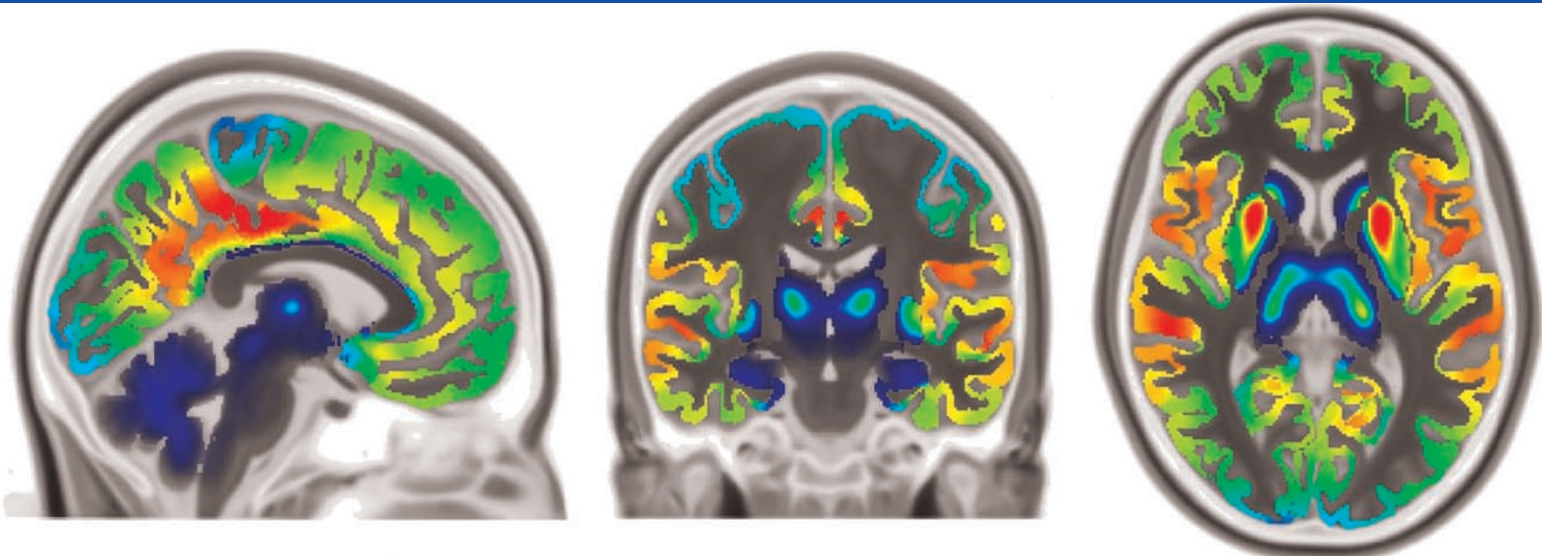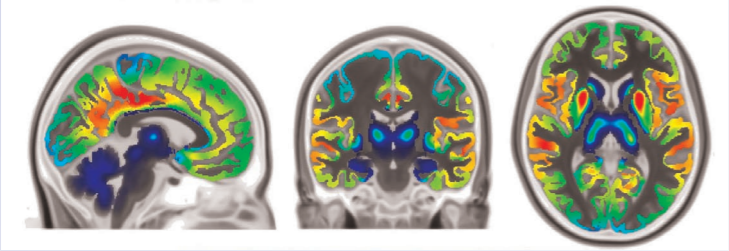# Neurobiology Research Unit

Annual Report 2024

Department of Neurology, Neuroscience Centre
Copenhagen University Hospital, Rigshospitalet

www.nru.dk

Cover page: Subcortical (voxel-based) SV2A density maps (Bmax; pmol/mL) in the MNI152 volume space. From [47], Copyright © 2024, the authors.

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Preface

Once more, it is my pleasure to present you with the 2024 annual report describing the activities of the Neurobiology Research Unit (NRU).

In the year 2024, we welcomed 63 new members and affiliates, including 2 new PhD-students, 2 research assistants, 6 scholarstipend students, 17 pre-graduate students, 19 student assistants, and 17 guest researchers. As of December 2024, our NRU family encompassed 135 individuals representing 18 different nationalities.

Funding from external sources is vital for us in advancing our mission. Throughout the year, 29 successful research grant proposals of ours secured more than 24 million DKK in external funding. NRU became a partner in the Danish National Research Foundation Center on headache, led by professor Messoud Ashina. Also, we joined as partners in the large EU infrastructure proposal "EBRAINS 2.0: A Research Infrastructure to Advance Neuroscience and Brain Health" which was funded by around 38 million EUR.

NRU remained steadfast in its commitment to scholarly output. Three PhD students successfully defended their theses, marking significant milestones in their academic journeys. Many of our researchers showcased their pioneering work at international congresses, conferences, and meetings, and we published a total of 89 peer-reviewed scientific papers.

I extend heartfelt gratitude to all NRU staff for their unwavering dedication, as well as to our host institution, Rigshospitalet, and our invaluable national and international collaborators. Their steadfast support has been integral to ensuring another year of resounding success for NRU.

I invite you to delve into the pages of this 2024 annual report, and encourage all interested readers to stay abreast of our latest developments through our website, https://nru.dk.

On behalf of the NRU management group

Gitte Moos Knudsen
Professor, Head of Department

The NRU management group was in 2024 composed of professor Gitte Moos Knudsen (photo credit to Royal Academy of Sciences and Letters) and (from left to right, top row first) professor Vibe G. Frøkjær, chief engineer Claus Svarer, associate professor Patrick M. Fisher, professor Lars H. Pinborg, professor Jens H. Mikkelsen, associate professor Dea S. Stenbæk, and laboratory manager Arafat Nasser.

Our Mission & Activities

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

We make use of neuropsychological and behavioural assessments combined with MRI, PET, SPECT and EEG in humans to investigate basic neurobiological mechanisms in the healthy brain and brain disorders, as well as neuropharmacological effects on the brain. Advanced image processing and statistical methods are applied to our data. We also use animal and cell models to bring pre-clinical discoveries into healthy volunteers and patients as early as possible.

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 research
4) Open science, AI, and advanced data analysis
5) Neuroimaging research
6) Diagnostic brain imaging of neurological patients
7) Neuropsychology research
8) Cohort studies of patients with epilepsy and major depressive disorder
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.

Education

NRU is a major training site for pre- and postgraduate students. In 2024, we supervised more than 20 bachelors- and master theses for University of Copenhagen, Technical University of Denmark and University of Southern Denmark. 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 international speakers and well-attended programs, including the Master's program in Neuroscience, and an international PhD course on pharmacokinetics. During the semester, we have a fixed meeting program with at least 5 weekly research presentations and journal clubs, where the pre- and postgraduate students can train their presentation skills.

NRU faculty members and senior researchers are engaged in research-based teaching and education within their fields of expertise, for example medicine, medicine and technology, and human biology. 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 which was started in 2020. 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. Every year the program experiences a large interest from students from all over the world. Many applicants come from China, North America and throughout Europe, but unfortunately, only a limited number of qualified applicants can be accepted. 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 who do their Master's 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 Creativity", "Neuroscience of Fear", and "Neurological Disorders and Disease".

Basic Kinetic Modelling in PET and MR Imaging

In the period Mar 4-8, 2024, we hosted our annual one-week PhD course on pharmacokinetics with participation by a record high number of 23 national and international researchers. The course organizers are Gitte Moos Knudsen, Henrik Larsson, Claus Svarer and Dorthe Givard.

Joint lab meetings with PET-centers at NIHM, Yale, and Karolinska

Since 2023, NRU has held monthly online seminars with colleagues from PET-centers at NIHM (Innis), Yale (Carson), and the Karolinska Institute (Varrone). The laboratories take turns to present their novel data with PET neuroimaging and to enjoy joint discussions.

OpenNeuroPET hackathons

Since 2021, the OpenNeuroPET group has been involved in teaching activities around PET open science: Brain Imaging Data Structure training and tools developed by the group: *PET2BIDS* and *PET-prep*. In 2024, we organized a Nordic BrainHack, bringing together Danish researchers to discuss open science and BIDS, and a workshop at the Neuroreceptor Mapping (NRM) conference in Montreal, and participated in NeuroHackademy to teach a module on PET data processing.

Facilities

NRU facilities cover more than 1,400 m² 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 m², including 15 offices with space for 62 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 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 m² of well-equipped facilities for basic neuroscience *in vitro* studies. We have four GMO-1 approved laboratories, 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 build-in room fridge, as well as a small office. 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 m²) freezer-core facility for biobank material together with our colleagues from the Danish Dementia Research Centre and the Memory and Neuromuscular clinics.

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 m² 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 m² state-of-the-art facilities on the ground floor in the North Wing. Dept of Radiology has access to MR001 for clinical scanning 50% of working hours with the remaining time available for NRU research. In the basement of the North Wing, we have a Siemens mock-up MR scanner installed, 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 next to the Dept of Radiology 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-pinhole collimator. The SPECT laboratory also has a dedicated storage room in the basement and thereby occupy in total 130 m².

The well-established Cimbi database and the Cimbi biobank which represent unique and valuable research instruments for NRU. Over the last 20 years, we have systematically acquired 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 RH 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 2024, 20 new official Cimbi applications for data access were approved and several papers based on data from the Cimbi database and biobank were published. Currently, there are 47 active projects using data from the database. The PET neuroimaging data are also an asset to the OpenNeuroPET project, you can read more about it on page 37.

Staff in 2024

NRU wishes our staff to reflect the diversity of the scientific community, and we actively seek to have a group of staff composed of many different nationalities and spanning a wide variety of educational backgrounds.

