyclotron Unit at RH, which provides NRU with key access to radiochemistry production and to PET- and combined PET-MR scanner facilities. Our MRI facilities include the NRU brain research dedicated 3 Tesla Siemens Prisma MR-scanner (MR001) which is located in 120 m^2 state-of-the-art facilities on the ground floor in the North Wing. In the basement of the North Wing, we have a Siemens mock-up MR scanner installed (see photo to the right), mimicking our real scanner environment in MR001. The mock-up scanner can be used as a training facility to prepare persons, especially children or people with claustrophobia, for scanning in a real MR-scanner.

The SPECT laboratory of NRU is located on the ground floor in the North Wing. The facility is used both diagnostically and for research purposes. The laboratory consists of an office, a type B approved isotope laboratory, waiting room facilities for patients, and a scanner room equipped with a newer 3-headed dedicated brain SPECT/CT scanner (Mediso AnyScan) with unique multi-pine-hole collimator. The SPECT laboratory also has a dedicated storage room in the basement and thereby occupy in total 130 m^2.

Worth mentioning is also the Cimbi database and the Cimbi biobank which represent unique and valuable research instruments for NRU. Over the last 20 years, we have been very systematic in acquiring high-resolution brain imaging data (PET, MRI, rsMRI, and fMRI) from thousands of carefully screened and well-characterized healthy individuals and patients with various neuropsychiatric disorders. These data have been collected along with a wide range of associated data including demographic, neuropsychological, biochemical, and genetic data. The wealth of acquired data is stored in the Cimbi Database in a highly structured and safe manner. 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. The biobank is stored safely in the dedicated freezer-core facility in the basement of the North Wing. The Cimbi database and biobank provide quality-controlled resources for future hypothesis-generating and hypothesis-driven studies, and from an international perspective, the comprehensive nature and the sample sizes are exceptional. In 2022, a total of 41 official Cimbi applications for data access were approved or extended and several papers based on data from the Cimbi database and biobank were published. Currently, there are 55 active projects using data from the database.

Staff in 2022

A fraction of the NRU staff photographed in May 2023.

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

Chief technologist
Gerda Thomsen

Administration and research
Arafat Nasser (biobank manager)
Birgit Tang (HR)
Dorthe Givard (finances)
Peter S. Jensen (center manager)

Senior researchers
Anjali Sankar, PhD
Brice Ozenne, assistant professor, PhD
Cyril Pernet, PhD
Hanne D. Hansen, instructor, PhD
Louise M. Jørgensen, associate professor, MD, PhD
Melanie Ganz-Benjaminsen, associate professor, PhD
Mikael Palner, associate professor, PhD

Post docs
Cheng T. Ip, PhD
Jonas Svensson, PhD
Martin Korsbak Madsen, PhD
Martin Nørgaard, PhD
Pontus Plavén-Sigray, PhD
Sanjay Aripaka, PhD
Sofi da Cunha-Bang, MD, PhD
Vibeke Dam, PhD
Vincent Beliveau, PhD

PhD students
Agata C. Sainz, molecular biomedicine
Annette Johansen, MD
Camilla B. Larsen, MD
Drummond McCulloch, pharmacologist
Gjertrud L. Laurell, medical nuclide techniques
Kristian H.R. Jensen, MD
Maja R. Marstrand-Jørgensen, MD
Nakul Raval, medical nuclide techniques
Sara Marie Larsen, MD
Silvia E.P. Bruzzone, neuroscience
Sophia Armand, psychology
Stinne Høgh, midwifery
Søren V. Larsen, MD

Research assistants
Catharina Messell, music therapist
Christel Bormann, MD
Clara Madsen, molecular biomedicine
Emily Beaman, human biologist
Joan M.A. Gomez, medicine & technology
Kristian Larsen, neuroscience
Lise Berg, psychoanalyst
Martin Prener, MD
Miriam L. Navarro, pharmacist
Niels Lorenzen, molecular biomedicine
Sidsel H. Andersen, psychologist

Technical staff
Ajla Sabitovic, MRI-student assistant
Amalie B.E. Nielsen, EEG-student assistant
Anders Buch-Larsen, psychology
Arthur Diness, EEG-student assistant
Asta Vølund, MRI-student assistant
Astrid T. Mikkelsen, medicine
Astrid F. Vestereng, psychology
Cecilie R. Hvass, MRI-student assistant
Christina C. Schnohr, MRI-student assistant
Delal Yücel, psychology
Elisabeth K. Frandsen, neuroscience
Emilia A. Steenstrup, MRI-student assistant
Emilie S. Engdal, EEG-student assistant
Emilie L. Henriksen, radiographer
Emma Balsby, psychology
Emma Højte, psychology
Erik Mogensen, psychology
Kathrine S. Christensen, psychology
Kristoffer Brendstrup-Brix, MRI-student assistant
Laxmy Krishnapillai, EEG-student assistant
Lone I. Freyr, project nurse
Lærke V. Kristiansen, MRI-student assistant
Maria S. Christiansen, psychology
Maria Grzywacz, psychology
Marie Linneberg, psychology
Mille Rasmussen, HPLC-student assistant
Minna H. Litman, project nurse
Ofelia F. Godske, EEG-student assistant
Oliver Overgaard-Hansen, psychology
Paw P. Randrup, psychology
Philip A. Erichsen, MRI-student assistant
Robert D. Pedersen, EEG-student assistant
Sandra N. Madsen, HPLC-student assistant
Sarah Bargmeyer, HPLC-student assistant
Sif G. Kaad, biomedical & molecular biology
Simon G. Sabroe, MRI-student assistant
Sofie Ølgod, psychology
Stine S. Olsen, psychology
Svitlana Olsen, medical technologist
Theodor J.H. Labianca, EEG-student assistant
Thilde K. Nielsen, psychology
Thomas W. Jørgensen, IT-support
Thurid W. Madsen, project nurse

Visiting professors
Adriaan Lammertsma, professor, VUmc, Netherlands
Todd Ogden, professor, Columbia University, USA

Visiting scientists
Ali Ebrahimifard, PhD student, Univ. Tehran, Iran
Anders S. Olsen, PhD student, Technical University of Denmark
Anna Maresova, PhD student, Univ. Copenhagen
Barbara Nordhjem, post doc, Dept of Paediatrics and Adolescent Medicine, Righospitalet
Fiona Ballorin, Intern, Université de Paris
Hector L. Mebenga, Erasmus student, Univ. Copenhagen
Ida Vang Andersen, PhD student, Univ. Copenhagen
Isabel Noachtar, PhD student, Univ. Salzburg, Austria
Kat F. Kiilerich, research assistant, Univ. of Southern Denmark
Kathrine S. Madsen, docent, University College Copenhagen
Lourdes C. Arevalo, associate professor, Univ. Copenhagen
Ludovica S. Sirocchi, PhD student, Univ. Copenhagen
Marko Rosenholm, PhD, post doc, Univ. Copenhagen
Markus Hjorth, MD, Psychiatric Center Ballerup, Denmark
Martin Schain, PhD, Antaros Medical, Sweden
Mengfei Xiong, PhD stuedent, Uppsala University, Sweden
Natalie Beschorner, PhD, post doc, Univ. Copenhagen
Natasha Bidesi, PhD student, Univ. Copenhagen
Nikolaj Daugaard, PhD student, Univ. of Southern Denmark
Oliver Hovmand, PhD student, Mental Health Services South
Sara Lopes van den Broek, PhD student, Univ. Copenhagen
Silas Haahr Nielsen, MD, Dept of Neurosurgery, Rigshospitalet
Thomas Wünsche, PhD student, Univ. Copenhagen
Tobias Gustavsson, post doc, Univ. Copenhagen
Vladimir Shalgunov, PhD, Univ. Copenhagen

Pregraduate students
Ahmad Al-Baka, pharmacy
Aje Al-Awssi, medicine
Alaa Alawadi, radiography
Allan Al-Dawaski, medicine
Ally Mahon, pharmacy
Andrea Juvik, medicine
Anders S. Munch, psychology
Anine E. Østerby, psychology
Anna Kauffmann, medicine
Anna Søndergaard, medicine
Annika L. Rasmussen, medicine
Avneet Kaur, computer science
Camilla M. C. Xu, medicine
Cansu Gürel, radiography
Caroline E. Brugge, neuroscience
Cecilie Eiby, psychology
Elisa Bouet-Garcia, neuroscience
Elisabeth B. Pedersen, medicine
Emil Colliander, medicine
Emilie Mauritzon, medicine
Emilie Ø. Lange, medicine
Evangelos Vouros, medical physics
Hanaeli Hamzu, radiography
Haowen Lyu, neuroscience
Inger Marie M. Sørensen, medicine
Joanna Wilkosz, neuroscience
Johan B. Nielsen, psychology
Jonas Ingerslev, human physiology and psychology
Jonas Kendal, medicine
Josephine O. Thestrup, neuroscience
Juliane C. Vestergaard, medicine
Lea L. Larsen, biotechnology & biology
Malene Ravn-Eriksson, medicine
Malene V. Andersen, medicine
Malthe T. Andersen, medicine
Marcus K. Riis-Vestergaard, psychology
Mette Clausen, medicine
Michelle Dait, psychology
Naja S. Jessen, pharmaceutical sciences
Nina Fultz, neuroscience
Nora D. Falck, medicine
Philip Fink-Jensen, medicine
Ruben Dörfel, biomedical engineering
Shuhan Yang, neuroscience
Silas Aagaard, psychology
Simon Chemnitz-Thomsen, mathematical sciences
Sofie Hvitved, medicine
Youssef Zeaiter, medicine
Victoria Garre, medicine
Victor Neufeld, medicine

Selected Staff Highlights of the Year

In April 2022, NRU colleagues surprised senior researcher Vibe G. Frøkjær in the NRU conference room with a celebration of her 50 years birthday.

November 1st 2022, NRU senior researcher Patrick M. Fisher was appointed associate professor (part-time) for a 5-year period at the Dept of Drug Design and Pharmacology, Univ. Copenhagen.

October 26th 2022 was a very special day at NRU as we hosted a large and well-deserved farewell reception for our dear colleague and NRU founder, Olaf B. Paulson. Many of Olaf's current and previous colleagues and collaborating partners, close friends and family members participated in the festive celebration of his well-deserved professor emeritus title.

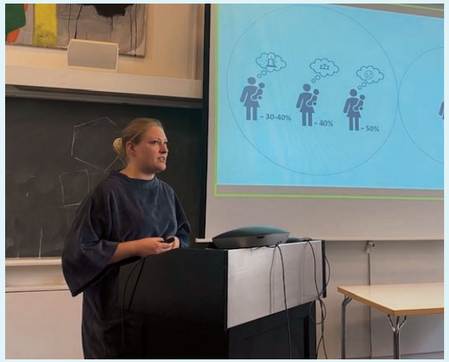
PhD Degrees in 2022

Three PhD-students defended their thesis at the Graduate School of Health and Medical Sciences, Univ. Copenhagen

Camilla Borgsted Larsen, PhD

Structural and functional brain signatures of sex hormone transitions and implications for perinatal mental health

The aim of this thesis was to determine the associations between mental distress, the estrogen estradiol, markers of serotonergic signaling and hippocampal volume in relation to pharmacological and natural models of sex-hormone transitions in healthy women. We find that healthy women' brains generally adapt well to sex-hormone transitions and that estradiol and serotonergic signaling seem important for hippocampal plasticity during sex-hormone transitions. The length and magnitude of estradiol fluctuations may, however, affect hippocampal volume and subclinical depressive symptoms. Our data points towards potential risk mechanisms for depressive responses during sex-hormone transitions but further evaluation in clinical and high-risk samples is required.



Camilla Borgsted Larsen's PhD work was done at NRU under the main supervision of associate professor Vibe G. Frøkjær from NRU and Dept of Clinical Medicine, Univ. Copenhagen. Primary co-supervisor was professor Gitte Moos Knudsen from NRU and Dept of Clinical Medicine, Univ. Copenhagen, and professor Anja Pinborg from Dept of Clinical Medicine, Univ. Copenhagen was co-supervisor.

Dr. Larsen successfully defended her thesis on June 16th, 2022, with professor Poul Videbech, Dept of Clinical Medicine, Univ. Copenhagen, as chair and with professor Liisa Galea, Dept of Psychology, The University of British Columbia, Canada, and professor Birgit Derntl, Dept of Psychiatry and Psychotherapy, University of Tübingen, Germany, as opponents.

Nakul Ravi Raval, PhD

Translational Positron Emission Tomography - Animal Models and *In Vitro* Autoradiography for Radioligand Development

The aims of this thesis were to 1) establish a pig model with intracerebral protein injection to assess novel radioligands, and 2) perform i*n vitro* and *in vivo* quantification of presynaptic density using the radioligand [3H]/[11C]UCB-J for synaptic vesicular protein 2A (SV2A) in neurodegeneration and to assess the synaptoplastic potential of drugs.

Nakul Raval completed his PhD at NRU under the main supervision of professor Gitte Moos Knudsen from NRU and Dept of Clinical Medicine, Univ. Copenhagen. Co-supervisors were Mikael Palner, Hanne Demant Hansen, and Louise Møller Jørgensen from NRU, Stinna Syvänen from Dept of Public Health and Caring Science, Molecular Geriatrics, Uppsala University, Sweden, and Pekka Kallunki from H. Lundbeck A/S, Denmark.