We provide a supportive and enriching environment for researchers at all levels, fostering professional growth and development. The corporate language at NRU is English.

During 2024, the following 195 people were affiliated to NRU.

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, professor, MD, DMSc
Patrick M. Fisher, associate professor, PhD
Vibe G. Frøkjær, professor, MD, PhD
Arafat Nasser, laboratory manager, PhD

Administration and research

Birgit Tang (HR)
Dorthe Givard (finances)
Peter S. Jensen (center manager)

Senior researchers

Anjali Sankar, PhD
Brice Ozenne, associate professor, PhD
Cyril Pernet, PhD
Gerda Thomsen, medical technologist
Louise M. Jørgensen, associate professor, MD, PhD
Melanie Ganz-Benjaminsen, associate professor, PhD
Mikael Palner, associate professor, PhD
Olaf B. Paulson, professor emeritus, MD, DMSc
Pontus Plavén-Sigray, PhD
Vibeke Dam, PhD

Postdocs

Annette Johansen, MD, PhD
Burcu Azak Pazarlar, PhD
Cassis Varlow, PhD
Friederike Holze, PhD
Sofi da Cunha-Bang, MD, PhD
Sophia Armand, PhD
Stinne Høgh, midwifery, PhD
Søren V. Larsen, MD, PhD
Vincent Beliveau, PhD

PhD students

Clara Madsen, molecular biomedicine
Drummond McCulloch, pharmacology
Elisabeth Kolesnik, neuroscience
Kristian R. Jensen, MD
Kristian Larsen, neuroscience
Kristín H. Magnúsdóttir, biomedical medicine
Maja R. Marstrand-Jørgensen, MD
Miriam L. Navarro, pharmacy
Qi Wang, MD
Ruben Dörfel, biomedical engineering
Sara Marie Larsen, MD
Sidsel H. Andersen, psychology
Silvia E.P. Bruzzone, neuroscience

Research assistants

Anne Sofie T. Schneider, psychology
Camilla Iavazzo, neuroscience
Catharina Messell, music therapy
Charlotte H. Nykjær, MD
Emilie Kibsgaard, data science

Martin Prener, MD
Tim Ruschke, computer science

Technical staff

Emilie L. Henriksen, radiographer
Lone I. Freyr, project nurse
Minna H. Litman, project nurse
Robin de Nijs, Medical physicist
Svitlana Olsen, medical technologist
Thurid W. Madsen, project nurse

Student assistants

Andrea Præstmark, MRI-student assistant
Arthur Diness, EEG-student assistant
Asta K. Vølund, MRI-student assistant
Cecilie R. Hvass, MRI-student assistant
Emilia A. Steenstrup, MRI-student assistant
Frederikke Petersson, MRI-student assistant
Holger Lyng, EEG-student assistant
Ida-Sofia B. Wehner, MRI-student assistant
Johanne M. Pedersen, MRI-student assistant
Julius L. Søgaard, EEG-student assistant
Kasper Skjærbæk, HPLC-student assistant
Kristian G. Lambertsen, MRI-student assistant
Lauge A. Rasmussen, IT-support
Marc Cummings, IT-support
Mille Rasmussen, HPLC-student assistant
Ofelia F. Godske, EEG-student assistant
Robert D. Pedersen, EEG-student assistant
Sarah Bargmeyer, HPLC-student assistant
Simon Sabroe, MRI-student assistant
Wilma Eis, EEG-student assistant

Student helpers

Asta Aakjær, student helper
Astrid W. Jensen, student helper
Astrid S.N. Nielsen, student helper
Astrid F. Vestereng, student helper
Ban Shiwalia, student helper
Delal Yücel, student helper
Emma Højte, student helper
Freya Kretzschmar, student helper
Ingrid Amundrud, student helper
Kristina Jacobsen, student helper
Lea Saarup, student helper
Leona Schwinger, student helper
Line Christiansen, student helper
Louise Le, student helper
Maria Grzywacz, student helper
Maria Schriver, student helper
Peter M. Skov-Andersen, student helper
Sofie Larsen, student helper
Sofie Ølgod, student helper
Stine S. Olsen, student helper
Tami Jacobsson, student helper

Pregraduate students

Adam Ujhelyi, neuroscience
Aitana Martínez Velasco, neuroscience
Aje Al-Awssi, medicine
Alexander T. Ysbæk-Nielsen, psychology
Alma Mouritzen, psychology
Anders Spanggaard, medicine
Anna Melchior, medicine
Anne Tophøj, medicine

Asmus T. Dalsgaard, biomedical engineering
Bóas S. Majurnarson, medicine
Camilla M. C. Xu, medicine
Christopher L. Porterfield, bioinformatics
Despoina Kazani, neuroscience
Dilja Ketilsdottir, medicine
Elisa Nabizada, human biology
Emilie Mauritzon, medicine
Emna Daadouche, medical and molecular biology
Frederikke Hansen, medicinal chemistry
Hannah W. Julsgart, biomedical engineering
Hannah K. Sørensen, pharmaceutical sciences
Helene Kaas, medicine
Helga Appel, medicine
Jan Tagscherer, computer science
Janne Bostrup, psychology
Jayson Teruo Guo, neuroscience
Jonas Kendal, medicine
Jonathan Gelvan, psychology
Josephine Tyron, medicine
Julie Wedel-Heinen, pharmaceutical sciences
Kalle Falk, medicine and technology
Kamilla M. Lindegaard, molecular biomedicine
Kamilla G. Nielsen, medicine
Katarina Bubulovic, human biology
Kirstine H. Andersen, medicine
Lauren French, biophysics
Louise Jensen, medicine
Lydia Arias Vázquez, pharmaceutical science
Marie B. Gad, medicine & technology
Matilde Rasmussen, medicine
Mathilde E. Brøgger-Jensen, medicine

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Mette Hochheim, medicine
Migle Barkauskaite, psychology
Nikita Morel, psychology
Noa Roumimper, psychobiology
Nora D. Falck, medicine
Oliver Iversen, medicine
Phoebe Linde-Atkins, molecular biomedicine
Randi T. Kjær, medicine
Rikke B. Bangsgaard, medicine
Rói Hansen, medicine
Sara V. Rehtmar, medicine
Sarah F. Akobe, medicine
Sif Olsen, psychology
Sofie Hvitved, medicine
Thereza Rørvik, psychology
Tobias B.A. Andersen, computer science
Travis Kovaleinen, medicine
Valdemar Kruse, psychology
Victor Neufeld, medicine
Zinet Ritschel, psychology

Visiting scientists
Adrian G. Rossebø, NAD fellow, Univ. Copenhagen
Aline Morais de Souza, PhD-stud, Univ. Copenhagen
Alper Erdogan, Assoc. Prof, İzmir Katip Çelebi Univ., Turkey
Anders S. Olsen, PhD-stud, Technical University of Denmark
Barbara Nordhjem, postdoc, Dept of Paediatrics and Adolescent Medicine, RH
Camilla Xu, MD
Dan Peters, PhD, DanPET, Sweden
Dogukan Koc, PhD-stud, Eramus MC, The Netherlands
Edvin Marklund, MD

Frederik Gudmundsen, PhD-stud, Univ. Southern Denmark
Gjertrud Laurell, postdoc, Columbia Univ., USA
Hanne D. Hansen, H. Lundbeck A/S, PhD
Janika Ruuska, NAD fellow, Univ. Copenhagen
Janus Magnussen, Aixial Group, UK
Kristian Sandberg, associate professor, Univ. Aarhus
Kristoffer Brendstrup-Brix, MD
Luisa Drescher, machine learning, Charité, Berlin, Germany
Malthe T. Andersen, MD
Marta Tataryn, NAD fellow, Univ. Copenhagen
Martin Korsbak Madsen, MD
Martin Nørgaard, assistant professor, Univ. Copenhagen
Martyna Strzelec, PhD-stud, Jagiellonian University, Poland
Merlin Zabrocki, PhD-stud, Univ. Copenhagen
Nadia B. Pedersen, PhD-stud, Univ. Copenhagen
Niccolò Milani, PhD-stud, Charité, Berlin, Germany
Nicolaj Daugaard, PhD-stud, Univ. Southern Denmark
Nina Fultz, research assistant, Massachusetts General Hosp., USA
Renxiang Qiu, computational neuroscience, Univ. Copenhagen
Philip Fink-Jensen, MD
Pilar Ramirez, biomedicine, Univ. Int. de Catalunya, Spain
Samantha Delaney, postdoc, Univ. Copenhagen
Silas Haahr Nielsen, MD, Dept of Neurosurgery, RH
Sophie Stotz, postdoc, Univ. Copenhagen
Sumit Pandey, PhD-stud, Univ. Copenhagen
Thomas Wünsche, research assistant, Univ. Copenhagen
Thorhalla Sigurardottir, neuroscience, Univ. Copenhagen
Tobias Gustavsson, postdoc, Univ. Copenhagen
Vladimir Shalgunov, postdoc, Univ. Copenhagen

Honors and Awards

Professor Gitte Moos Knudsen received the prestigious Kuhl-Lassen Award 2024 (see photo to the right). This is the highest award from the Society of Nuclear Medicine and Molecular Imaging's (SNMMI) Brain Imaging Council, and it is given annually to a researcher who has made outstanding research and contributions in the field of functional brain imaging.

Several of our younger researchers have been honored with different prizes and awards during the year, including PhD student Drummond Mc-Culloch who received the Lundbeck Foundation Talent Award 2024 (photo below, second person from the right) based on his research into the mechanisms of action of psychedelic drugs, including LSD and psilocybin.