Dr. Raval was funded by the EU via a MC-ITN-ETN action and successfully defended his thesis on May 12th, 2022, with associate professor Birgitte Rahbek Kornum from Dept of Neuroscience, Univ. Copenhagen as chair, and associate professor Anne M. Landau, Dept of Clinical Medicine – Translational Neuropsychiatry, Aarhus University, and professor Kristina Herfert from Werner Siemens Imaging Center, Eberhard Karls University of Tübingen, Germany, as opponents.

Sagar Sanjay Aripaka, PhD

Molecular biology in the pain generation in lumbar intervertebral discs

The aim of this thesis was (I) to evaluate the association of inflammatory mediators with low back pain, (II) to examine the association of several *matrix metalloproteinases* (MMPs) and *A Disintegrin and Metalloproteinase with Thrombospondin motifs* (ADAMTSs) subtypes in intervertebral disc (IVD) with degeneration and (III) to investigate the expression of *Transient Receptor Potential* (TRP) ion channels in IVD and its association with inflammatory mediated pain.

Sagar Sanjay Aripaka completed his PhD at NRU under the main supervision of professor Jens H. Mikkelsen from NRU and Dept of Clinical Medicine, Univ. Copenhagen and with associate professor Rachid Bech-Azeddine from Centre for Rheumatology and Spine Diseases, Rigshospitalet and Dept of Clinical Medicine, Univ. Copenhagen as co-supervisor.

Dr. Aripaka successfully defended his thesis on April 8th, 2022, with professor Tiit Illimar Mathiesen from Dept of Clinical Medicine, Univ. Copenhagen as chair, and professor Flemming Bach, Institute for Clinical Medicine - Neurology, Aarhus University Hospital, and professor Karin Wuertz-Kozak, Dept of Biomedical Engineering, Rochester Institute of Technology, USA, as opponents.

Education

NRU is a major training site for pre- and postgraduate students. We train national and international research staff at all levels; medical students, graduate students, PhD students and post docs. We organize pre- and post-graduate courses with prominent speakers and well-attended programs, including the Master's program in Neuroscience, and an international PhD course on pharmacokinetics. We also organize regular meetings and seminars where the pre- and postgraduate students are expected to present their work.

NRU faculty members are engaged in research-based teaching and education within their fields of expertise. Below are some of the major contributions to teaching programs.

The Master's program in Neuroscience in Copenhagen

Professor Jens H. Mikkelsen, PhD from NRU and Institute of Neuroscience, University of Copenhagen, is the study director of a two-year Master of Science program and education in neurosciences. 2022 was the third year for this master program. Courses are offered in cellular neuroscience, neural circuits, higher brain functions, and experimental neuroscience, as well as elective courses in animal models, drug discovery and computer science. Every year the university enroll about 30 bachelor students in the Master's program in Neuroscience. We receive every year a large interest from all over the world for this program. Many applicants come mostly from China, North America and throughout Europe. Unfortunately, we are not able to accept all qualified applicants. The NRU faculty provide teaching in neuropharmacology, homeostasis, cognition, drug discovery and imaging in the form of lectures, exercises, and journal clubs, and we have every year Neuroscience students to do their master thesis here.

Danish Institute of Study Abroad

Each semester, associate professor Patrick Fisher guest lectures for the following university-level courses at the Danish Institute of Study Abroad: "Neuroplasticity", "Neuroscience of Fear" and "Neurological Disorders and Disease".

Basic Kinetic Modelling in PET and MR Imaging

In the period Feb 28th to Mar 4th, 2022, we hosted our annual one-week PhD course on pharmacokinetics with participation by 17 national and international researchers.

PET Pharmacokinetics Course

The international PET Pharmacokinetics Course was resumed in 2022 and held in conjunction with the Brain&BrainPET 2022 meeting in Edinburgh, and it attracted about 40 international students (see photo above). Professor Gitte M Knudsen was responsible for organizing the course in collaboration with a local team at University of Edinburgh, Scotland. The 10 faculty members are all internationally renowned experts in brain PET modelling and quantification.

OpenNeuroPET Hackathon

A hackathon was organized in December 2022 under the brain hack global framework (brainhack.org) with 2 days of hacking (presenting, discussing software, testing codes) and a 1 day educational on state-of-the-art version control for code, data and for PET data analysis pipeline. The hackathon had 10 to 15 people, depending on days, coming from Denmark, Norway, Sweden, Germany, and the UK.

Strategic Collaborations

Strong collaborations are fundamental for excellent brain research to happen. We have for many years worked closely together with colleagues within Dept of Neurology and 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 neuroimaging collaborators, please refer to page 28.

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 nine years, the Dept of Radiology has graciously provided NRU with key access to their 3T MR-scanner facilities, to be used after regular working hours. During 2022, we will move all of our MR research projects over to our own newly-installed Siemens Prisma 3T MR scanner. Our well-established collaboration with Dr. Vibeke Andrée Larsen, professor Adam Espe Hansen, chief radiographer Susanne Stampe and project radiographer Christian Hammer Nielsen will, however, continue.

Dept of Obstetrics and Gynaecology, Rigshospitalet, Herlev, Hvidovre and Hillerød

NRU collaborate in translational clinical trials with senior consultants Kristina Renault, Eleonora Cvetanovska, Ellen Løkkegaard and Anette Kjærbye-Thygesen at Obstetrics Depts in the Capital Region of Denmark in projects aiming at evaluating preventive strategies for perinatal depression in high-risk groups. Also, we collaborate with professor Øjvind Lidegaard in epidemiological studies on the brain and mental health consequences of oral contraceptive use.

Dept of Growth and Reproduction, Rigshospitalet

We collaborate with professor Anders Juul at Dept of Growth and Reproduction on determination of sex steroids in large clinical populations related to brain signatures of hormonal rhythms.

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 (Dr. Herth, professors Kristensen and Jensen). Likewise, we also appreciate our long-standing collaboration on biostatistics with Section of Biostatistics, Faculty of Public Health, with whom we share a biostatistician (Dr. Ozenne) and a PhD-student (Dr. Ziersen) through the *BrainDrugs* project, The Center for Translational Neuromedicine (professor Nedergaard), and with the Dept of Psychology with whom we share an associate professor (Dr. Stenbæk). Finally, we also highly appreciate our strategic collaboration with Dept of Computer Science, facilitated by a joint associate professor (Dr. Ganz) as well as cooperation in the *BrainDrugs* project. Last but not least, professor Jens Mikkelsen heads the Master's program in Neuroscience.

Copenhagen Business School

Together with professor Toke Reichstein, we are conducting a study of cognition, risk-related decision making and brain function in entrepreneurs.

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 *NeuroPharm* and *BrainDrugs*, 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*, the collaborative network has been expanded to also include professor Poul Videbech and Klaus Martiny.

For our *BrainDrugs* project, we benefit greatly from our close collaboration with Allan Lohmann-Olsen and Eva Hundrup from CVD ('Center for Visitation og Diagnostik'), a unique central referral site for 'treatment packages', e.g., for patients with depression or obsessive-compulsive disorder who can be treated in outpatient settings.

University of Cambridge, UK

We are collaborating with professors Trevor Robbins and Barbara Sahakian from University of Cambridge on two joint research projects funded by the Lundbeck Foundation; the collaboration includes bilateral secondments. The data acquisition for the project with Sahakian was completed in 2021 and we expect to complete data acquisition for the Robbins project in 2023.

Stanford University, National Institutes of Health, and Martinos Center, US

The OpenNeuroPET project, funded through the BRAIN initiative and the Novo Nordisk foundation has been going on since 2019. You can read more about the project on page 35.

Martinos Center, Massachusetts General Hospital, US

We have since 2011 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 instructor at Harvard University, Dr. Hansen, as well as bilateral exchange of scientists. Joint research areas include PET-MR of animals, PET data modelling and motion correction, and the collaboration has so far resulted in more than 20 publications.

When Dr. Hansen was based at the Martinos Center in 2019 and 2020, she conducted two large PET/MRI studies in non-human primates. In collaboration with assistant professor Christin Sander, she investigated the internalization and recycling of dopamine 1 and 2 receptors upon repeated amphetamine interventions. This study provides insight into the timeline and differentially lasting effects of amphetamine exposure on D1 vs. D2 receptor dynamics in vivo. Furthermore, using simultaneous molecular and functional in vivo imaging, this study provides an important non-invasive and translational bridge from in vitro mechanistic studies to preclinical and clinical behavioural studies (**Figure 1**).

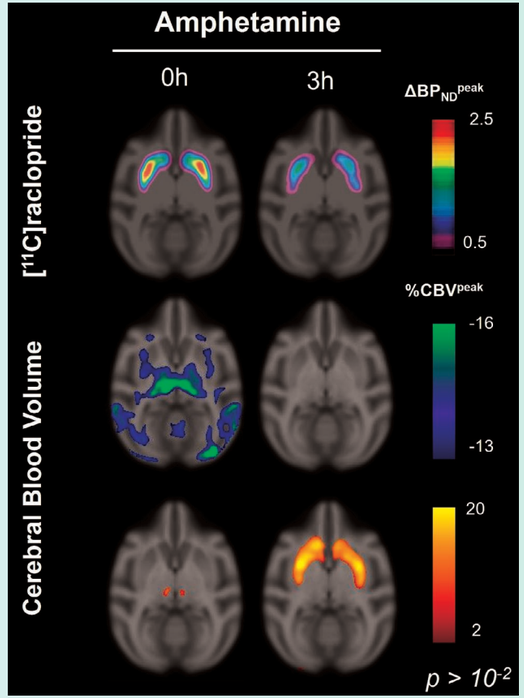
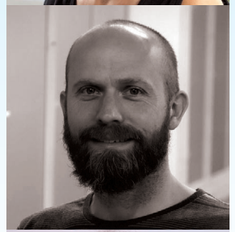


Figure 1: Decreased D2 receptor availability three hours after a naïve amphetamine challenge together with a remarkable sign change in cerebral blood volume (CBV) signal provide evidence for inhibitory D2 receptors being internalized but excitatory D1 receptors being available for functional signaling. From [Preprint: https://www.biorxiv.org/content/10.1101/2022.06.10.493955v1.full], Copyright © 2022 by the authors.

Preclinical Neurobiology

By Hanne D. Hansen, Mikael Palner & Jens H. Mikkelsen



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

For many years we have been involved in developing novel PET radiotracers for targets in the central nervous system (CNS), primarily classical G-protein coupled receptors such as the 5-HT2A and 5-HT7 receptor. In later years, we have also worked on developing a large animal model of protein aggregates in the brain [69] (**Figure 2**), allowing us to evaluate PET tracers targeting for example α-synuclein. One such novel PET tracer is (d3)-[^{11}C]MODAG-001 which was evaluated in the pig model [70]. In a series of experiments, we demonstrated in vivo detection of α-synuclein preformed fibrils in pigs using (d3)-[^{11}C] MODAG-001 (**Figure 3**).

In 2022, we published the results from a long going in vivo investigation of the effects of dorsal striatal dopamine release [14]. Using chemogenetics we selectively activated these dopaminergic neurons. Following stimulation we were able to assess whole-brain changes in neuronal activity [^{18}F]FDG-PET and metabolic markers (MR Spectroscopy) and found distal effects in the prefrontal cortex. Furthermore, we assessed a range of behaviors and found reduced anxiety and grooming. The paper was published in Neuropsychopharmacology and made the front cover.

Measuring plastic changes in the epileptic brain

More than 15 million people in the world have epilepsy; a neurological disease characterized by abnormal neuronal excitation and on enduring tendency to recurring seizures. These seizures may be few or many, mild or severe, focal or generalized, and have different origins. Notably and irrespective of the cause, one-third of the patients with epilepsy will at some stage develop drug-resistant epilepsy. The period from the causing injury to occurrence of the first seizure is traditionally denoted the latent phase (or silent phase), however, recent evidence from clinical and experimental research has documented that this period is indeed very active and critical for the development of seizures. Today, we are still unable to predict and prevent patients to enter into this

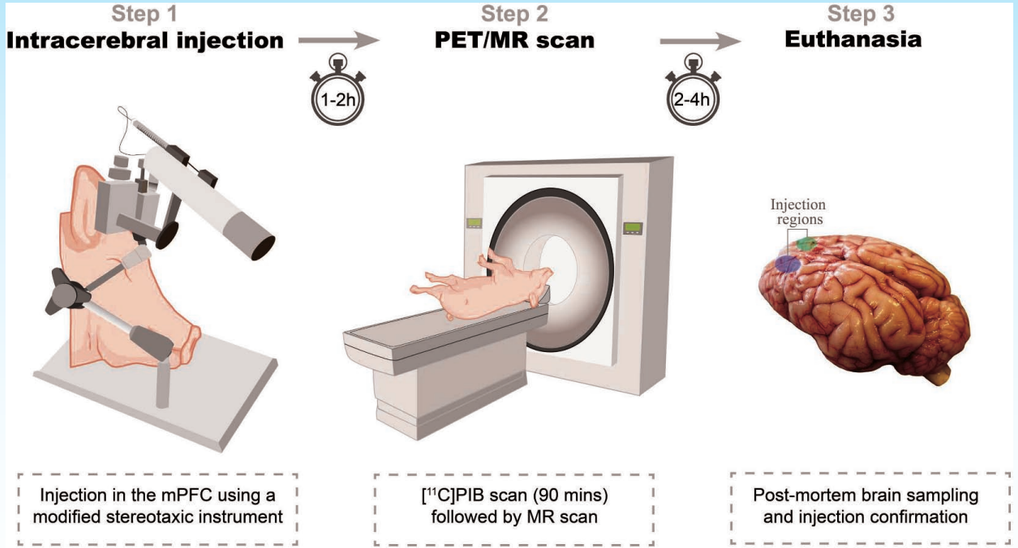
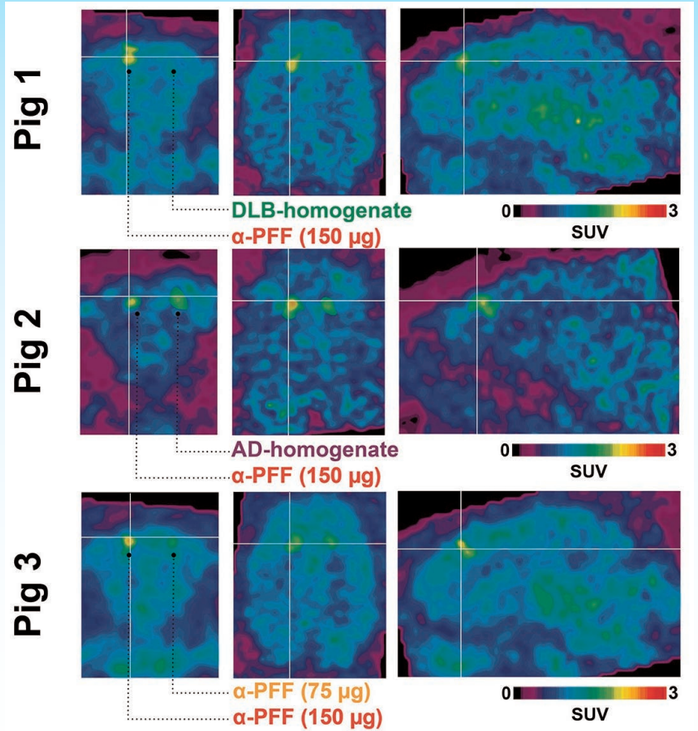


Figure 2: Schematic representation of the protein aggregate pig model. Step 1: Intracerebral injections of protein aggregates e.g., α-synuclein preformed fibrils or homogenate from Alzheimer's disease patients. Step 2: Animals are PET scanned with [^{11}C]PIB which binds to protein aggregates. Step 3: After the final scan, animals are euthanized, their brains removed, and the injection sites' pathology is confirmed by immunohistochemistry. From [69], Copyright © 2022 by the authors.



more severe and chronic phase. For example, patients that do not become seizure free on anti-seizure medication (ASM) do not differ from patients that respond to ASM based on magnetic resonance imaging (MRI) and electroencephalography (EEG).

In the epileptic brain, alterations in morphology and pathophysiology of the neurons and glia cells occur. The neuronal excitability in networks may eventually become high enough to generate unprovoked repetitive seizures. Therefore, measuring and perhaps preventing such changes are the aim of our work.

NRU researchers have been using the radioligand UCB-J that binds to the (pre)synaptic vesicle glycoprotein 2A (SV2A) for both imaging and ex vivo. The concentration of SV2A and the binding capacity for UCB-J is considered a marker of synaptic density. In human temporal cortical resections ex vivo obtained from patients

Figure 3: Summed PET images of (d3)-[^{11}C]MODAG-001 in pigs following injection of homogenate from Dementia with Lewy Bodies patients (DLB), Alzheimer's Disease patients (AD), or preformed fibrils of a-synuclein (a-PFF). The cross-hair indicates the injection site. From [70], Copyright © 2022 by the authors.

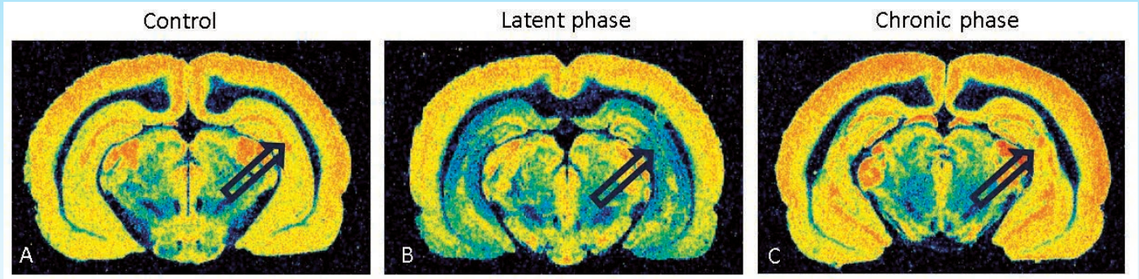


Figure 4: This figure illustrates the binding of the SV2A radiotracer, 3H-UCB-J, to brain sections from rats exposed to a single dose of the chemoconvulsant pilocarpine that induces status epilepticus acutely in the animal compared to control (A). The binding is lower in the hippocampus (arrows) in the latent phase about 10 days after the convulsions (B) that returns to control levels in the chronic phase about 3 months after the status epilepticus (C). Modified from [64], Copyright © 2022 by the authors.

with temporal lobe epilepsy, we found that SV2A is expressed in all cortical neuronal subtypes, and SV2A mRNA and binding levels are lower in epilepsy brains compared to matched post-mortem controls without neurological disease [63]. We have also studied spatial and temporal changes in SV2A binding in three chemiconvulsant models of epilepsy in rats [52, 64], and demonstrate that [^{3}H]-UCB-J radioligand binding decreases in the latent phase in the models while the level rises in the chronic phase (**Figure 4**), demonstrating a direct comparison between epileptogenesis occurring in patients and in these animal models of disease.

A major difference between animal model(s) and the human pathology is that all animals can develop epilepsy, but humans do not. We are therefore highly interested in comparing and understanding the biology and pathophysiology using SV2A as a marker in humans, and hypothesize that SV2A is a reliable marker of epileptogenesis in patients.

The NRU Neuroimaging Laboratory

By Patrick M. Fisher
Group leader

3T MRI scanner

Magnetic resonance imaging (MRI) is central to nearly all NRU research projects. Our research goals include facilitating collaborative, high-quality clinical brain imaging research studies at Rigshospitalet. We acquire MRI data primarily at MR001, NRU's own Siemens 3T Prisma scanner in the North Wing building. MR001 is shared with Dept of Radiology for clinical scanning 50% of working hours with the remaining time available for NRU research. We maintain trained MR-assistants, enabling us to complete research studies during working hours as well as evenings and weekends.

We continue to enjoy a great collaboration with Siemens, including the invaluable support from Karen Kettless, Siemens MRI Applications Specialist. This collaboration shortens the time from new ideas to implementation on the scanner.

Below is a brief overview of on-going MRI-based collaborations in 2022:

- In collaboration with professors Trevor Robbins and Barbara Sahakian from Cambridge University (UK) we are evaluating SSRI effects on cognitive processing in healthy individuals and individuals with OCD.
- The NEAD group led by professor Kamilla Miskowiak from Psychiatric Center Copenhagen acquires structural and functional MRI to evaluate brain imaging markers associated with mood disorders including bipolar disorder as well as associated treatments and alterations in cognition.
- The REFORM project with professor Messoud Ashina from the Danish Headache Center at Rigshospitalet-Glostrup continues a large data collection endeavor to evaluate structural and functional brain markers of an antibody treatment for migraine.
- The Entrepreneurship project with professor Toke Reichstein from the Copenhagen Business School aims to identify distinguishing aspects of reward- and risk-related brain function in serial entrepreneurs.
- The REVIVAL project with professor Christian Hassager from the Dept of Cardiology at Rigshospitalet is examining structural and functional imaging markers of cognitive recovery in patients following the experience of a cardiac arrest event.
- CONNECT-ME with associate professor Daniel Konziella from the Dept of Neurology at Rigshospitalet aims to identify brain connectivity markers in patients with disordered consciousness and prognostic indicators of recovery.
- NeuroPharm Project 2, an NRU-centered project, aims to identify brain imaging markers of serotonin 2A receptor modulation, including a focus on the serotonin psychedelic, psilocybin.
- The EPOCH project with professor Rigmor Jensen from the Danish Headache Center at Rigshospitalet-Glostrup evaluates clinical and imaging effects of psilocybin administration to patients with Chronic Cluster Headache.
- Two elements of the BrainDrugs center grant have started collecting MRI data in cohorts with depression and epilepsy.
- BIND (Brain Involvement in Dystrophinopathies) is a multi-site clinical research study with professor John Vissing from the Dept of Neurology at Rigshospitalet with an arm that will acquire structural and functional imaging in Becker Muscular Dystrophy patients.
- OLF fMRI with professor Christian von Buchwald from Ear-Nose-Throat Surgery at Rigshospitalet aims to evaluate brain imaging measures of smell in patients with impairment following Covid-19.
- The EU-funded R-Link project with professor Lars Kessing from Psychiatric Center Copenhagen aims to optimize response to Lithium treatment through personalized evaluation of individuals with bipolar I disorder.
- The KME project with professor Anders Fink-Jensen from Psychiatric Center Copenhagen uses MRS to investigate if a dietary supplement of a Ketone Mono Ester (KME) beverage reduces the use of benzodiazepines in alcohol withdrawal syndrome.
- The ECAC project with professor Tiit Mathiesen from the Dept of Neurosurgery at Rigshospitalet aims to investigate correlations between arachnoid cysts and cognitive dysfunction, to elucidate the eventual role played by inflammation and glymphatic flow dysfunction and to identify the impacted functional networks.
- Associate professor Melanie Ganz from NRU is continuing the application of real-time motion correction to assist with clinical brain imaging of small children, mitigating the need for general anesthesia.
- The UFMR project with NRU PhD student Sara Marie Larsen applies an ultra-fast and non-invasive MRI tool for measuring brain pulsations to aid diagnosing patients with increased intracranial pressure.
- The Pill Project led by associate professor Vibe Frøkjær at NRU, is a longitudinal study evaluating effects of oral contraceptives on cognition and the brain in healthy women.
- The Stroke Project led by professor Gitte Moos Knudsen at NRU applies MRI to evaluate structural and functional brain changes following stroke.
- The Neuromelanin project led by NRU chief technologist Gerda Thomsen aims to compare methods for estimating DAT levels in the brain with PET and MRI.

SPECT-CT system

The SPECT laboratory of NRU is located next to the Dept of Radiology on the ground floor in the North Wing of Rigshospitalet. The facility is used both diagnostically and for research purposes. Our 3rd generation high-resolution AnyScan SPECT-CT Mediso scanner provides very good images, and we continue to develop new methodologies in collaboration with Mediso.

Clinical work

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

Regional cerebral blood flow (CBF) 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. In 2022, we have completed collection of a new diagnostic reference material for CBF with [^{99m}Tc]HMPAO, including two males and two females in each decade from 20-80 years.

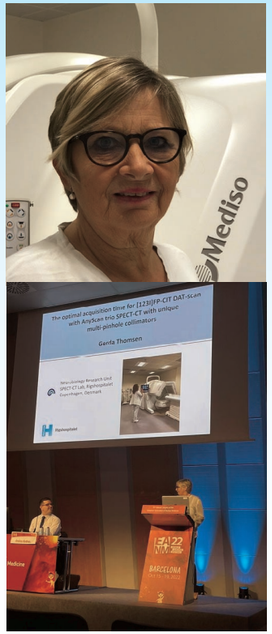
Striatal dopamine transporter imaging with the SPECT ligand [^{123}I]FP-CIT

This is a robust technique for early detection of dopaminergic deficits and is used diagnostically in patients with movements disorder and/or dementias of uncertain origin. The diagnostic report comes with a reference to a healthy age-matched population and is evaluated by a neurologist specialized in reading DAT-SPECT scan data. We are currently completing the acquisition of a new diagnostic reference material for FP-CIT.

Research projects

We have in collaboration with professor Anders Fink-Jensen and Mette Kruse Klausen from Psychiatric Center Copenhagen, published results from a clinical trial with exenatide in patients

By Gerda Thomsen
Chief technologist



with alcohol use disorder (AUD) [38]. Our data revealed that although exenatide did not significantly reduce the number of heavy drinking days compared with placebo, it significantly attenuated fMRI alcohol cue reactivity in the ventral striatum and septal area, which are crucial brain areas for drug reward and addiction. In addition, dopamine transporter availability was lower in the exenatide group compared with the placebo group (**Figure 5**). Exploratory analyses revealed that exenatide significantly reduced heavy drinking days and total alcohol intake in a subgroup of obese patients. Adverse events were mainly gastrointestinal. Also, we have enrolled and scanned patients referred for dopaminergic investigation as part of an ongoing study which is a 'head-to-head' comparison of the [^{123}I]FP-CIT SPECT-CT and [^{18}F]FE-PE2I PET-CT modalities as well as an evaluation of the usefulness of adding MR based neuromelanin measurements. Data acquisition for this study continues in 2023.