Research administrator Dorthe Givard celebrated an impressive 40th anniversary at RH in the fall. We marked this special achievement with a small surprise reception for her on October 1. Later, Dorthe was celebrated at Regionsgården in Hillerød (see photo to the right) where she received her medal of merit.

Based on a recommendation from NRU, our long-time collaborator Professor Russell A. Poldrack from Stanford University received (see photo below) Rigshospitalet's International KFJ Prize 2024 for his groundbreaking work in neuroscience and open science.

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PhD Degrees

Søren Vinther Larsen - **Hormonal contributions to depressive episodes in women. Insights from register-based cohort studies from Denmark**

This thesis aimed to use cohort studies based on Danish national health registry data to investigate the link between progestin exposure and depression risk, to determine if depressive episodes across different reproductive events are linked, and if hormonal contraceptive use in the postpartum period is linked to an increased risk of depression. In all studies, hormonal contraceptive exposure started when a prescription was filled, while depression was identified either through filled prescriptions of antidepressant medication recorded in the National Prescription Register or through hospital diagnoses of depression in the National Patient Register.

Søren Vinther Larsen completed his PhD under the main supervision of professor Vibe Frøkjær from NRU and Dept of Clinical Medicine, Univ. Copenhagen. Co-supervisors were professor Øjvind Lidegaard from Dept of Gynaecology, Fertility and Obstetrics, RH, and professor Annamaria Giovanna Elena Giraldi from Sexological Clinic, RH and Mental Health Services CPH.

Dr. Larsen's successful defense took place on May 8th, 2024, with professor Maj Vinberg from Dept of Clinical Medicine, Univ. Copenhagen as chair, and professor Søren Dinesen Østergaard from Dept of Affective Disorders, Aarhus University Hospital - Psychiatry, and professor Birgit Derntl, Dept of Psychiatry and Psychotherapy, Women's Mental Health & Brain Function, University of Tübingen, Germany, as opponents.

Stinne Høgh - **Biological aspects of postpartum mental health: prevention opportunities and mother's perceptions**

This thesis aimed to contribute to the existing evidence of biological transitions during the perinatal period and the impact on maternal mental health in the early postpartum period while possibly identifying potential prevention targets. Taken together, the results of the four papers included in this thesis indicate that the transition from high cortisol and Growth Differentiation Factor 15

(GDF15) levels during pregnancy to low levels postpartum presents different effects on early postpartum mental health. The results suggest that dysregulation of the HPA axis might serve as a mentally adaptive response, while GDF15 seems to have no direct relation to mental health outcomes. Finally, it is essential to consider the ambiguity demonstrated by women regarding the testing for genomic risk markers linked to hormonal sensitivity and postpartum depression before introducing new genomic risk marker technologies.

Stinne Høgh completed her PhD under the main supervision of professor Vibe Frøkjær from NRU and Dept of Clinical Medicine, Univ. Copenhagen, and co-supervised by professor Hanne Kristine Hegaard, Dept of Obstetrics, RH, senior researcher Laura Emdal Navne, Danish Centre for Social Science Research, VIVE, Denmark, Kristina Martha Renault, Dept of Obstetrics, RH, and professor Mette Nordahl Svendsen, Dept of Public Health, Univ. Copenhagen.

Dr. Høgh successfully defended her thesis on Aug 9th, 2024, with associate professor Anders Jørgensen from Dept of Clinical Medicine, Univ. Copenhagen as chair, and professor Inger Sundström Poromaa, Dept of Women's and Children's Health, Uppsala University, Sweden, and professor Charlotte Overgaard, Dept of Public Health, University of Southern Denmark, as opponents.

Janus Houe Magnussen - **Exploring nicotinic receptors and histone deacetylases through neuroimaging**

Janus' thesis highlights PET imaging's versatility and significance in studying the α7-subtype of the nicotinic acetylcholine receptor (nAChR), histone deacetylase (HDAC) levels, and α7 nAChR ligand engagement, offering valuable insights into radioligands' in vitro and in vivo properties and their potential as tools in drug development.

The research presented in this thesis was conducted at NRU in the period 2014-24. During this period, Janus Houe Magnussen also held various positions in the pharmaceutical industry, and managed to combine this research into a PhD thesis. Janus completed his PhD under the supervision of professor Gitte Moos Knudsen.

Dr. Magnussen successfully defended his thesis on Sep 6th, 2024, with associate professor Birgitte Rahbek Kornum, Dept of Neuroscience, Univ. Copenhagen, as chair, and with associate professor Anne M. Landau, Dept of Clinical Medicine - Translational Neuropsychiatry Unit, Aarhus University, and Dr. Francisco Lopez Picon, Preclinical Imaging Unit of the Turku PET Centre University of Turku, Finland, as opponents.

Positions of Trust

Professor Gitte Moos Knudsen
Past-president of European College of Neuropsychopharmacology (ECNP), chair of the ECNP Psychedelics Network, board member of the Neuroscience Academy Denmark, the Bridge Program, and the Elsass Foundation and the Warawara Larsen Foundation, and member of Scientia Fellows program assessment committee at the University of Oslo, Norway. Representing Professor for Neurology at Univ. Copenhagen. Scientific advisor for the Savværksejer Jeppe og hustru Ovita Juhls mindelegat, and reviewer for Swiss National Science Foundation. Adjunct professor at University of Vienna, Austria. In 2024, PhD-examiner of Dr Maarten Laroy, Department of Neurosciences, Leuven Brain Institute, Belgium, and reviewer for a number of journals, including Nature Neuroscience, Nature, and Molecular Psychiatry.

Professor Emeritus 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. Member of the International Advisory Board for the NeurInsight LLC project, a program led by Prof. Stefan Posse, Albuquerque, USA and supported by the NIH. Auditor for Danish Society for Neuroscience.

Professor Jens D. Mikkelsen
Deputy Chairman for external evaluations of medical educations in Denmark (Censorformandskabet for Lægeuddannelsen i Danmark). Reviewer for several journals including, PNAS and Translational Psychiatry.

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, the Psychedelics Thematic Working Group and the Meta network on depression of ECNP. Board member of Danish Society for Affective Disorders. Research advisory board member for "Sygeforsikring Danmark" donations and Independent Research Council Norway. PhD-assessor at Karolinska University, Sweden, Tübingen University, Germany, and Univ. Copenhagen, Denmark, and reviewer for several scientific journals including Nature Mental Health and Molecular Psychiatry.

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

Associate professor Patrick M. Fisher
Member of the ECNP Psychedelics Network. 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. Auditor for the Danish Society for Neuroscience. Reviewer for several scientific journals.

Associate professor Dea S. Stenbæk
Member of the ECNP Psychedelics Network. 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). Member of 'Innovation Working Group' (SUND, Univ. Copenhagen), 'Strategic Partnerships' (DTU and Rigshospitalet) and 'New National Research Network for Spine Surgery' (DRKS). Course co-leader of "Innovation" (SUND, Univ. Copenhagen). Reviewer for scientific journals (Acta Neurochirurgica, Brain Sciences).

Senior Research Software Developer Cyril Pernet
Co-chair of the Organization for Human Brain Mapping (OHBM) Best Practice Committee. Steering group member of the Brain Imaging Data Structure (BIDS) working group. Member of the International Neuroinformatic Coordinating Facility (INCF) Council for Training, Science and Infrastructure. Member of the Ethic and Society committee for EBRAINS, the EU neuroscience infrastructure. Editorial board member for Scientific Data, Scientific Reports and Brain Topography. Reviewer for several scientific journals.

Strategic Collaborations

Strong collaborations are fundamental for excellent brain research to happen. We have for many years worked closely together with many different researchers, both within Denmark and internationally. Listed below are some of our major strategic collaborations outside the Dept of Neurology.

PET and Cyclotron Unit, Rigshospitalet

We highly appreciate our long-lasting and outstanding collaboration with all the 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 (Jacob Madsen, Nic Gillings and Vladimir Shalgunov), 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 decade, we have had a well-established collaboration with the Dept of Radiology. In 2024, worked closely together with Dr. Vibeke Andrée Larsen, professor Adam Espe Hansen, chief radiographer Susanne Stampe and radiographers Kevin Robert Brow and Rasmus Nagstrup Jensen.

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. Our collaboration with professor Øjvind Lidegaard in epidemiological studies on the brain and mental health consequences of oral contraceptive use continues.

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

For two decades, we have had a close collaboration on PET radioligand development with Dept of Drug Design and Pharmacology (professors Herth, Kristensen and Jensen). The collaboration was launched through our previous Cimbi project, and today, it includes various joint projects focusing on preclinical evaluation of novel radiopharmaceuticals. The Cimbi group meet regularly, and in September 2024 they arranged an annual symposium (see photo to the right).

Likewise, we have had a long-standing collaboration on biostatistics with Section of Biostatistics, Faculty of Public Health, with whom we share a biostatistical associate professor (Dr. Ozenne) and a biostatistical PhD-student (Dr. Ziersen) through the *BrainDrugs* project. Also, we appreciate our important collaboration with The Center for Translational Neuromedicine (professor Nedergaard), and with the Dept of Psychology with 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. Professor Jens H. Mikkelsen heads the Master's program in Neuroscience.

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 professors Martin Balslev Jørgensen and Lars Vedel Kessing who are both directly involved in *BrainDrugs*, with professor Kamilla Miskowiak and her Neurocognition and Emotion in Affective Disorders (NEAD) group through, e.g., *BrainDrugs*, as well as with professor Anders Fink Jensen.

For our *BrainDrugs* project, we benefit greatly from our close collaboration with 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 professor Trevor Robbins from University of Cambridge on a joint research project funded by the Lundbeck Foundation. The collaboration has included bilateral secondments. Data acquisition was completed in 2024, and data are currently being analysed.