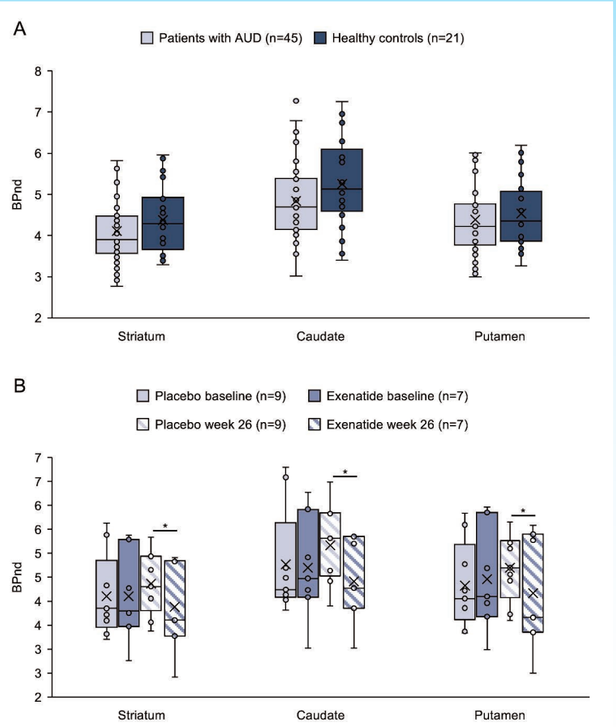


*Figure 5: (A) Baseline dopamine transporter (DAT) availability in striatum, caudate, and putamen in AUD patients did not differ from that in healthy controls (HC). Data were analyzed with a 1-way ANCOVA, adjusted for baseline DAT availability. HC, n = 21; patients at baseline, n = 45. (B) At the week 26 rescan, DAT availability in striatum, caudate, and putamen was significantly lower in the exenatide group compared with the placebo group. Data were analyzed with an ANCOVA adjusted for age. Placebo, n = 9; exenatide, n = 7. *P < 0.05. (A and B) Boxes represent upper and lower quartiles, the line represents the median, and the X represents the mean. From [38], Copyright © 2022 by the authors.*

Data Analysis

By Claus Svarer
Chief engineer

In the NRU data analysis group, we have continued to optimize strategies for analysis of PET- and MR-imaging data, to improve reproducibility and sensitivity. By improvement of statistical or quantification methods of molecular neuroimaging studies, one can better handle noisy data from smaller samples sizes. Through data sharing initiatives, e.g., the NovoNordisk Foundation funded OpenNeuroPET project which started in 2021, we can increase the number of observations and thereby improve the statistical power. We are also working on improving our methods for automatized analysis of patient data from our Mediso Anyscan SPECT scanner.

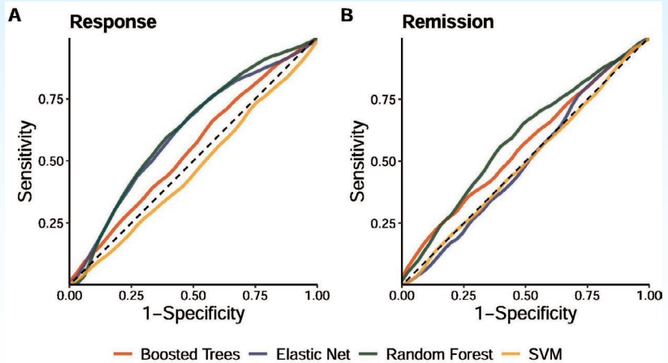


Figure 6: Predictive performance measured by the receiver operating characteristic curves of different classifiers for the classification of (A) response and (B) remission in the NP1 dataset. The top left corner corresponds to perfect predictive performance and the dotted line to chance. From [8], Copyright © 2022 by the authors.

By capitalizing on our NeuroPharm 1 (NP1) dataset with MDD patients, we have evaluated if structural brain MRI can predict the outcome of initiated drug treatment [8]. The random forest, boosted trees, support vector machines and elastic net classifiers were evaluated for their ability to predict treatment response and remission (**Figure 6**). Our primary findings in the NeuroPharm cohort show some but limited predictive value and most importantly, the models did not generalize to an independent cohort (ENIGMA), suggesting limited clinical applicability.

Drug occupancy measures with PET have become key to demonstrate target interaction and to define the right dose in clinical drug trials. In simulation studies with ^{11}C-Cimbi36, we evaluated the outcome of different study designs for a PET baseline-block occupancy experiment [43]. We find that drug doses corresponding to less than 40% receptor occupancy has limited value in describing the drug exposure/receptor occupancy relationship. We also compared three different analytical methods: the widely established Lassen plot, and two newer maximum likelihood-based estimators (LEO and LEA), and find that the likelihood-based methods are superior and require fewer people.

We have developed and assessed a pipeline for processing of multisite images in order to curate, preprocess, quality control (QC), and compute image-derived phenotypes (IDPs) from the European Prevention of Alzheimer Dementia (EPAD) MRI dataset [45]. Also, in an MRI case-control cross-sectional study of adults with relapsing remitting multiple sclerosis with or without chronic neuropathic limb pain we found functional and structural changes compatible with dysfunction of the descending pain modulatory system (https://doi.org/10.1093/braincomms/fcac124).

We have also taken part in a survey of lab practices which show that the adoption rate of open practices for transparent, reproducible, and collaborative science still is in its infancy [58]. Clearly, information required for implementing open science practices throughout the different steps of a research project is scattered between many different sources (**Figure 7**). In the paper, we review tools and practices supporting study inception and planning, data acquisition, research data management, data processing and analysis, and research dissemination. We argue that it will be helpful for researchers and institutions alike to make a successful and sustainable move towards open and reproducible science.

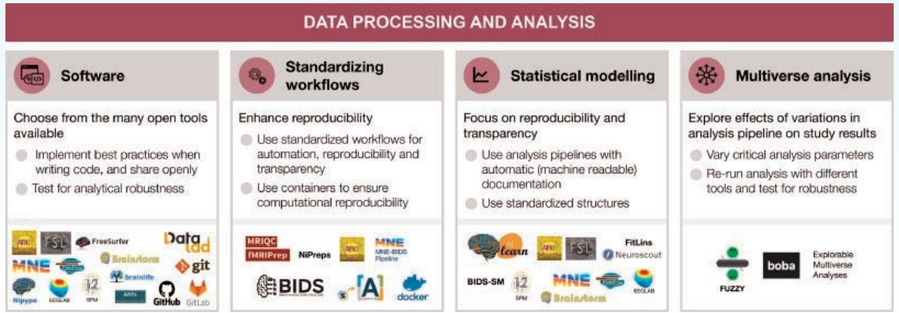


Figure 7: Data processing and analysis: For each step, the figure contains the main goals (headings), specific recommendations (bullet list), and useful tools (icons). Sources: Icons from the Noun Project: Software by Adrien Coquet; Workflow by D. Sahua; Statistics by Creative Stall; Chaos Sigil by Avana Vana; Logos: used with permission by the copyright holders. From [58], Copyright © 2022 Published by Elsevier Inc.

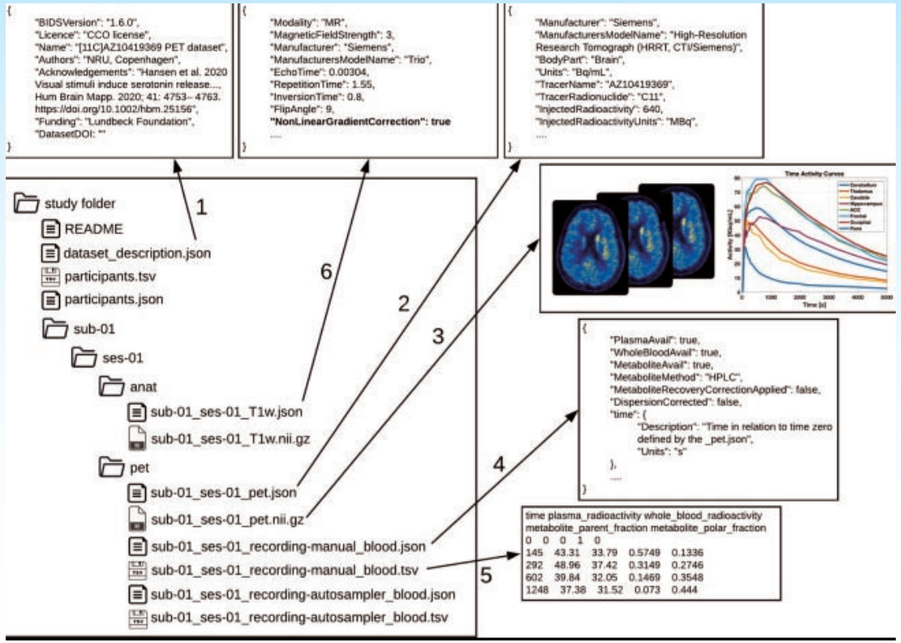


Figure 8: Exemplary PET-BIDS dataset with a dataset description, including adequate acknowledgements (1). The left side shows a directory tree of a common PET-BIDS dataset, with files in the root directory describing the dataset (README and data description.json), a file with participant-specific information (participants.tsv), and a JSON sidecar file describing the metadata needed to understand the corresponding TSV file. Next to the files in the root directory, there are subject directories named sub-<label> for each study participant. In the subject directory lies all acquired data divided into modalities (anat and pet, for the structural MRI and PET, respectively). The content of the pet directory is displayed in the right side of the figure, including the metadata of the raw PET data (2), and the associated imaging data (3). The metadata for the blood data acquired using manual sampling is stored in a JSON sidecar file (4), with the corresponding blood specified in the TSV file (5). Blood data acquired using an autosampler is also available following a similar structure as (4) and (5). The PET data may be accompanied with MRI data for coregistration and region definition (6). In this case, it is required to specify if the MRI data has been corrected for gradient non-linearities (NonLinearGradientCorrection) to allow for correct co-registration with the PET data. From [59], Copyright © 2022 by the authors.

Our OpenNeuroPET extension of the BIDS standard to include PET-data, also known as PET-BIDS (**Figure 8**), has enabled several open-access datasets to be curated according to PET-BIDS standards and tools for conversion, validation and analysis of PET-BIDS datasets are now ready, as presented in [59].

We have adapted existing efficient methods to adjust for multiple comparisons in the context of clinical trials resulting in advanced latent variable models (LVMs) which can be used to analyze PET data for investigation of, e.g., associations across multiple brain regions [61]. We also extended the original procedure to better handle small samples and provide more reliable diagnostic tests in the LVM framework. The former point is illustrated in **Figure 9**, where the lower right panel shows the type 1 error of the proposed procedure which is much closer to its nominal level compared to competitors such as Bonferroni adjustment. We are now developing a similar adaptation for linear mixed models (LMMs), another popular model in neuroscience.

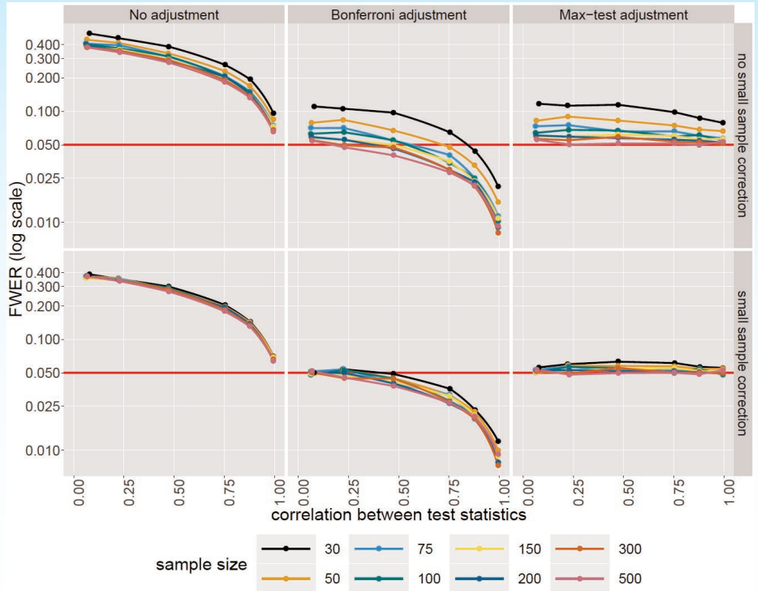


Figure 9. Family-wise error rate (FWER) when testing nine null hypotheses with Wald tests using different procedures to adjust the p-values for multiple comparisons (columns). The rows indicate whether a small sample correction is used. For instance in the third column, the upper row uses a max-z test while the lower row uses a max-t test. The correlation reported in the x-axis is the median Pearson correlation between the test statistics computed over the repetitions. For the y-axis, a logarithmic scale was used. From [61], Copyright © 2022 by the authors.