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 37. The collaboration with Stanford was further strengthened in 2024 by the international KFJ Award being given to professor Russ Poldrack (page 19).

Martinos Center, Massachusetts General Hospital, US

We have for the last 15 years had a fruitful collaboration with the Athinoula A. Martinos Center for Biomedical Imaging in Boston, US. 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. The collaboration has so far resulted in more than 26 joint publications.

The Serotonin and Beyond European Training Network (ETN)

We have been partners in the consortium *Serotonin and Beyond* (www.serotonin-and-beyond-project.eu/) since its establishment in 2021. The consortium aims to establish fundamental insights in how early life changes in serotonin caused by genetic or environmental factors alter brain development and thereby contribute to brain health. NRU PhD-student Silvia EP Bruzzone who handed in her thesis in 2024 has been funded through this ETN.

GoodVibes (Neurodegenerative Disease Research, JPND)

In this project funded jointly by EU and the Innovation Fund Denmark, we collaborate with University of Copenhagen, University of Oulu, Semmelweis University, University Hospital of Porto, and Radboud University to establish neuroimaging methods to assess the brain fluid fluxes during sleep and other interventions.

EBRAINS

EBRAINS (www.ebrains.eu) is an EU-funded project (38 million Euro) that provides a digital research infrastructure to accelerate collaborative brain research between leading organizations and researchers across the fields of neuroscience, brain health, and brain-related technologies. We are collaborating with sites in Padova, Munich and Vienna to acquire state-of-the art simultaneous PET, MRI, and EEG data from more than 200 healthy individuals.

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.

Every year, NRU receives interns through the ECNP visiting scientists' program. Also, NRU is involved in several of the ECNP Networks and in September 2024, several NRU scientists were represented with orals or posters at the 37th annual ECNP Congress in Milan, Italy. Here, NRU PhD-student Søren Vinther Larsen received an Excellence award for his abstract "*Association between intrauterine system hormone dose and depression risk*" (see photos below).

As president of ECNP from 2019-22, professor Gitte Moos Knudsen is now board member as ECNP past-president, from 2022-25. She is also chair of the ECNP Network on Psychedelics, a European network on translational research in classic psychedelics.

The NRU Neuroimaging Laboratory

3T MRI scanner

Magnetic resonance imaging (MRI) is central to many of our research projects. We also facilitate 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. We have trained MR-assistants that help with research studies during working hours as well as evenings and weekends.

We continue to enjoy a great collaboration with Siemens which facilitates the implementation of new plans to be established at the scanner.

Below is a brief overview of on-going MRI-based studies in 2024:

- 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 ALTIBRAIN, CAVIR and TRANSCIN studies rooted in the NEAD group led by professor Kamilla Miskowiak from Psychiatric Center Copenhagen acquires structural and functional MRI (fMRI) to evaluate brain imaging markers associated with mood disorders, associated treatments, alterations in cognition, and neuroplasticity.
- The BrainDrugs initiative collects 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 sense of smell in patients with impairment following Covid-19.
- 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.

Emilie Henriksen
Radiographer

- Projects using ultra-fast and non-invasive MRI tool for measuring brain pulsations in collaboration with profs. Rigmor Jensen and Steen G Hasselbalch to aid diagnosing patients with increased intracranial pressure and idiopathic normal pressure hydrocephalus, respectively.
- The Pill Project led by professor Vibe Frøkjær at NRU, is a longitudinal study evaluating effects of oral contraceptives on cognition and the brain in healthy women.
- The MAMA project with professor Vibe Frøkjær examines the effect of breast-feeding and oxytocin on brain structure and function.
- The Stroke Project led by professor Gitte Moos Knudsen from NRU applies MRI to evaluate structural and functional brain changes following stroke.
- The ADHD project led by Sofi da Cunha at NRU uses fMRI and spectroscopy to evaluate brain activation during reward, response inhibition, and working memory in individuals with ADHD.
- The NP2-P2c project led by Patrick Fischer uses structural and functional MRI scans to investigate whether a single dose of psilocybin induces lasting changes in brain activity and how music influences the experience and effects.
- The COG-iEEG project with Drs. Pascal Stevens and Ron Kupers aims to compare responses to sensory, cognitive, social, and affective stimuli measured with sEEG with functional MRI responses to the same type of stimuli in epilepsy patients.
- The QUANTUM Trip Trial with professor Anders Fink Jensen from Psychiatric Center of Copenhagen is a randomized trial that aims to compare placebo vs. psilocybin treatment in alcohol abuse disorder.
- The SEMALCO study with professor Anders Fink Jensen investigates GLP-1 receptor agonist treatment for reducing alcohol intake in patients with alcohol use disorder and comorbid obesity, it applies fMRI and MRS Spectroscopy (MRS) to evaluate brain effects.
- The RESETTLE project led by professor Signe Sørensen Torekov acquires structural and functional MRI data to characterize brain effects of lifestyle-intervention treatment of obesity in young adults.
- The BHB project led by professor Nadia Micali from Center for Eating and feeding Disorders research applies fMRI and MRS to evaluate tolerance of a ketone-based nutritional supplement in refeeding in patients with anorexia nervosa.
- The MECT study with associated professor Anders Jørgensen from Psychiatric Center Copenhagen aims to examine brain morphology and focus on cognition and brain age in relation to ECT treatment.

SPECT-CT system

Our 3rd generation high-resolution AnyScan SPECT-CT Mediso scanner provides high-resolution 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 for localizing the epileptic focus in patients with drug-resistant epilepsy that are candidates for epilepsy surgery. We are the only laboratory in Denmark to conduct ictal-interictal SPECT imaging with co-registration to MRI (SISCOM) This requires personnel specifically trained to inject as soon as the epileptic activity commences.

Striatal dopamine transporter (DAT) 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. All hospitals can refer patients suspected for dopaminergic deficits for a diagnostic scan. The diagnostic report comes with a reference to healthy age-matched individuals and is evaluated by a neurologist specialized in reading DAT-SPECT scan data.

Gerda Thomsen
Medical technologist

Ongoing research projects

DAT-neuromelanin
We have enrolled and scanned patients referred for diagnostic molecular neuroimaging to conduct 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 analysis is ongoing.

SPECT scan time
We are currently conducting the final data analysis to establish how much we can shorten the scan time for patients referred for diagnostic neuroimaging.

ADHD
We are finalizing data acquisitions from 60 ADHD patients in order to evaluate the dopamine transporter in these patients.

Glymphatics
In a series of pig experiments in the GoodVibes project (page 26) we are employing cisterna magna injections of Tc99m-DTPA and following the tracer distribution in the brain by kinetic analysis.

Preclinical Neurobiology

Much of the preclinical research at NRU is directed to validation and measurements of the binding of known and novel radioligands. The laboratory also conducts biochemical analyses of, e.g., BDNF. The binding to targets in the diseased brain can be an important marker for a disease process and consequently, potentially be used for diagnostic neuroimaging in patients. We are working on several classes of radioligand targets in the brain:

Synapses in Alzheimer's disease

Synaptic alterations are seen in many, if not all, CNS disorders. Neuronal and synapse losses are seen under the progression of Alzheimer's disease (AD). Previously we have published that the binding to the synaptic vesicle glycoprotein 2A (SV2A) using the selective radioligand [3H]UCB-J was reduced in frontal cortex from AD patients. Recently, we have found that the reduction in SV2A binding is highly significant only in AD patients not carrying the ApoE ε4 allele and, in contrast, that patients with one or two ApoE ε4 alleles had SV2A binding levels not different from controls. Because ApoE4 is an important genetic risk and strongly linked to late-onset AD, our research raises an interesting new and unexpected association to SV2A, synapse loss, and function.

Novel radioligands for neuroinflammation

Radioligands targeting microglia cells have been developed to identify and determine neuroinflammation in the living brain. Previously we have published the validation of a novel radiotracer JNJ-64413739 that binds selectively to the purinergic receptor P2X7R, which is a receptor that has an increased expression under neuroinflammation. Now, we have validated another interesting radioligand [3H]T-401 that binds selectively to monoacylglycerol lipase (MAGL); a cytosolic serine hydrolase involved in the endocannabinoid system (**Figure 1**) [69]. MAGL is considered not only a marker of neuroinflammation, but also a potential novel drug target for the treatment of CNS disorders.

Occupancy of two alpha7 nicotinic acetylcholine receptor (α7-nAChR) compounds

The α7-nAChR has long been considered a promising target for treatment of cognitive impairments and the α7-nAChR ligands, TC-5619 and encenicline have been tested, but failed, in clinical trials. By use of the α7-nAChR radioligand [11C]NS14492, we

Jens H. Mikkelsen
Professor

characterized binding both with in vitro and in vivo occupancy in the pig brain [62]. We find that whereas TC-5619 achieves about 40% α7-nAChR occupancy, encenicline exhibits more limited α7-nAChR occupancy. This study underscores the importance of preclinical PET imaging to determine target engagement for informing clinical trial strategies.