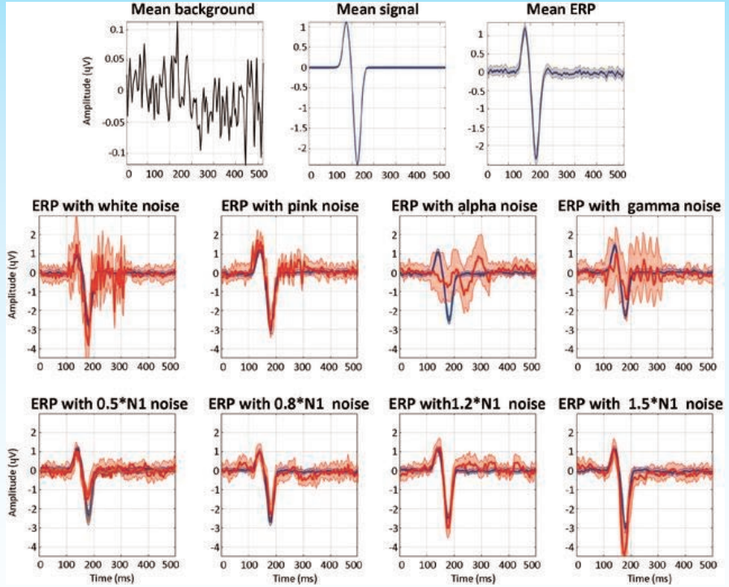


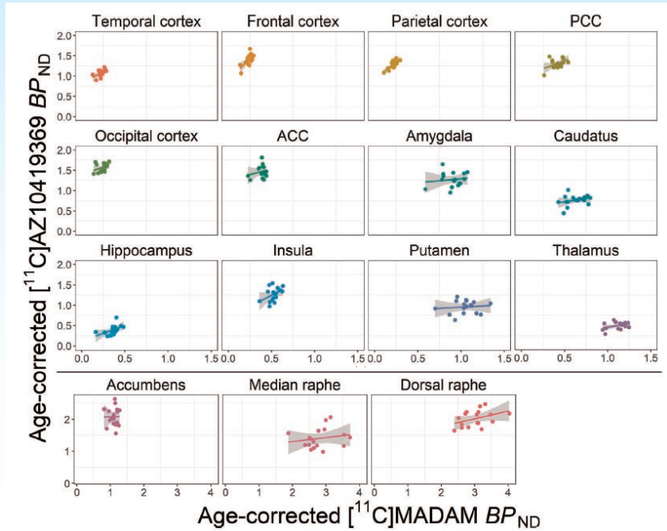
Figure 10. Illustration of simulated event-related potentials (ERPs) ground truth with the different types of outlier trials. At the top is shown the mean background, mean signal and resulting generated ERP with its 95% confidence intervals. In each subsequent subplot is shown the mean ERP ground truth from 160 trials with their 95% confidence intervals (blue) with an SNR of 1. The first row shows in red the mean ERP from outlier trials generated by adding white noise, pink noise, alpha or gamma oscillations; the second row shows the mean ERP from outlier trials generated with variable outlier-to-signal ratio (OSR) on the N1 component. From [65], Copyright © 2022 by the authors.

We also present a new EEG data analysis method for weighting trials based on their dynamic [65]. The method is fast and robust to outliers and is a least squares solution for whole space EEG data statistical modelling. **Figure 10** demonstrates a possible increase of statistical power depending on the inference method in question.

In a systematic review, we provide an overview of quantitative molecular neuroimaging methods that potentially can identify adverse side effects of cancer therapy in normal-appearing brain tissue [66]. Seventy studies identified through MEDLINE and Web of Science databases and reporting changes in normal-appearing brain tissue using MRI, PET, or SPECT quantitative biomarkers, related to radio-, chemo-, immuno-, or hormone therapy for any kind of solid, cystic, or liquid tumor were included. For each imaging method, this review provides the methodological background, and the benefits and shortcomings of each method from the imaging perspective. Finally, a set of recommendations is proposed to be implemented in future research studies.

In a meta-analysis [68] we showed that patients with first-episode-psychosis or schizophrenia had lower dopamine D2-receptor availability in the thalamus, compared to healthy controls. When including only radioligands that display good affinity for extrastriatal D2-receptors in the analysis, a similar pattern was observed. The overall effect size is, however, of smaller magnitude, emphasizing the need for large sample sizes or data pooling initiatives for this research question.

The regional relationship between the brain 5-HT1B receptor and 5-HT transporter were also established in healthy individuals examined twice with PET, using the radioligands [11C]AZ10419369 (5-HT1BR) and [11C]MADAM (5-HT transporter) [74]. The two targets are in all examined brain regions positively correlated, suggesting a link between these two key proteins regulating synaptic serotonin levels (**Figure 11**).



The serotonin system is implicated in several psychiatric disorders where cognitive impairment is a common feature. Several markers for the serotonin system have been associated with cognitive function. We failed, however, in a group of 43 healthy individuals, to replicate a previous report of a positive association between 5-HT1B receptor availability in the dorsal brainstem and visuospatial memory performance [77]. Exploratory analysis showed higher 5-HT1B receptor availability associated with more false positive responses and faster reaction time, but lower performance in planning and problem-solving.

Figure 11. Scatter plots of [11C]AZ10419369 and [11C]MADAM binding in different brain regions. Plotted BP_{ND} values are corrected for age. For purposes of visualization separate scales have been used in the three lowest panels (Accumbens, median and dorsal raphe nuclei, situated below the black horizontal line). Regression lines with 95% confidence interval in shaded gray. ACC=Anterior cingulate cortex, PCC=Posterior cingulate cortex, BP_{ND}= non-displaceable binding potential. From [74], Copyright © 2022 by the authors.

Neuropsychology

By Dea S. Stenbæk
Group leader

In 2022, we continued our research on psilocybin as a major theme for the psychology group, investigating quantitative and qualitative aspects of the psychedelic experience focusing on the Mystical Experience (**Figure 12**), and further associations between the Mystical Experience and long-term outcomes [49, 75]. We also established and described a novel music program, i.e., the Copenhagen Music Program [51], which is used in our studies of alcohol use disorder [31] and OCD (in collaboration with Imperial College London) and which will be used in a future study of depression as well as in studies of healthy volunteers. At Dept of Psychology at Univ. Copenhagen, we established the Copenhagen University Clinic for Psychedelic Research headed by associate professor Dea S. Stenbæk where some of our psychedelic sessions will take place in future studies.

Another theme was affective cognition in healthy volunteers and somatic patients [5, 33] as well as psychological factors related to experiencing a cardiac arrest [4, 83]. We have continued fruitful collaborations with the Cambridge Cognition Group and Imperial College London where we are continuing data collection for two studies of the effects of sub-chronic treatment with SSRI in patients with OCD and neurocognitive mechanisms of psilocybin treatment in patients with OCD, respectively.

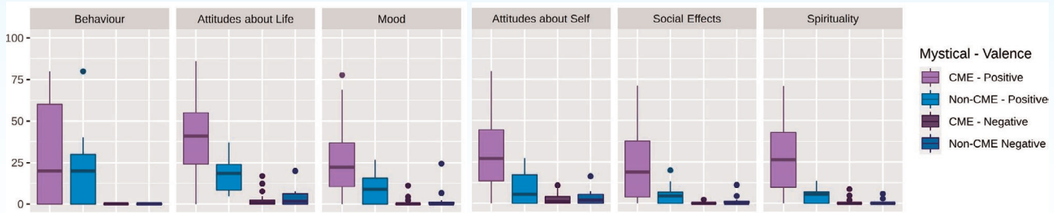


Figure 12. Boxplots showing Persisting Effect Questionnaire (PEQ) scores relating to either Complete Mystical Experiences (CME) (purple) or non-CME (blue). Each plot represents the positive (lighter colours, left) and negative (darker colours, right) aspects of each PEQ subscale. The middle line in each box represents the median. Lower and upper hinges represent first and third quartiles. Datapoints more than 1.5 interquartile range beyond the hinges are plotted as outliers. Modified from [49], Copyright © 2022 by the authors.

Clinical Psychiatry

By Vibe G. Frøkjær
Group leader

To provide a rationale for targeted prevention and treatment of mental disorders, we search for risk and resilience biomarkers which can serve to assist precision medicine approaches. This is done through our many cross-disciplinary collaborations [36, 37, 46, 47]. We hold a special expertise in molecular brain imaging of neurotransmitter systems [29] involved in neuropsychiatric disorders and their treatments. In particular, we are interested in serotonin brain biology in the treatment mechanisms for depression [18, 21, 32, 40, 42] and as a driver of healthy adaptation to stressors [57], genetic make-up, and sex-steroid hormones shifts [11].

Major depressive disorder (MDD)

Building on data acquired in NeuroPharm, we continue to search for relevant biomarkers to define subtypes of MDD that respond differently to treatment, to predict the outcome. Examples of these outcomes are given in the BrainDrugs section (page 48). As part of an international collaboration on the effect of electroconvulsive treatment (ECT) in severe depression, we have demonstrated that compared to nonpsychotic major depression (NPMD) psychotic major depression (PMD) shows lower gray matter volume (GMV) in the prefrontal, temporal and parietal cortex before ECT [76]. Also, following ECT, lower GMV in the medial prefrontal cortex was consistently identified in PMD.

Sex-steroid hormones and reproductive mental health

The dynamic interplay between brain biology and sex-steroid hormone systems represents a potent driver of risk and resilience for neuropsychiatric disorders and a better understanding of this could identify targetable risk and disease mechanisms. We have proposed that maladaptation to hormone transitions, such as across pregnancy and the postpartum period and perimenopause, may play a role in distinct subgroups within MDD. This we study in pharmacological models [10] as well as across the perinatal transition. We have found that the presence of anxiety during pregnancy can increase susceptibility to postpartum distress even in healthy women, although most healthy women adapt well to the abrupt drop in estradiol postpartum [11].

In collaborative and ongoing studies of high-risk women, Vibe Frøkjær and her group currently attempt to identify risk for perinatal depression [35, 56], and to protect mental health across reproductive age, including mother and infant mental health during pregnancy and at the postpartum [9, 12].

Clinical Neurology

By Olaf Paulson
Group leader

Hypoxia, cerebral blood flow, and metabolism

Exposure to moderate hypoxia leads to cerebral lactate production. The mechanism by which the lactate production is triggered was explored by MR in volunteers where the same degree of reduced arterial oxygen concentration was induced by inhaling either hypoxic air or carbon monoxide. In both groups, cerebral blood flow increased and cerebral metabolic rate of oxygen remained unchanged, whereas lactate production only increased with inhalation of hypoxic air. These results point toward a mechanism of lactate production by upregulation of glycolysis mediated by sensing a reduced arterial oxygen pressure [79].

Glucocorticoid treatment for non-cerebral diseases in children

Previous studies from our groups have shown that glucocorticoid treatment for non-cerebral diseases in children may lead to changes both in mental function and in brain structure. The present study is a follow up, demonstrating alterations in the microstructure of the uncinate fasciculus [80].

Epilepsy

By Lars Pinborg
Associate professor

At NRU and the Epilepsy Clinic at Rigshospitalet we aim at optimizing existing and developing new tools for precise and high-quality diagnostics and treatment of patients with epilepsy. Together with national and international partners, we work both within the Danish Epilepsy Surgery Program and the precision medicine initiative BrainDrugs.

Within the MELD consortium (https://meldproject.github.io) we published two studies on the use of machine learning for diagnosing subtle focal cortical dysplasias [73] and an MRI atlas demonstrating the anatomical location of focal cortical dysplasia [84] in epilepsy patients (**Figures 13 and 14**).

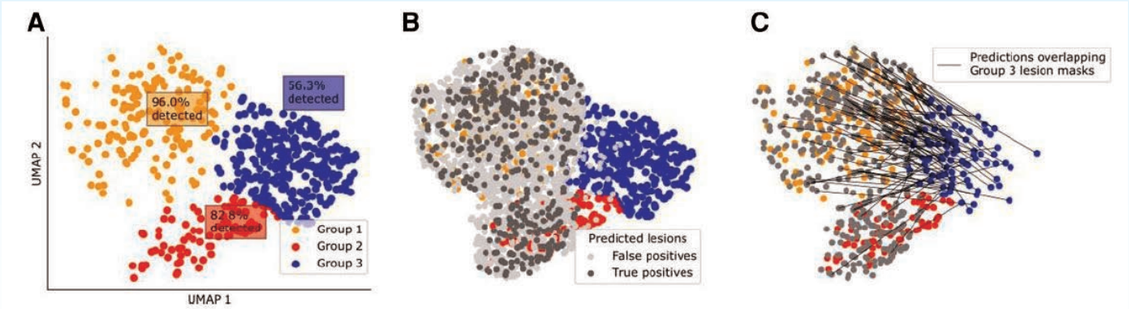


Figure 13. UMAP embedding of classifier predictions. (A) Data-driven clustering of UMAP embedding of lesional T1 features reveals three distinct groups of lesions. (B) True positive and false positive clusters derived from the neural network superimposed on A. Feature values in true positive and false positive clusters are similar to either group 1 or 2. Clusters are not similar to healthy cortex or group 3. (C) Predicted clusters overlapping lesion masks from group 3 lesions are superimposed. The feature values in the predicted clusters are similar to group 1 or 2, i.e. the network has identified vertices exhibiting characteristically abnormal MRI features in FCD. From [73], Copyright © 2022 by the authors.

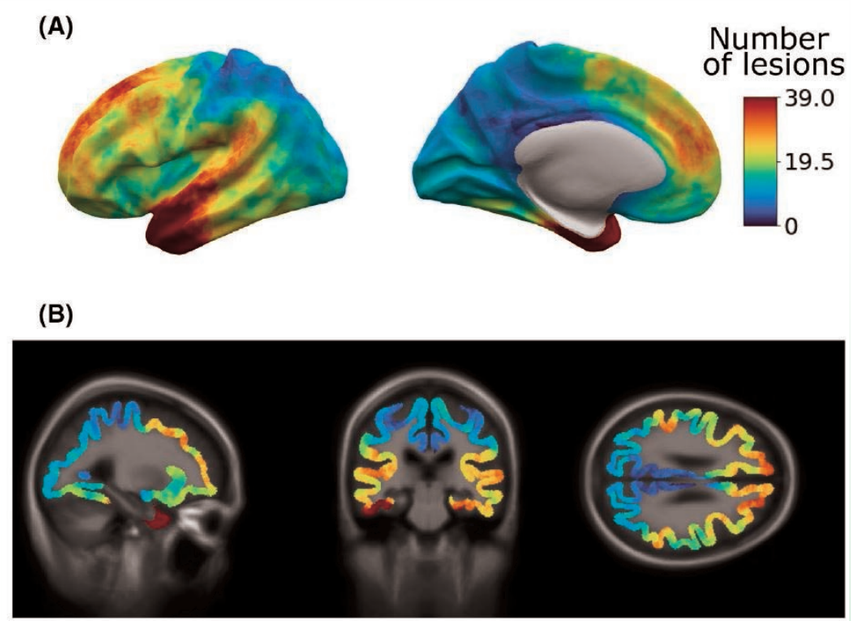
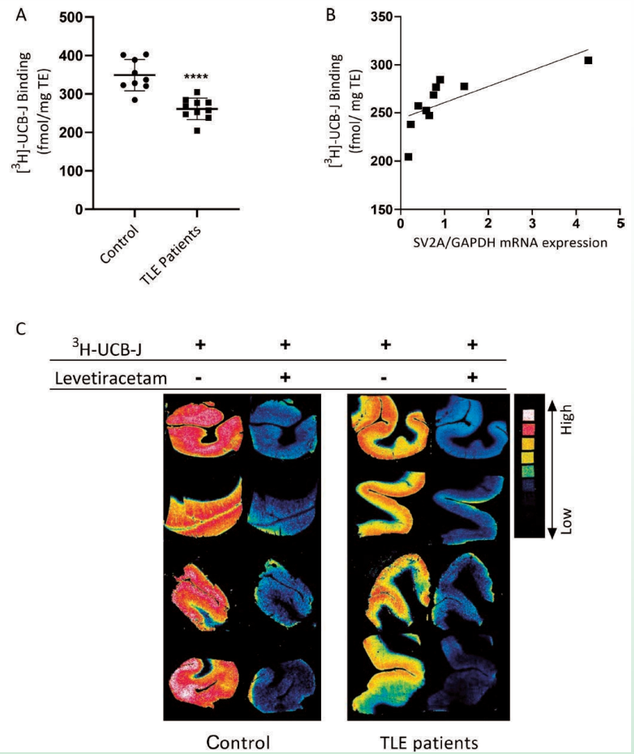


Figure 14. Distribution of focal cortical dysplasia (FCD) lesions across the cerebral cortex. (A) All FCD lesion masks mapped to the left hemisphere of the template cortical surface. The distribution of FCDs across the cerebral cortex is nonuniform, with higher concentrations in the superior frontal sulcus, frontal pole, temporal pole, and superior temporal gyrus. (B) Three-dimensional lesion likelihood atlas. Aggregated surface-based lesion map values were normalized to between 0 and 1 and mapped back to the template magnetic resonance imaging volume. Modified from [84], Copyright © 2021 by the authors.

Biomarkers for early identification of abnormalities in new-onset epilepsy are key to developing precision medicine. In 2022, we contributed to studies aiming at optimizing the use of both standard [6] and HD-EEG [27]. We demonstrated SV2A binding sites in hippocampal tissue (**Figure 15**) from epilepsy surgery patients [63] which we use with PET in BrainDrugs to demonstrate changes in the levetiracetam binding site and synaptic integrity already at the time of diagnosis in epilepsy patients. We initiated a special issue on epilepsy in the Danish Medical Journal, and contributed with an article on co-morbid depression and anxiety [67] which in many patients is present already at the time of epilepsy diagnosis and even before the first seizure.

*Figure 15. [^{3}H]-UCB-J binding level in cortex tissue and correlation of SV2A mRNA level with [^{3}H]-UCB-J binding. Quantitative autoradiographic measurements of cortical [^{3}H]-UCB-J density is expressed as specific binding in nCi/mg tissue in cortex of TLE (temporal lobe epilepsy) patients (n = 10) and non-epileptic postmortem controls (n = 9) (Student's t-test; p < 0.001, t = 5.506, df = 17, 95% confidence interval). All the values are in Mean ± SD (**A**). Positive correlation between SV2A gene expression levels and [^{3}H]-UCB-J binding levels of patients (n = 10, r = 0.72, p = 0.018, 95% confidence interval). r represents the Pearson's correlation coefficient. p < 0.05 is considered statistically significant for all comparisons. Investigated correlations were linear. (**B**) Four different representative autoradiogram images of cortex from both TLE patients and controls. Non-specific binding was shown with 10 mM levetiracetam addition to incubation solution of adjacent slice (**C**). From [63], Copyright © 2022 by the authors.*



Innovation Fund Denmark

NeuroPharm

Center for Experimental Medicine Neuropharmacology

Center director
Gitte Moos Knudsen

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 Univ. Copenhagen and three from university hospitals in the Capital Region of Denmark. International partners include Massachusetts General Hospital/Harvard and the British-based enterprise, Invicro LLC. Imperial College London is involved as affiliated partner. 2022 has been the final year of NeuroPharm and the successful completion of the research in the center will be celebrated with a festive closing symposium in April, 2023, in the Royal Danish Academy of Sciences and Letters in Copenhagen, Denmark.

The goal of *NeuroPharm* has been 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 latest status of the research in 3 of the 4 *NeuroPharm* work packages is described below. Work package 3 (NP3) was completed a few years back.

By 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 also illuminate basic mechanisms of action of pharmacological treatment of Major Depressive Disorder (MDD) and will help provide a rationale for tailored treatment choice for MDD patients rather than - as is the case today - rely exclusively on clinical assessment.

We have collected a rich deep phenotyping dataset in a population of 100 MDD patients and examined how different markers (neuropsychology, MRI, PET, EEG, functional genomics, biochemistry) relate to the outcome of a standard antidepressant treatment, i.e., escitalopram. Patients have been followed across a period of 12 weeks from treatment start.

We are in the dissemination phase and in 2022 have showed that antidepressant treatment improve cognition in a manner independent improvement in mood symptoms, emphasizing that cognitive disturbances are a distinct symptom and treatment target in MDD [18], unmedicated patients with prominent anxiety in their depressed state have particularly low serotonin 4 receptor brain binding pre-treatment and appear to benefit more from the treatment [40], and in women reproductive state may matter for treatment efficacy of serotonergic drugs [42]. Meanwhile, brain response when processing emotions as captured by fMRI does not distinguish depressed individuals from healthy controls, nor is it predictive of antidepressant treatment response [21]. Also, while treatment is associated with reduction in markers of oxidative stress this does not map onto clinical antidepressant response [32].

We are currently evaluating to what extent prediction models of treatment outcomes can be improved by integrating baseline deep phenotyping outcomes. Also, we collaborate in consortium structures to provide cross-validation resources for findings in related cohorts, e.g., the COORDINATE-MDD consortium led by Dr Fu, Imperial College London (UK). To this end we have showed that using pretreatment structural brain MRI to predict drug treatment outcome is not valid across independent cohort suggesting limited clinical applicability [8].

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

By Patrick Fisher
NP2 WP-leader

NP2 applies an experimental medicine strategy coupled with human functional and molecular neuroimaging to elucidate the effects of 5-HT$_{2A}$ receptor (5-HT$_{2A}$R) modulation on brain function and mood in healthy individuals. We compare 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 three planned projects was completed in 2021!

Although there was not much data collection for NP2 in 2022, we busily worked on the data that we did collect. We published a study evaluating questionnaire and free-form descriptions of the acute psilocybin effects [49], as well as an international, collaborative review on the field of psychedelic resting-state brain imaging, promoting good practices for balancing replication and novel analyses [50]. Also, we have reported on lasting positive effects of psilocybin on mystical-type experiences and increased trait mindfulness [75], and on acute psilocybin effects on brain connectivity dynamics and their association with drug levels and the psychedelic experience [60]. We nearly completed an evaluation of acute psilocybin effects on cerebral blood flow, but did submit a preprint publication on psilocybin effects in treating chronic cluster headache (Horton's). Finally, in 2022 we finished data collection for an off-shoot project that will evaluate lasting effects of psilocybin administration on synaptic density in healthy humans. We look forward to sharing those data and results from other projects as we continue to leverage the wealth of data that was collected across the NP2 projects, even beyond the conclusion of NeuroPharm in 2023!

By Brice Ozenne
NP4 WP-leader

NP4: Bioinformatics, statistical and predictive models

Based on data collected in NP1, NP4 is finishing its work on predicting recovery following SSRI prescription. As described on page 32, structural brain MRI shows limited predictive ability [8]. Taking advantage of measurements from several modalities (e.g., PET, MR, EEG, and cognition) being available for patients in the NP1 dataset, we have also developed and evaluated a refined predictive model and will disseminate the results in the near future.

To facilitate the use of appropriate statistical models, we also developed a new implementation of linear mixed model with a user-friendly interface and functionalities often requested by NRU researchers (e.g., partial residual plots, and adjustment for multiple comparisons). This implementation is an R package called LMMstar available at https://cran.r-project.org/web/packages/LMMstar/index.html.

NP4 continued to assist other work packages with analysis of their data, e.g., we have developed:

- Latent Variables Models to relate cognitive biases, concurrent anxiety, contraceptive use to serotonin brain levels [5, 40, 42].
- Competing risks models for registry data to study whether the risk of Alzheimer's disease can be lowered by increasing brain clearance of neurotoxic protein [7].
- A statistical framework to evaluate the impact of reducing the number of saliva samples on the estimation of the cortisol awakening response [57]. We also studied how the time at which the saliva samples were taken influenced the results (**Figure 16**) and suggested a regression model to mitigate the bias.

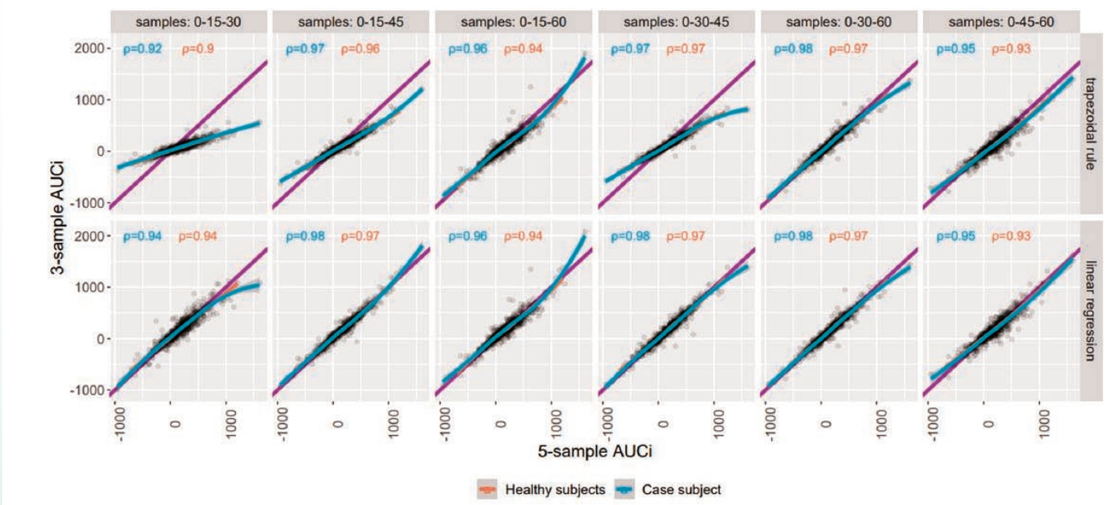


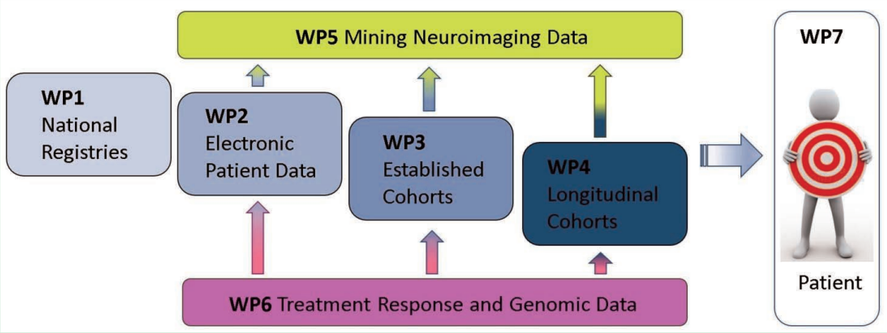
Figure 16: Scatterplot of the estimated 3-sample AUCi (area under the curve with respect to increase) and the estimated 5-sample AUCi and their estimated correlation (denoted by ρ). The estimates for both healthy and case subjects are shown with black points. The colored lines show the trend separately for the healthy subjects (orange) and case subjects (turquoise). The lines are not always visible because the two study groups are almost superimposed. The purple line is the identity line corresponding to no bias. From [57], Copyright © 2022 ElsevierLtd.

BrainDrugs

Center director
Gitte Moos Knudsen

The strategic research alliance *BrainDrugs* (2019-26) is our large-scale precision medicine project in epilepsy and depression (https://braindrugs.nru.dk). The alliance is 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 vision is that *BrainDrugs* can serve as a model to be implemented internationally, and for other brain disorders.

The alliance builds on strong cross-disciplinary research environments within universities and hospitals in Denmark and by affiliated 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, Univ. 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 project consists of seven coherent work packages, as depicted in the diagram below. In the following, we present status on the work in WP1-WP5.



The overall project is well underway and to ensure maximal synergy between the work packages and campuses, in 2022 we have continued our BrainDrugs Early Career Forum (ECF) bi-weekly meetings and our quarterly Work Package Leader meetings. In June we hosted the third *BrainDrugs* annual meeting at Comwell Borupgaard (see photo above) and again this was a very productive 1½-day meeting where the status of the various work packages was presented and diligently discussed, and where time was also spent on two parallel break-out discussion sessions focusing on MDD and epilepsy. Furthermore, apart from the scientific discussions, the annual meeting was an excellent opportunity for informal social interactions.