Other targets

Together with professor Matthias Herth at Univ. Copenhagen, we are working on a range of different radioligands, including postsynaptic density marker [25] as well as biased 5-HT2A receptor radioligands.
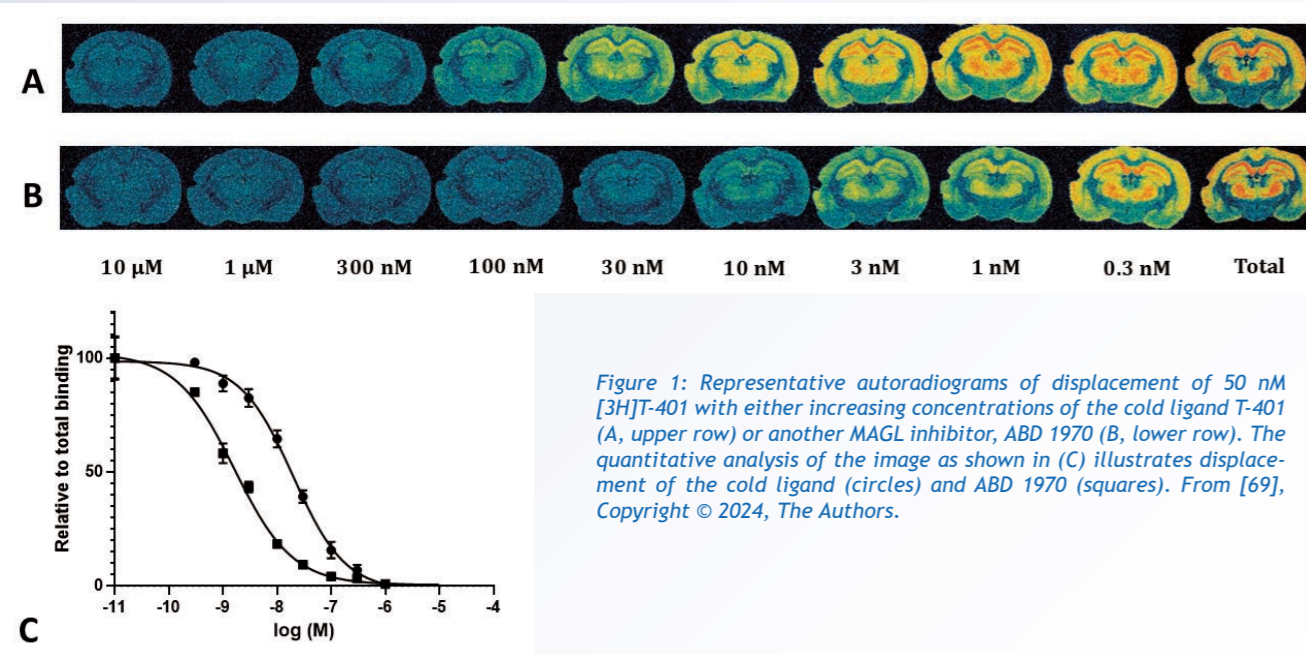

Figure 1: Representative autoradiograms of displacement of 50 nM [3H]T-401 with either increasing concentrations of the cold ligand T-401 (A, upper row) or another MAGL inhibitor, ABD 1970 (B, lower row). The quantitative analysis of the image as shown in (C) illustrates displacement of the cold ligand (circles) and ABD 1970 (squares). From [69], Copyright © 2024, The Authors.

Psychedelics

Psychedelics is an intriguing class of drugs due to emerging evidence for their therapeutic potential for hard-to-treat brain disorders. Our psychedelic research program at NRU aims to characterise psychedelic drugs from receptor interactions to clinical and experiential effects. Our experience with psychedelic research enables us to participate in the broader discussion about how basic research on psychedelics can productively inform clinical development. NRU has taken a main role in papers detailing knowledge gaps in the field [65, 66]. We also collaborate with clinical and university departments to facilitate this research, including Copenhagen Psychiatric Center (PCK) and NOESIS (https://psy.ku.dk/noesis/), the University of Copenhagen Psychedelic Research Clinic, led by associate professor Dea S. Stenbæk.

Through animal and human studies, and in collaboration with the Martinos Center in Boston, we have characterised pharmacological properties of psychedelic and related compounds and related effects on brain activation (**Figure 2**) [8, 9, 31]. Continuing to build on our psychedelic-related NeuroPharm projects, we evaluated acute psychedelic effects on emotional face processing in healthy individuals [7]. The psychological state of participants can meaningfully shape acute drug effects; we explore these dimensions through questionnaire assessments and survey-based responses [32, 33]. Finally, in collaboration with professor Rigmor Jensen and colleagues at the Danish Headache Center, we completed an open-label trial of psilocybin treatment for chronic cluster headache, showing promising relief for patients [61]. We look forward to sharing future accomplishments from both on-going data collection and data analysis activities.
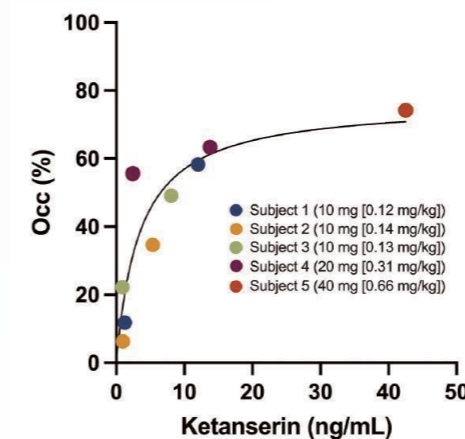
Dea S. Stenbæk & Patrick Fisher Senior researchers

Figure 2: Relationship between mean plasma ketanserin concentrations over the 120 min PET-scan and neocortical 5-HT2A receptor occupancy. Estimated EC50 (95 % CI) was 2.5 (0.8; 8.1) ng/mL and Occmax (95 % CI): 77 (54; 114)%. From [31], Copyright © 2024 Published by Elsevier B.V.

Clinical Neuropsychiatry

We identify brain-based mechanisms involved in neurological and psychiatric disorders and translate our insights to improve prevention and treatment strategies.

These endeavors are pursued through our many cross-disciplinary collaborations with Depts of Neurology, Psychiatry, and Psychology, with computer science, molecular genetics, and through participation in international data sharing consortia, e.g., COORDINATE-MDD (https://doi.org/10.1186/s12888-022-04509-7) led by professor Cynthia Fu from Centre for Affective Disorders, University of East London, and ENIGMA (https://enigma.ini.usc.edu/) led by professor Paul Thompson, Imaging Genetics Center, University of Southern California.

Chronic cluster headache
The results from this study are described on page 33 (Psychedelics).

Disorders of consciousness
It is important to recognize patients with disorders of consciousness for residual awareness and current guidelines recommend that cerebral glucose brain metabolism measured with PET can help categorize patients correctly. We examined if arterial spin labeling (ASL) with MRI could serve as a proxy for brain metabolism, but that was not the case [29]. By contrast, EEG and fMRI features in combination with clinical data could predict short-term outcome of patients with acute disorders of consciousness and further, EEG can predict 12-month outcome after discharge [1,2].

Sleep disorders
Several ongoing projects relate to the effects of sleep and brain oscillations. Capitalizing on the Human Connectome Project data from 916 healthy individuals aged below 40 years, we found that perivascular space diffusivity and brain microstructural measures are associated with circadian time and sleep quality [10]. Our findings suggest that sleep downregulates the intra-neurite volume in healthy adults, with positive impact on cognitive function.

Professors Gitte Moos Knudsen and Lars Pinborg, senior researcher Vibeke Dam, and Professor Vibe G. Frøkjær (from left to right, top row first)

Major depressive disorder (MDD)
Together with our collaborators at Dept of Psychiatry, University of Copenhagen and international collaborators, and building on existing data acquired in our Center for Experimental Medicine Neuropharmacology (NeuroPharm, https://np.nru.dk/) we have identified relevant clinical profiles and biomarkers to define subtypes of MDD that respond differently to treatment [41, 42]. This includes brain network organization and dynamics where our data provides mechanistic evidence that non-responder patients are less sensitive to stimulation and, consequently, less prone to respond to treatment [24], and epigenetic candidate biomarkers of antidepressant treatment response suggesting that the methylation status of genes involved in synthesizing serotonin are informative of antidepressant treatment outcome, but unlikely to prove useful as clinical predictor tools [12].

We have also shown that 5-HT4 receptor brain binding is markedly reduced in unmedicated patients with moderate to severe MDD relative to healthy controls. Intriguingly, the 5-HT4 receptor levels appear to change with antidepressant treatment regulating serotonin tonus in a manner that maps onto cognitive treatment outcomes in terms of memory performance [17]. Our data thus support the hypothesis that direct 5-HT4 receptor stimulation may be beneficial in the treatment of MDD, which we will pursue in our next clinical trials.

Other research outcomes in patients with MDD, as part of BrainDrugs, are described on pages 40-45 (BrainDrugs).

Epilepsy
Our studies in patients with epilepsy are also described on pages 40-45 (BrainDrugs).

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. We have proposed that maladaptation to hormone transitions may play a role in distinct "hormone sensitive" subgroups within MDD, while others adapt well [34]. Intriguingly, in first time users of hormonal intrauterine devices, used for contraception by many women, we have documented a hormone-dose-dependent risk for depression (**Figure 3**) by leveraging data form the National Health Registers [53].

Neuropsychology
Here, we study the link between brain function and behaviour, focusing on cognitive and psychological traits in brain disorders, to improve treatment strategies. We also examine how cognitive performance relates to brain structure, function, and interventions in healthy individuals. As a service to other researchers, the neuropsychology team conducts cognitive testing of patients and healthy controls.

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We have demonstrated reductions in ruminative thought patterns following antidepressant treatment [80] and, building on previous research, continued to expand our understanding of the interplay between serotonin and personality and how this translates to risk of depression [37, 68, 79].

We have also showed that SSRI intervention altered frontal and occipital responses to emotional stimuli but did not significantly affect amygdala activity, suggesting SSRIs may act through cortical modulation rather than direct amygdala attenuation [6]. Additionally, we found that oxytocin intervention had effect on social cognition in the healthy brain, suggesting a more complex interplay of neurochemical pathways in emotional processing [16].

Subtle cognitive impairment can occur also in out-of-hospital cardiac arrest survivors who are eligible for home discharge and we have found that functional MRI can identify alterations in brain networks that correlate with cognitive outcomes [88].
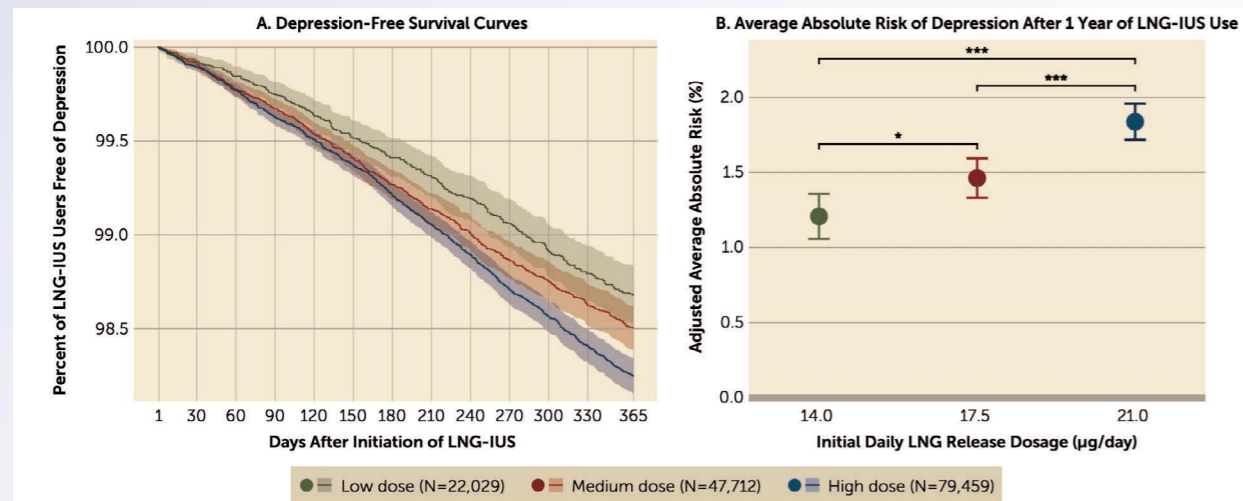

Figure 3: Depression among first-time users of low-, medium-, and high-dose levonorgestrel-releasing intrauterine system (LNG-IUSs). Panel A shows depression-free survival curves for the different LNG-IUS dosages during the year following initiation. Shading represents 95% confidence intervals. Panel B shows the 1-year estimated depression risks for the different LNG-IUS dosages, standardized over calendar period, age, education level, parental history of mental disorders, endometriosis, polycystic ovary syndrome, dysmenorrhea, menorrhagia, leiomyoma, and postpart¤
Authors.

OpenNeuroPET

The NovoNordisk Foundation funded OpenNeuroPET initiative is done in collaboration with NIHM, the Martinos Center, and Stanford University and aims to enable PET data sharing to, e.g., increase sample sizes and thereby improve the statistical power and validity of research findings. Expensive PET neuroimaging data must be shared in a FAIR way (Findable, Accessible, Interoperable, and Reusable).

Having previously extended the Brain Imaging Data Structure (BIDS) to cover PET data, we have now published the companion software PET2BIDS (https://github.com/openneuropet/PET2BIDS) to convert raw PET data and blood recordings to BIDS [27]. Atlasing activities are ongoing with *PET-prep*, a software that allows for the automatic processing of data prepared according to BIDS. We have also worked on a new multivariate atlas for beta-amyloid from ADNI data and this will be published soon. The platform for data sharing, *publicneuro.eu*, is now open, and we were invited to present it during the 2024 Organization for Human Brain Mapping (OHBM) annual meeting in Seoul, Korea. NRU has since joined CrossRef as a publisher, and the platform now hosts multiple datasets for which we can issue DOIs.

Cyril Pernet
Senior researcher

Data Analysis

The NRU Data Analysis Group specializes in optimizing methods and algorithms for analyzing data collected in research projects that NRU participates in. Our primary focus is to develop more robust techniques that can effectively handle smaller sample sizes and noisy data. The data we work with include SPECT, PET, and MR imaging, EEG, as well as various neuropsychological and other state or trait markers collected from participants. NRU is also engaged in several international data sharing initiatives.

Traditionally, the "biological age" of the human brain has been estimated using structural MR brain images. We have explored whether other imaging modalities, such as serotonin PET brain scans, can improve the estimation of "chronological age" of research participants [19]. To this end, we included 5-HT2A receptor PET images from 209 healthy individuals to predict brain age and compared the results to more conventional brain age estimation methods based on structural MR images. Our findings demonstrate that the precision of the PET imaging approach is comparable to that of structural MR imaging. However, when combining 5-HT2A receptor PET and structural MRI, one could predict the biological age much better, suggesting that 5-HT2A receptor binding contains unique information about brain aging beyond volumetric changes. The results show that multimodal approaches are potentially valuable for developing more sensitive biomarkers for brain aging.

We hold a special expertise in molecular brain imaging and we have now created the first in vivo human brain atlas of synaptic density. The atlas is created by utilizing high-resolution PET neuroimaging in healthy humans to develop a 3D truly quantitative atlas of the synaptic marker SV2A [47]. The resulting atlas (**Figure 4**) reveals distinct cortical and subcortical gradients of synapse density, which correspond to functional topography and a hierarchical progression from core sensory regions to higher-order integrative areas. Notably, this distribution differs from patterns observed in SV2A mRNA. This new resource will significantly enhance our understanding of brain physiology and the development of brain disorders, serving as a valuable tool for future neuroscience research.
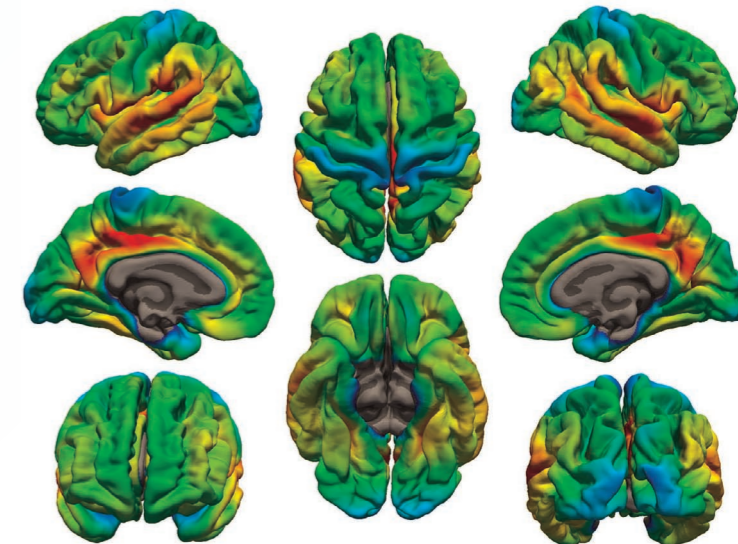
Claus Svarer
Chief engineer

We have also shown how to biostatistically handle right-censoring when doing survival analyses in oncology [73]. The work builds on previous research that assess the benefit/risk balance of new treatments by jointly analysing multiple outcomes. Right-censoring, such as patient drop-out, complicates estimation, particularly when limited follow-up time restricts the ability to fully estimate survival curves. We have published a solution that incorporates a restricted time-limiting comparison between treatment groups to a predefined time horizon, and this new method is implemented in the R package *BuyseTest* (https://cran.r-project.org/web/packages/BuyseTest/index.html).

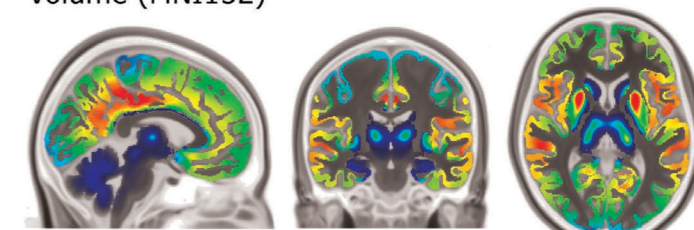*Figure 4: Average in vivo SV2A density maps (Bmax; pmol/mL) on the FreeSurfer fsaverage surface (top) and in the MNI152 volume space (bottom), displaying the distribution of synapses in the human brain. The atlas shows high in vivo SV2A density in the neocortex, with highest densities in the posterior cingulate, precuneus, and gyri of the temporal cortex and lowest in the pre- and postcentral gyri. For the subcortical regions, the highest density is seen in the putamen and caudate while the lower density is in the hippocampus, thalamus, pallidum, and cerebellum. The atlas is based on high-resolution PET images from 33 healthy humans, calibrated to absolute density values by leveraging postmortem human brain autoradiography data. From [47], Copyright © 2024, the authors.*

BrainDrugs

The strategic research alliance *BrainDrugs* (2019-26) is our large-scale precision medicine project in epilepsy and major depressive disorder (MDD) (https://braindrugs.nru.dk); five of its workpackages are described below. The alliance receives 40 mio DKK basic funding from the Lundbeck Foundation and its aim is to establish key features predictive of drug response in patients with epilepsy or MDD.

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 the three mental health centers: Psychiatric Center Copenhagen, Psychiatric Center Glostrup, and Mental Health Center Sct. Hans.