WP1: National registries

WP1-leader: Professor Lars V. Kessing

Danish registries represent a unique opportunity to explore enormous data amounts with respect to health data, e.g., registries of prescriptions combined with morbidity data and other patient record data with phenotypic information. Within this WP, we focus on both patient groups' drug intake to identify comorbidity, potential side effects, and drug response. We also use Danish population-based registries to validate the outcome of various pharmacological interventions. The national registries also play an increasing role in WP3 and WP5.

Over the last 12 months, WP1 has published three nation-wide population-based longitudinal register linkage studies. Here, we show that patients with comorbid epilepsy and depression have a poorer response to antidepressants compared to patients with depression only (doi: 10.1016/j.jad.2021.11.046). Similarly, patients with bipolar disorder and comorbid epilepsy have a poorer response to lithium than patients without comorbid epilepsy, but lamotrigine and valproic acid are as effective in both groups (doi: 10.1016/j.jad.2022.04.098). We also identified a bi-directional relationship between depression and epilepsy: The risk of depression was highest in the few years preceding and after an epilepsy diagnosis, and vice versa, but remained elevated. Getting a diagnosis of depression after an epilepsy diagnosis is associated with a 1.20-fold hazard ratio of acute hospital admission with seizures (doi: 10.1212/wnl.0000000000201542).

WP2-leaders: Professors Søren Brunak & Anders Søgaard

WP2: Electronic patient data: Text mining and machine learning

WP2 uses text mining methods to extract detailed, phenotypic features from free text in Electronic Patient Records (EPRs). EPRs come from two sources: the Capital Region of Demark and Region Zealand from 2009-2018 and from the specialized national epilepsy hospital, Filadelfia.

In 2022, we have finished and submitted a central WP2 paper on subgrouping epilepsy patients into focal and generalized subcategories. ICD-10-coded epilepsy diagnoses in the National Prescription Registry (NPR) exhibit a low positive predictive value, which reduces appropriate use of the register for in-depth studies in *BrainDrugs*. We demonstrate how text-mining can be used to discard patients who despite being coded as such in the NPR are unlikely to have an epilepsy diagnosis. Furthermore, text-mining can be used to drive the initial epilepsy subtype classification. Of 17,954 patients with a registered epilepsy diagnosis in NPR, 58.2% were classified as likely true epilepsy patients by the text mining algorithm; we were further able to classify 85.4% of these patients into focal, generalized, or unclassifiable epilepsy types. In 48.6% of these cases, we confirmed the NPR diagnosis (whether that be focal, generalized, or unknown) and in 26.9% of the cases, the text-mining pipeline assisted in assigning an epilepsy type, beyond the unspecific epilepsy diagnosis coded in the NPR. These subgroupings will now be employed going forward when examining adverse drug reactions based on the EPRs, and for pharmacogenomics work when genotypes are available.

We capitalize greatly from the epilepsy expertise available in WP1 and WP4 and have started discussions with WP5 about opportunities for further collaborations. WP2 has recently recruited a new PhD student (Wenyan Li) who will be working with natural language processing in the context of WP2.

WP3. Deep phenotyping data from established research cohorts

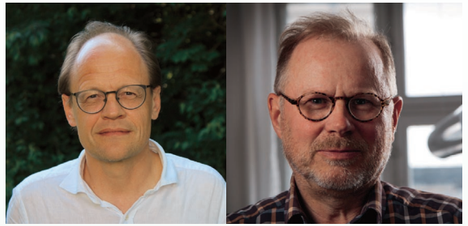
WP3-leaders: Associate professor Vibe Frøkjær & professor Kamilla Miskowiak

By exploiting existing data from the NRU-anchored Lundbeck Foundation Center Cimbi database and from the Neurocognition and Emotion in Affective Disorders (NEAD) Group database, WP3 aims to identify biomarkers that are predictive of symptom resilience or vulnerability, or treatment outcome; e.g., certain genetic, epigenetic, cognitive, molecular and functional neuroimaging features. These existing cohorts are particularly important because they also contain deep phenotyping data from a large number of healthy controls which serve as an important reference for our patient studies. They also uniquely enable us to conduct register-based follow-up studies to establish which features in clinically healthy individuals can predict later development of depressive episodes; information which can be extracted from the national registries.

In 2022, we have worked with "deep phenotyping" data from the Cimbi Database and the NEAD database in combination with data from the National Health Register and the drug prescription register. Two papers have been submitted for publication.

As part of an EU-funded innovative training network and in collaboration with Karl-Peter Lesch' lab in Würzburg in Germany, NRU PhD student Silvia Bruzzone has determined epigenetic signatures of MDD and SSRI treatment which now can be analysed in association with neuroimaging data. WP1 PhD student Simon Ziersen continues to support the work by bridging methods used in WP1 and WP3.

WP4. Deep phenotyping data from new research cohorts



WP4-leaders: Associate professor Lars Pinborg & professor Martin B. Jørgensen

With the aim to increase power to detect biomarkers and treatment response, in this WP we are establishing new cohorts of patients with epilepsy and MDD, and these are followed longitudinally. With the experience gained from the other WP's, we plan to use these cohorts to replicate previous findings and to empower additional research findings.

In close collaboration with the Mental Health services in the Capital Region, MDD patients are recruited for the BDD study through the central visitation and all six clinics. We enroll patients in three different cohorts, and so far, more than 100 patients have been included, accounting for approximately 10% of the region's annual patient flow. We acquire either basic (cohort 1) or expanded (cohort 2+3) clinical, cognitive, psychometric, and biological data, and for cohort 2 we also collect MRI and EEG data. Cohort 3 is the most data rich cohort, and there we collect the same data as in cohort 2 as well as PET imaging data with the [^{11}C]-UCB-J tracer of synaptic density.

In March 2022, the epilepsy study group started enrolling patients for the epilepsy cohort in close collaboration with the epilepsy clinic at Rigshospitalet. Implementation of the prospective BDE project in the clinic has necessitated changes in many routines, involving most of the staff, in particular doctors specialized in epilepsy. During the summer, we have tested most routines including regular follow-up visits with nurses and doctors, documentation in the EPRs, new routines for MRI, EEG and cognitive testing. Currently, we are enrolling 2-4 patients/week but we expect to begin soon also recruiting patients from Herlev and Bispebjerg Hospitals and youth between 16-18 from Rigshospitalet. We have submitted a detailed account of our hypotheses, rational and methodology as a paper to BMC Neurology and registered the project on clinicaltrials.gov.

WP5. Mining neuroimaging data

WP5-leaders: Associate professor Melanie Ganz-Benjaminsen & professor Gitte Moos Knudsen

This work package focuses on establishing models to identify structural abnormalities relevant to epilepsy in structural MR images in order to assist clinicians in their diagnosis. To train these models, we leverage existing MR data available from the PACS medical imaging archival system of the Capital Region of Denmark. We aim to create language models able to process the associated radiology reports and provide corresponding labels characterizing the pathologies described.

In 2022, we started the extraction of radiology reports and MR images of epilepsy patients from PACS. Due to the large number of files involved and the physical limitations of PACS, the data extraction is still on-going. The extracted radiology reports will be used to train language models used to provide labels for the associated radiology images. With the WP2 staff we have successfully discussed collaboration in the development and implementation of language models, and this work will continue when all data has been extracted from PACS. Furthermore, necessary steps have been made to secure the computational infrastructure that will be required to train the language models by gaining access to DTU's Computerome 2.0 infrastructure.

We have completed extraction of a confined dataset containing the radiology reports and MR images of all epilepsy patients seen at Rigshospitalet. This dataset (N=250) is currently being used in a proof-of-concept investigation focusing on the assessment of hippocampus in epilepsy. Due to the limited size of the dataset, language models are not necessary to provide labels at this stage. We do, however, expect that the methods and models being implemented will be transferable to larger datasets and brain regions/pathologies, and the results will provide initial guidance for further development as well as allow us to identify potential caveats and roadblocks.

Positions of Trust

Professor Gitte Moos Knudsen:

President of European College of Neuropsychopharmacology (ECNP), chair of the ECNP Psychedelics Thematic Working Group, chair of the Scientific Advisory Board for The Human Brain Project, Member of the Brain Prize Council, board member of the Elsass Foundation, and member of the Scientific Advisory Board of the Kristian G. Jebsen Foundation, Norway, of the Scientia Fellows program at the University of Oslo, Norway, and of the Hospital del Mar Medical Research Institute Foundation, Barcelona, Catalonia. Representing Professor for Neurology at Univ. Copenhagen. Honorary professor at University of Vienna, Austria. Board member of The Danish Academy of Neuroscience. In 2022, chair of the assessment committee of the Amsterdam Neuroscience program, PhD-assessor at Turku and Vienna Universities and reviewer for a number or journals, including Nature Neuroscience, Nature, and Molecular Psychiatry.

Professor Olaf B. Paulson:

Member of the Research Ethical Committee for Science and Health at Univ. Copenhagen and of the Research Ethical Committee of the Capital Region of Denmark. Auditor for Danish Society for Neuroscience.

Professor Jens D. Mikkelsen:

Chairman for external evaluations of medical educations in Denmark (Censorformandskabet for Lægeuddannelsen i Danmark); Deputy Chairman Censorforeningen.

Associate professor Lars Pinborg:

Member of the board of the Danish Epilepsy Society, and chair of the Danish Epilepsy Surgery Programme.

Associate professor Vibe G. Frøkjær:

Appointed Danish representative in the management committee for the EU-based Riseup-Post Partum Depression (PPD) COST Action, and member of the Neuroimaging Network of ECNP. Board member of Danish Society for Affective Disorders. Research advisory board member for “Sygeforsikring Danmark” donations. PhD-assessor at Karolinksa University, Sweden, Tübingen University, Germany, and Univ. Copenhagen, Denmark, and reviewer for several scientific journals.

Associate professor Patrick M. Fisher:

Member of the ECNP Psychedelics Thematic Working Group. Member of the Lundbeck Foundation Investigator Network. Editorial Board member of the Psychedelic Medicine peer-review journal publication. Scientific Committee Member of psychedelicsEUROPE, a group advocating to the European Union for consideration of evidence-based medical applications of psychedelics.

Associate professor Dea S. Stenbæk:

Member of the ECNP Psychedelics Thematic Working Group. Guest editor of research topic on psychotherapeutic framing of psychedelic drugs, Frontiers Psychology. Committee member of The Ethical Committee, Dept Psychology, Univ. Copenhagen.

Associate professor Melanie Ganz:

Member of the Cross-Academy Collaboration sub-committee under the Danish Data Science Academy.

Associate professor Louise Møller Jørgensen:

Committee member of The National Medical Ethical Committee (National Ethic Center). Chairman of the committee for spine surgery (DNKS). Appointed member (IKM-SUND, Univ. Copenhagen) of working group for (i) new study program (medicine) > 2026 (innovation), and (ii) New Strategy and Vision for Innovation at both faculty-level (SUND, Univ. Copenhagen) and across faculties (Univ. Copenhagen). Member of Innovation Working Group (SUND, Univ. Copenhagen). Reviewer for scientific journals (Acta Neurochirurgica, Brain Sciences).

ecnp Neuroscience applied

For the science and treatment of disorders of the brain

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.

Professor Gitte Moos Knudsen is president of ECNP in the period 2019-22 and in October 2022, she stepped down to become the ECNP past-president from 2022-2025 (see photo to the left).

In April, the ECNP Tranosological Working Group on Psychedelics was approved, with Gitte Moos Knudsen as chair, and Drummond McCulloch as co-chair.

Every year, NRU receives interns through the ECNP visiting scientists' program. NRU is involved in several of the ECNP Networks and in 2022, 18 NRU scientists were represented at the annual congress in Vienna (see photo to the right).

Dissemination in 2022

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.

Since the beginning of 2022, NRU has published a total of 3 PhD dissertations, 17 Master's or Bachelor theses and reports, and 88 scientific peer-reviewed papers, and 2 conference papers and proceedings. All papers that have either been printed or online ahead of print during 2022 are included.

PhD dissertations

- Camilla Borgsted Larsen. Structural and functional brain signatures of sexhormone transitions and implications for perinatal mental health. University of Copenhagen, Faculty of Health and Medical Sciences. Defended Jun 16, 2022
- Nakul Ravi Raval. Translational Positron Emission Tomography - Animal Models and In Vitro Autoradiography for Radioligand Development. University of Copenhagen, Faculty of Health and Medical Sciences. Defended May 12, 2022.
- Sagar Sanjay Aripaka. Molecular biology in the pain generation in lumbar intervertebral discs. University of Copenhagen, Faculty of Health and Medical Sciences. Defended Apr 8, 2022.