Center director
Gitte Moos Knudsen

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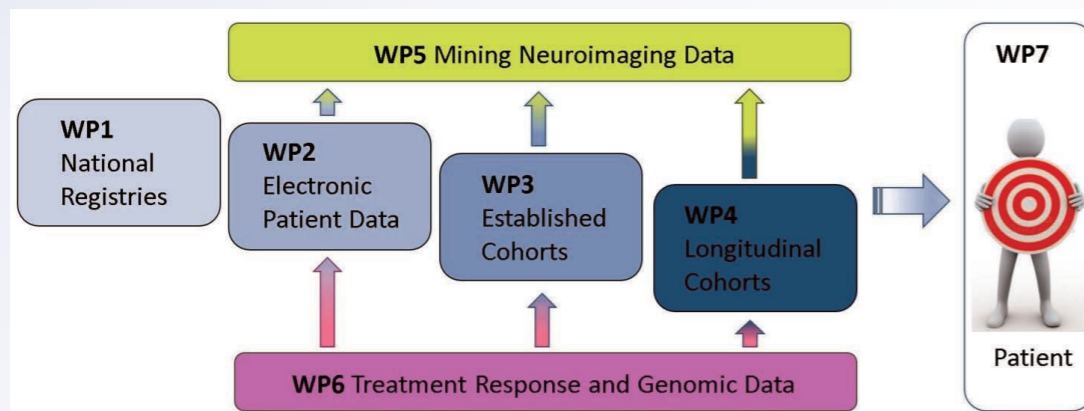
Through 2024 the overall project has progressed as expected. Several work packages have entered their final stage where the focus has been research dissemination, while data acquisition in large patient cohorts is still taking place. To coordinate and to ensure maximal and timely synergy between the work packages and campuses, we have continued our bi-annual Work Package Leader meetings and Early Career Forum (ECF) meetings. In late May we hosted a productive *BrainDrugs* annual meeting with 42 participants (see photo above). Below is a short introduction and update from each of the work packages.

WP1-leader: Professor
Lars V. Kessing

WP1: National registries

Within WP1, we have used unique Danish population-based registries to study patients' drug intake. This allows for identification of comorbidity, potential side effects, and drug response to various pharmacological interventions. We have also employed the national registries in WP3 and WP5.

Over the last 12 months, WP1 PhD student Simon Ziersen submitted his PhD thesis entitled "*Causal inference in time-to-event analysis*" which he successfully defended in December. Also, WP1 has published five papers, three of which are NRU-papers [50, 73, 84].

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WP2: Electronic patient data: Text mining and machine learning

WP2 makes use of text mining methods to extract detailed, phenotypic features from free text in Electronic Patient Records (EPRs) which come from either the Capital Region of Denmark and Region Zealand from 2009-2018 or from the specialized national epilepsy hospital, Filadelfia.

WP2-leaders: Professor Søren Brunak & associate professor Desmond Elliott

Last year, WP2 received a second round of data export from Region Zealand to complete the collection of all relevant EPRs from Filadelfia. The WP2 postdoc quality-checked the new dataset in order to prepare it for use with the subgrouping algorithm published previously by WP2.

We further leveraged a model developed in another context to uncover potential adverse drug events related to anti-epileptic medications by identifying initial exposure to anti-epileptic drugs and detect first-time occurrences of abnormal laboratory test results. The Cox multistate model developed computes hazard ratios for changes in laboratory test results before and after exposure to anti-epileptic medications. We identified several potential adverse drug events following specific anti-epileptics, which we aim to investigate further using free text from the EPRs of the respective patients.

WP3. Deep phenotyping data from established research cohorts

By exploiting existing data from our 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 or functional neuroimaging features. These existing cohorts are particularly important because they contain also 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 2024, we continued working with our deep phenotyping data from the Cimbi and NEAD databases in combination with data from the National Health Register and the drug prescription register, and this has resulted in a total of seven

WP3-leaders: Professors Vibe Frøkjær & Kamilla Miskowiak

publications, most of which are discussed in other sections of this annual report. We have confirmed our earlier findings of a link between personality-based risk factors for depression, likely to shape how we navigate stressors and brain chemistry in terms of cerebral serotonin 2A receptor (5-HT2AR) [37]. Further, we showed that the combination of such personality risk factors and high levels of 5-HT2AR availability in healthy individuals is associated with future risk for depression [79]. This resonates with the idea that interventions targeting the 5-HT2AR, such as classic psychedelics, may be beneficial in promoting brain health.

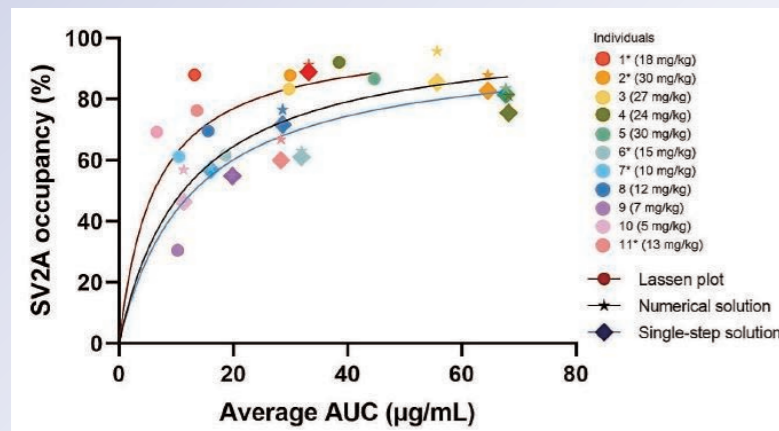## WP4. Deep phenotyping data from new research cohorts

In WP4, we have continued data collection in the two growing cohorts of patients with MDD and epilepsy, most of them with a first-time diagnosis. Patients are deep phenotyped and followed longitudinally. With the experience gained from the other work packages, we use these cohorts to address new research questions and if relevant, to replicate previous findings.

As for the MDD cohort, we work in close collaboration with the Mental Health services in the Capital Region, where patients are recruited through the central visitation and six clinics. We acquire either basic or expanded clinical, cognitive, psychometric, and biological data, and for a subset of patients, we also collect MRI and EEG data, and in another subset PET imaging data with the [^{11}C]-UCB-J tracer of synaptic density is also done. So far, we have included 380 patients, accounting for approximately 10% of the Region's annual patient flow. Five papers [41, 42, 43, 67, 86] were published in 2024.

WP4-leaders: Professors Lars Pinborg & Martin B. Jørgensen

To continue the establishment of a large prospective cohort of deeply phenotyped first-seizure patients and newly diagnosed epilepsy patients, NRU collaborates closely with dedicated neurologists from Rigshospitalet, Bispebjerg Hospital, and Herlev Hospital across the Greater Copenhagen area. At Rigshospitalet, 6 specialist doctors, 1 neuropsychologist, and a project nurse are directly involved in the project on a daily basis. All workflows have been optimized so patients are promptly seen in the epilepsy clinic and undergo an extensive examination program. Currently, around 220 patients have been enrolled and they are followed in the epilepsy clinic with frequent check-ups, distribution of questionnaires, and through self-reporting via a smartphone app developed for the project. We have successfully implemented experiences generated through the project into the clinical routine. A subset of the enrolled patients, along with a group of healthy controls, has undergone PET imaging with [11C]UCB-J which is a radiotracer that binds to the SV2A binding site in the brain, i.e., the primary target of levetiracetam, one of the most widely used anti-seizure medications. Utilizing a method developed at NRU, we demonstrated the classical hyperbolic dose-occupancy curve (**Figure 5**) for various clinically relevant doses of levetiracetam [64].

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Figure 5: Plasma levetiracetam (LEV) concentration versus brain SV2A occupancy. Average AUC of plasma LEV concentration (µg/mL) and maximum SV2A occupancy calculated with the Lassen plot, the Numerical solution, and the Single-step solution. AUC: Area under the plasma levetiracetam-time curve. *: Individuals scanned twice on the same day. From [64], Copyright © 2024, The Authors.

WP5. Mining neuroimaging data

WP5 focuses on establishing models to identify structural abnormalities relevant to epilepsy in structural MR images in order to establish criteria to assist clinicians in their future diagnostic work. 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 2024, we have concerted our efforts on establishing and evaluating models for processing text (i.e., natural language processing [NLP] models) in order to extract relevant labels from the radiological reports to be associated with the related MR images. Even though the NLP field has made enormous strides forward in recent years, progress is particularly hindered by the relatively small number of labelled reports, the strong class imbalance intrinsically present in the data induced by low

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

disease prevalence, and that that the reports are in Danish). The main outcomes of this endeavour are:

1)   A dataset of radiological reports from approximately 4,500 patients for which brain MRI abnormalities relevant for epilepsy have been identified. This process identified a large number of patients with rare brain abnormalities, a resource that is very valuable and unique.

2)   NLP models which can filter radiological reports and substantially reduce the effort required for labelling new reports.

A preliminary evaluation of the NLP models has been presented at the Medical Imaging in Deep Learning (MIDL) 2024 conference (Beliveau et al. 2024); a full manuscript is in preparation. Leveraging the labelled radiology reports, we established a brain MRI dataset of 175 patients with focal cortical dysplasia (FCD) and evaluated the performance of state-of-the-art FCD classifiers which outlined issues with the specificity of the current approaches. This is among the largest dataset on FCD ever reported and that this was made possible through the data mining efforts. We are extending this analysis by including more patients, longitudinal data, and a new model in the evaluation. Preliminary results for this study were presented at the AI in Epilepsy 2024 conference and a manuscript is in preparation.

Dissemination in 2024

Since the beginning of 2024, NRU has published a total of 3 PhD dissertations, 21 Master's or Bachelor theses and reports, and 89 scientific peer-reviewed papers, including 1 multicenter study. The list below encompasses all papers that have either been printed or were online ahead of print during 2024.

PhD dissertations

- Stinne Høgh. Biological aspects of postpartum mental health: prevention opportunities and mother's perceptions. University of Copenhagen, Faculty of Health and Medical Sciences. Defended Aug 09, 2024
- Søren Vinther Larsen. Hormonal contributions to depressive episodes in women. Insights from register-based cohort studies from Denmark. University of Copenhagen, Faculty of Health and Medical Sciences. Defended May 08, 2024
- Janus Houe Magnussen. Exploring nicotinic receptors and histone deacetylases through neuroimaging. University of Copenhagen, Faculty of Health and Medical Sciences. Defended Sep 09, 2024.

Master's and Bachelor theses and reports

The following list of NRU-affiliated students have successfully defended their theses or research year reports during 2024:

- Aje Al-Awssi - *Correlation Between Cognition and Inflammatory Biomarkers in the Epileptic Brain*. Master's thesis in medicine, University of Copenhagen. Primary supervisor: Jens H. Mikkelsen
- Astrid Skytte Nielsen - *B-waves in healthy people - and how to measure it*. Bachelor thesis in medicine, University of Copenhagen. Primary supervisor: Gitte Moos Knudsen
- Bóas Sore Marjunarson - *Assessing geographic health inequity within the Danish Commonwealth - A retrospective cohort study of presurgical disability scores in lumbar spinal surgery patients*. Master's thesis in medicine, University of Copenhagen. Primary supervisor: Louise Møller Jørgensen
- Elisabeth Kolesnik - *The effects of repeated low-dose psilocybin administration on behavioural tasks involving learning and memory in rats*. Master's thesis in neuroscience, University of Copenhagen. Primary supervisor: Gitte Moos Knudsen
- Gudrun Dilja Ketilsdottir - *The usefulness of serotonergic activity estimated by EEG loudness-dependent auditory evoked potentials as a marker of SSRI-induced sexual dysfunction*. Master's thesis in medicine, University of Copenhagen. Primary

supervisor: Martin Balslev Jørgensen
- Helene Kaas - *The Assessment of Selected Neural Networks' Performances in Detecting Focal Cortical Dysplasia*. Bachelor thesis in medicine, University of Copenhagen. Primary supervisor: Lars H. Pinborg
- Helga Uitterdijk Appel-Olsen - *Mapping late pregnancy clinical and psychometric profiles in women at high versus low risk for perinatal depression*. Master's thesis in medicine, University of Copenhagen. Primary supervisor: Vibe G. Frøkjær
- Holger Max Fløe Lyng - *Assessment of MRI myelin mapping using T1w/T2w*. Bachelor thesis in biomedical engineering, Technical University of Denmark and University of Copenhagen. Primary supervisors: Kristian Reveles Jensen & Cyril Pernet
- Jan Tagscherer - *Estimating Spatial Distortion Correction of Brain BOLD MRI Data with Machine Learning Models*. Master's thesis in informatics, Technische Universität München. Primary supervisors: Patrick Fisher & Cyril Pernet
- Josephine Meyer Tyron - *Loudness Dependent Auditory Evoked Potentials and Suicidality in Depression – a meta-analysis with replication in unmedicated patients*. Master's thesis in medicine, University of Copenhagen. Primary supervisor: Martin Balslev Jørgensen
- Kalle Falk - *Assessment of MRI myelin mapping using MP2RAGE*. Bachelor thesis in biomedical engineering, Technical University of Denmark and University of Copenhagen. Primary supervisors: Kristian Reveles Jensen & Cyril Pernet
- Kamilla Moll Lindegaard - *Activation fingerprints of the wild-type serotonin 2A receptor and natural single-nucleotide variants thereof activated by psychedelic and non-psychedelic agonists*. Master's thesis in molecular biomedicine, University of Copenhagen. Primary supervisor: Gitte Moos Knudsen
- Katarina Bubolovic - *Blood BDN changes in pregnancy and psilocybin intervention*. Master's thesis in human biology, University of Copenhagen. Primary supervisor: Gitte Moos Knudsen
- Lauren Elise French - *Biodistribution and Radiation Dosimetry of [18F]MH.MZ, A Radiotracer for PET Imaging of Serotonin 5-HT2A Receptors*. Master's thesis in Biophysics. Primary supervisor: Jens Jørgen Gaardhøje
- Mathilde Ehnhuus Brøgger-Jensen - *The Relevance of Sleep Electroencephalogram (EEG) at 12 Months Post-Epilepsy Surgery in Predicting Seizure Freedom and Informing Anti-seizure Medication (ASM) Management*. Master's thesis in medicine, University of Copenhagen. Primary supervisor: Lars H. Pinborg
- Matilde Laura Rasmussen - *Antenatal maternal mental health, brain serotonin markers and placenta weight - A study on late pregnancy maternal mental health factors effect on a marker with importance for fetal environment*. Master's thesis in medicine, University of Copenhagen. Primary supervisor: Vibe G. Frøkjær
- Peter Moltke Skov-Andersen - *Psychedelic Symphonies: Investigating LSD and Music Induced Brain Activity Using fMRI*. Master's thesis in neuroscience, University of Copenhagen. Primary supervisor: Patrick Fisher

- Phoebe Ann Linde-Atkins - *Synaptic Density in Alzheimer's Disease: Synaptic Vesicle Glycoprotein 2A as a Biomarker and Apolipoprotein-E Genotype Associations*. Bachelor thesis in molecular biomedicine, University of Copenhagen. Primary supervisor: Jens H. Mikkelsen
- Rói Hansen - *Geographical health inequities in the Danish Commonwealth - A comparative registry study of presurgical disability scores in cervical spinal surgery patients across selected Danish regions*. Master's thesis in medicine, University of Copenhagen. Primary supervisor: Louise Møller Jørgensen
- Sif Olsen - *Emotion Processing Deficits in Psychopaths - An Empirical Study in Violent Offenders*. Master's thesis in psychology, University of Southern Denmark. Primary supervisor: Christian Gerlach
- Victoria Mikkelsen - *Risk factors for developing impulse control disorder during pramipexole treatment for restless legs syndrome*. Bachelor thesis in medicine, University of Copenhagen. Primary supervisor: Kristian Reveles Jensen

Papers in peer-reviewed journals

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Multicenter studies without co-authorships

M1. Mellor S, Timms RC, O'Neill GC, Tierney TM, Spedden ME; MELD Project Consortium; Brookes MJ, Wagstyl K, Barnes GR. Combining OPM and lesion mapping data for epilepsy surgery planning: a simulation study. Sci Rep. 2024 Feb 4;14(1):2882.

Media attention

Jan 12: Gitte Moos Knudsen in the article "*Why do antidepressants take so long to kick in?*": https://interestingengineering.com/health/antidepressants-ssri-depression-anxiety

Jan 27: Gitte Moos Knudsen in the newspaper article "*Svigter hukommelsen? Hjerneforsker giver tre råd til, hvordan man holder hjernen skarp*" in Jyllandsposten.

Feb 1: PhD-student Kristian R. Jensen in "For en særlig gruppe kvinder kan cyklus påvirke dem ganske alvorligt" in Femina.

Mar 6: Gitte Moos Knudsen quoted in the Politiken article "Sådan forsøger neurologen selv at undgå at blive ramt af en hjerneblødning".

Mar 9: Olaf Paulson has together with Hans Hultborn written an obituary about Arne Schousboe, which has been published on the DSfN webpage: https://dsfn.dk/2024/03/10/arne-schousboe/

Mar 13: Gitte Moos Knudsen was interviewed in the radio program "Det gode selskab" on DR P5: https://www.dr.dk/lyd/p5/det-gode-selskab-2146894737000

Sep 4: Sara Marie Larsen contributed with an interview about being PhD-student in the field of sleep research in a book called "Søvn" (ISBN: 978-87-93647-95-4) used in the Danish Gymnasiums: https://nucleus.dk/boeger/trykte-boeger/s%C3%B8vn-detaljer

Sep 5: Dea S. Stenbæk in the DR-P1 radio program called "Udsyn" in an episode entitled "*Psykedelisk renæssance*": https://www.dr.dk/lyd/p1/udsyn/udsyn-2024/udsyn-psykedelisk-renaessance-11802401163?fbclid=IwY2xjawH6_ORleHRuA2FlbQIxMQABHYSxXwdF2rkFcJ9-3-TSKjl_8AESGp3-Rm-oz-egTnRnZirsO9e6FkYSCw_aem_-dWDm-eLmEBEkkcJ69EUwg

Sep 26: The HC-SSRI study with Barbara Sahakian was mentioned in an article in a British newspaper under the title "*Constipation drug may help treat depression - and boost memory*".

Sep 26: Gitte Moos Knudsen authored the article "6 gode grunde til at gå udenfor i løbet af din arbejdsdag" published on videnskab.dk.

Oct 2: Melanie Ganz' MoCo-project has been flashed on the webpages of both Innovation District Copenhagen and Rigshospitalet:

https://innovationdistrictcopenhagen.dk/apps-cartoons-and-training-reduces-need-to-anesthetise-kids/

https://www.rigshospitalet.dk/presse-og-nyt/nyheder/nyheder/Sider/2024/Oktober/apps-tegnefilm-og-en-legeskanner-reducerer-behovet-for-bedoevelse-af-boern.aspx

Oct 18: Kristian Reveles Jensen provided comment for the article "*Netværksændringer i hjernen ved depression lokaliseret*" in Ugeskrift for Læger: https://ugeskriftet.dk/videnskab/netvaerksaendringer-i-hjernen-ved-depression-lokaliseret

Oct 29: PhD-student Kristian R. Jensen in "PMD er en cyklisk lidelse hos kvinder, som vi mangler viden om herhjemme" in Woman.

Dec 03: Olaf Paulson has during the year published more than 20 articles on lex.dk covering topics within the categories "Neurodegenerative diseases and symptoms", "Symptoms, neurological" and "Neurological birth defects".

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