Master's and Bachelor theses and reports

The following list of NRU-affiliated students have successfully defended their theses or research year reports during 2022:

- Allan Al Dawaski – *The role of insomnia in depression. Results from the Neuropharmtrial*. Master's thesis in medicine, University of Copenhagen.
- Anna Søndergaard – *Psilocybin increases trait mindfulness for at least three months, correlated with profoundness of the mystical experience*. Master's thesis in medicine, University of Copenhagen.
- Annika Læbo Rasmussen - *Self-reported sexual function and serotonin 4 receptor brain binding in depressed patients – a Positron Emission Tomography study*. Master's thesis in medicine, University of Copenhagen.
- Astrid Tougaard Mikkelsen - *Serotonin 4 receptor and trait Neuroticism in depressed patients and healthy individuals – a positron emission tomography study*. Master's thesis in medicine, University of Copenhagen.
- Avneet Kaur - *Development of a robust and reproducible preprocessing pipeline for Positron Emission Tomography (PET) data*. Master's thesis in computer science, University of Copenhagen.
- Christian Gejl Christensen - *A Review of Neuroplasticity Induction as a Therapeutic Mechanism of Psilocybin*. Bachelor's thesis in medicine, University of Copenhagen.
- Evangelos Vouros – *Reducing the Need for General Anesthesia in Children Undergoing Neuroimaging by Preparation and Motion Correction*. Master's thesis in medical physics, University of Copenhagen.
- Haowen Lyu - *Detection of Inflammatory Processes in the Mammalian Brain using Radioligand Binding*. Master's thesis in neuroscience, University of Copenhagen.
- Joan Maria Arenas Gomez - *Split-half - A new approach for evaluation test-retest reliability of radioligands and methods in clinical positron emission tomography research*. Master's thesis in biomedical engineering, Technical University of Denmark and University of Copenhagen.
- Josephine Omonigho Thestrup - *Dopamine release in Long Evans rats following psilocybin injection*. Master's thesis in neuroscience, University of Copenhagen.
- Kristian Larsen - *Acute psilocybin effects on cerebral blood flow in healthy humans*. Master's thesis in neuroscience, University of Copenhagen.
- Louise Jakobe Bom - *Symptoms related to the 5-HT2A receptor in schizophrenia*. Bachelor's thesis in medicine, University of Copenhagen.
- Lærke Viuf Kristiansen - *Neuroplasticitet after stroke*. Bachelor's thesis in medicine, University of Copenhagen.
- Malene Ravn-Eriksson - *The interplay between sex hormones and serotonin brain signalling in men with and without depression – a Positron Emission Tomography study*. Master's thesis in medicine, University of Copenhagen.
- Mette Clausen – *Peripheral inflammation and serotonergic brain signaling in healthy individuals: implications for the risk architecture of Major Depressive Disorder?* Master's thesis in medicine, University of Copenhagen.
- Signe Kathrine Krogh Jørgensen - *Psilocybin and neuroplasticity*. Master's thesis in medicine, University of Copenhagen.
- Vera Claudius Welinder - *DMT, psilocybin and LSD's binding to the 5-HT2A receptor and the behavioral effects in consequence*. Bachelor's thesis in medicine, University of Copenhagen.

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Conference papers and proceedings

National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Board on Health Sciences Policy; Forum on Neuroscience and Nervous System Disorders. Exploring Psychedelics and Entactogens as Treatments for Psychiatric Disorders: Proceedings of a Workshop. Stroud C, Posey Norris SM, Matney C, Bain L, editors. Washington (DC): National Academies Press (US); 2022 Sep 1. PMID: 36049038.

Petersen E, Feragen A, da Costa Zemsch L, Henriksen A, Christensen OEW, Ganz M, the Alzheimers Disease Neuroimaging Initiative. Feature robustness and sex differences in medical imaging: a case study in MRI-based Alzheimer's disease detection. In: Wang, L., Dou, Q., Fletcher, P.T., Speidel, S., Li, S. (eds) Medical Image Computing and Computer Assisted Intervention – MICCAI 2022. MICCAI 2022. Lecture Notes in Computer Science, vol 13431. Springer, Cham. https://doi.org/10.1007/978-3-031-16431-6_9

Media attention and public lectures

Jan 2-3: Kristian Reveles Jensen on TV2 News, TV2 Echo, and TV2 Godaften Danmark about new premenstrual dysphoria diagnosis in ICD-11

Jan 4: Gitte Moos Knudsen in the University of Copenhagen podcast 'Tankelyn' in an episode about evilness:
https://tankelyn.simplecast.com/episodes/ondskaben-der-bor-i-dig

Jan 17: Melanie Ganz-Benjaminsen and the NRU MR-mock up scanner in DTU article:
https://www.dtu.dk/nyheder/nyhed?id=%7BBC8DA052-0688-4499-87D4-826911DA5220%7D

Jan 20: At the annual NeuroGrad Winter School at University of Copenhagen, PhD student Annette Johansen, MD, was awarded second place in the poster presentation competition for second year PhD students for her poster "Effects of escitalopram on synaptic density in the human brain"

Feb 20: Søren Vinther Larsen in a podcast episode on "P-piller på hjernen" as part of the podcast series '24 spørgsmål til professoren' with science journalist Lone Frank:
https://www.weekendavisen.dk/2022-7/24spoergsmaal/p-piller-paa-hjernen

Mar 29: Gitte Moos Knudsen served as panellist in a panel discussion on "Exploring three key research gaps" which took place on the public workshop "Exploring Psychedelics and Entactogens as Treatments for Psychiatric Disorders" arranged by the National Academies of Sciences, Engineering, and Medicine.

Apr 4: Lars Pinborg in a podcast on the introduction of minimal invasive surgery for the treatment of epilepsy in Denmark:
https://www.epilepsiforeningen.dk/epilepsi/materialer-om-epilepsi/podcast/

Apr 8: Martin Korsbak Madsen and David Erritzøe in an article in Ugeskrift for læger:
https://ugeskriftet.dk/nyhed/svampe-far-hjernen-til-svinge-i-takt-bryde-monstre-og-skabe-grobund-noget-nyt

Apr 11: Patrick Fisher was quoted in the NY Times, giving a perspective on a publication in Nature Medicine from the Imperial College London group:
https://www.nytimes.com/2022/04/11/health/psilocybin-depression.html

May 6: Martin Korsbak Madsen participated on the science podcast ”Kraniebrud”, episode titled ”Hjernen på svampe”:
https://podcasts.apple.com/gb/podcast/hjernen-p%C3%A5-svampe/id1490572243?i=1000559821013

May 12: Vibe Frøkjær in the podcast called Videnskabens Vidner in Episode 4 about Olaf Paulson´s scientific work:
https://podcastaddict.com/episode/139698769

May 22: Lars Pinborg in Neurologisk Tidsskrift: A New research project may turn the understanding of epilepsy upside down:
https://neurologisktidsskrift.dk/sygdomme/epilepsi/331-nyt-forskningsprojekt-kan-vende-op-og-ned-pa-forstaelsen-af-epilepsi.html

May 29: Vibe Frøkjær in the Bloom festival podcast episode 8 about “Østrogen mod testosteron”:
https://www.bloom.ooo/explore/oestrogen-mod-testosteron

Jul 24: Vibe Frøkjær in an article in Jyllandsposten entitled “Tidlige tegn i hjernen kan advare om fødselsdepression”:
https://jyllands-posten.dk/livsstil/familiesundhed/ECE14258092/tidlige-tegn-i-hjernen-kan-advare-om-foedselsdepression/

Aug 22: Sophia Armand in the article “Synes du, glasset er halvtomt? Så findes forklaringen måske i din hjerne-kemi” on videnskab.dk:
https://videnskab.dk/krop-sundhed/synes-du-glasset-er-halvtomt-saa-findes-forklaringen-maaske-i-din-hjerne-kemi

Aug 31: Vibe Frøkjær in the podcast called Vid&Sans in an episode about “Hvorfor rammes så mange af fødselsdepression?”:
https://vidogsans.dk/hvorfor-rammes-saa-mange-af-foedselsdepression/

Sep 1: Vibe Frøkjær interviewed in the podcast by Science Report for Danmarks Frie Forskningsfond called ”Mit store spørgsmål”:
https://dff.dk/forskningsprojekter/dff-podcasts/hvorfor-far-vi-fodselsdepressioner

Sep 6: Vibe Frøkjær in the podcast ‘Videnskabens veje’ in an episode about “Fødselsdepressioner: Klinisk forskningslektor i psykiatri”:
https://danske-podcasts.dk/podcast/videnskabens-veje/fodselsdepressioner-klinisk-forskningslektor-i-psy

Sep 13: Martin Korsbak Madsen gave a presentation entitled ”Hjernen på svampe” for Folkeunivsersitetet, an organization that disseminates scientific knowledge to a general audience.

Sep 25: Gitte Moos Knudsen lectured at “Hearts and Minds” Festival in Aarhus about “Psykedeliske stoffer – en vej til et sundt sind?” and “Ondskaben i os alle”.

Sep 29: Patrick Fisher was quoted in a recent article published in a Nature Outlook supplement:
https://www.nature.com/articles/d41586-022-02874-7

Oct 3: Gitte Moos Knudsen in Kristeligt Dagblad about “*Vinteren kommer. Og det gør vinterdepression også*”:
https://www.kristeligt-dagblad.dk/danmark/vinteren-kommer-og-det-goer-vinterdepressionen-ogsaa

Oct 25: Jonas Svensson in the article “*Hjerneforskere: Serotonin er ikke hjernens lykkestof*” on videnskab.dk:
https://videnskab.dk/naturvidenskab/hjerneforskere-serotonin-er-ikke-hjernens-lykkestof

Nov 10: Martin Korsbak Madsen was on national public radio P3 on a show called ”Påstand mod påstand”: https://www.dr.dk/lyd/p3/pastand-mod-pastand/pastand-mod-pastand-2022-11-10/01:13:01

Nov 23: Vibe Frøkjær gave a presentation entitled ”Hjernen og hormoner” for Folkeunivsersitetet.

Dec 15: Martin Korsbak Madsen was on the science podcast Vid&Sans, giving perspective on psychedelic science:
https://vidogsans.dk/svampe-kan-bloede-op-for-den-fastlaaste-depressive-hjerne/

Dec 17: Sara Marie Larsen and Kristoffer Brendstrup-Brix in the article “*Hvorfor føles det hårdere at stå op i december end i juni?*” on videnskab.dk:
https://videnskab.dk/forskerzonen/krop-sundhed/hvorfor-foeles-det-haardere-at-staa-op-i-december-end-i-juni

Dec 21: Gitte Moos Knudsen in NPR interview at Society for Neuroscience 2022 on the topic of psychedelics as treatment for brain disorders.
https://www.npr.org/2022/12/19/1144306776/brain-scientists-are-tripping-out-over-psychedelics

Dec 22: The BrainDrugs-Depression project is mentioned in a news on RH-intranet about a new study on depression:
https://intranet.regionh.dk/rhp/nyheder-og-kalender/Nyheder/Sider/Forskere-kortl%C3%A6gger.aspx

Dec 27: Gitte Moos Knudsen in NPR interview on the topic of psychedelics as treatment for brain disorders.
https://www.npr.org/sections/health-shots/2022/12/27/1145306096/psychedelic-drugs-psychiatric-disorders-brain-research

Acknowledgements

NRU research is primarily funded from external sources and we are extremely grateful to all the public and private foundations, organizations and companies that have generously provided support for our research activities.

NRU thanks our industrial collaborators:

- Arla Foods Ingredients
- COMPASS Pathways Limited
- H. Lundbeck A/S
- Invicro LLC
- Mediso Medical Imaging Systems
- Siemens Healthineers
- TracInnovations ApS

NRU has received larger grants from:

- **Lundbeckfonden** for the establishment of our thematic alliance within precision medicine in epilepsy and depression (**BrainDrugs**) and many other projects.
- **The Innovation Fund Denmark** for the establishment of *Center for Experimental Medicine Neuropharmacology* (**NeuroPharm**).
- **Kirsten og Freddy Johansens Fond** for the donation of a 3 Tesla MRI scanner dedicated for brain research.
- **Novo Nordisk Fonden** for supporting our Open Science program OpenNeuroPET.

NRU would like to thank the following list of funders for generous support during 2022:

- Augustinus Foundation
- Brdr. Hartmanns Fond
- Danish Ministry of Environment and Food - GUDP
- Danish Neurological Society
- Danish Psychiatric Society
- Danish Society for Neuroscience
- Elsass Foundation
- EU H2020 programme
- Fonden af 17-12-1981
- Fondsbørsvekselerer Henry Hansen og hustru Karla Hansens, f. Vestergaards Legat
- Gigtforeningen
- Helsefonden
- Hjärnfonden
- Independent Research Fund Denmark | Medical Sciences
- Ivan Nielsens Fond for personer med specielle sindslidelser
- Jascha Fonden
- Jordemoderforeningens forsknings- og udviklingsbeholdning
- Longevity Impetus Grants
- Læge Sofus Carl Emil Friis og Hustru Olga Doris Friis' legat
- Neuroscience Academy Denmark
- Novo Nordisk Fonden
- Research Council of Rigshospitalet
- Research Fund of the Mental Health Services - Capital Region of DK
- Rigshospitalets Jubilæumsfond
- Royal Academy of Sciences and Letters
- Savværksejer Jeppe Juhl og hustru Ovita Juhls Mindelegat
- Svend Andersen fonden
- The Michael J Fox Foundation for Parkinson's Research
- University of Copenhagen, Faculty of Health Sciences
- William Demant Fonden

This report is published by

Neurobiology Research Unit
Copenhagen University Hospital Rigshospitalet
Section 8057
Blegdamsvej 9
2100 Copenhagen Ø
Denmark

mail: info@nru.dk
tel: (+45) 3545 6711
fax: (+45) 3545 6713
web: www.nru.dk

Editing
Gitte Moos Knudsen
Peter Steen Jensen

Layout
Peter Steen Jensen

Annual Report 2022

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