Neurobiology Research Unit

Annual Report 2020

Department of Neurology, Neuroscience Centre
Copenhagen University Hospital, Rigshospitalet

www.nru.dk

Cover image: The Rockefeller building (left) and the new North Wing at Rigshospitalet (right), corresponding to the previous (2013-20) and new premises for NRU, respectively.

REGION Rigshospitalet

KØBENHAVNS UNIVERSITET
DET SUNDHEDSVIDENSKABELIGE FAKULTET

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Preface

It is a pleasure to present you with the 2020 annual report describing the activities of the Neurobiology Research Unit (NRU). The pandemic turned everything up and down and 2020 became a very different year, much more different than anyone could have imagined. Much effort was naturally directed towards combatting the virus, and the lock-down in the spring also heavily impacted research and teaching. Some staff members were over-burdened, trying to cope with their jobs while looking after their children at home. Others, particularly our international junior scientists, were experiencing loneliness and lack of a fruitful collegial training environment. Meetings and congresses that usually present a great opportunity for interaction with other scientists were now confined to online meetings. We all learned to communicate in new ways. The ongoing vaccination program will hopefully allow us some more mobility and interaction. Let's be together in our hopes for a much better 2021.

In September, we moved to the newly built North Wing. The massive undertaking to get the last details in place before our move turned out to pay off, and virtually everything was up and running within a few days. We are very grateful for the enduring support we have received from the construction company staff and the Department of Neurology. A special thanks goes to center manager Peter Steen Jensen who was instrumental to the success of the process. The move has provided us with more spacious and modern facilities, with some highly needed expansion for the research activities. The preclinical laboratory is now conveniently situated next to NRU and the close proximity to the scanners and to the Dept. Neurology has already turned out to be a clear advantage.

In the past two decades, we have seen an exponential growth in the scale at which neuroimaging research in psychiatry and neurology takes place in terms of sample size, technology advancements and number of disorders investigated. Yet, many research findings turn out to be hard to replicate, partly because of inconsistencies in data acquisition, preprocessing and analysis. One of our major research themes within NRU is to understand these sources of discrepancies and in a recent consensus paper, we lead an initiative that aims to standardize the way PET neuroimaging data are acquired, documented, analysed, and archived. Such an initiative will also help to establish data sharing of these costly experiments, enabling replications and increasing sample sizes. Achieving this requires having appropriate research infrastructure and fortunately, The Novo Nordisk Foundation decided in 2020 to fund our "OpenNeuroPET Archive" which is an infrastructure that will unite the scientific community to enable meta- and mega-analyses of brain imaging data by creating an expertly labelled, shared-access data repository and processing platform. The main ethos of the OpenNeuroPET will be: open, inclusive, participatory, and democratic.

Regardless of the pandemic, 2020 has generated substantial research output from the group. Four of our PhD students have successfully defended their theses and obtained their PhD degree (page 14-17). Many NRU-affiliated researchers have presented their work at a large number of international congresses, conferences, and meetings. In total, NRU published 46 peer-reviewed scientific publications (page 54).

I would like to take this opportunity to acknowledge and thank all of the NRU staff for their dedicated work as well as to thank our host institution, Rigshospitalet, and all our highly valued national and international collaborators (page 50) and the funding agencies that support our work (page 62). These have all been essential factors to ensure that 2020 was another very successful year for NRU.

I hope that you will enjoy reading this 2020 annual report and encourage interested readers to stay tuned on our website, 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 and (from left to right starting in the top row) Jens D. Mikkelsen, Vibe G. Frøkjær, Olaf B. Paulson, Claus Svarer, Patrick Fisher and Lars H. Pinborg.

Our Mission & Activities

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

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

The activities within NRU fall in 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
5) Research in use of modern statistical and machine learning methods
6) Neuroimaging research studies of patients with neurological or psychiatric disorders
7) Diagnostic brain imaging of neurological patients
8) Neuropsychology research and neuropsychological testing
9) Education and training
10) Dissemination of results

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

Facilities

After our move to the new North Wing of Rigshospitalet in September 2020, NRU now covers more than 1,400 m^2.

Our main premises can be found at fifth and sixth floor of the North Wing building, RH 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 for social interaction, two smaller quiet rooms for telephone calls, a laboratory for handling human specimens, a sterile storage room, two sound-proof rooms with facilities for neuropsychological and -physiological testing, a calm and relaxing 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. In the basement we have a 20 m^2 storage room.

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, 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 bath/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.

The SPECT laboratory of NRU is located next to the Department 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-pine-hole collimator. The SPECT laboratory also has a dedicated storage room in the basement and thereby occupy in total 130 m^2.

The NRU 3rd generation high-resolution AnyScan SPECT-CT Mediso scanner, installed in the Fall of 2019.

Also, on the ground floor in the North Wing, we run our own brain research dedicated 3 Tesla Siemens Prisma MR-scanner. The scanner (MR001) was installed late 2019 in 120 m^2 state-of-the-art facilities. We have made these facilities partly available for our close collaborators at the Department of Diagnostic Radiology for clinical investigations with a clear research potential. Likewise, we benefit from access to one of their clinical 3 Tesla Siemens scanners in the main building of Rigshospitalet which we use for some of our research projects.

In dedicated rooms in the basement of the North Wing, covering 75 m^2, we have a Siemens mock-up MR scanner installed in facilities mimicking the 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.

Last but not least, NRU has a close collaboration with the PET and Cyclotron Unit at Rigshospitalet, which provides NRU with access to radiochemistry production and to PET- and combined PET-MR scanner facilities.

Our Siemens 3T Prisma MR scanner, installed late 2019.

Staff in 2020

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

Chief technologist
Gerda Thomsen

Research administrators
Birgit Tang
Dorthe Givard
Peter S. Jensen

Junior faculty
Brice Ozenne, assistant professor, biostatistician, PhD
Dea S. Stenbæk, associate professor, psychologist, PhD
Hanne D. Hansen, instructor, molecular biologist, PhD
Louise M. Jørgensen, associate professor, MD, PhD
Melanie Ganz, assistant professor, computer scientist, PhD
Mikael Palner, engineer, PhD

Post docs
Martin Nørgaard, engineer, PhD
Martin Schain, engineer, PhD
Pontus Plavén-Sigray, clinical neuroscience, PhD
Sofi da Cunha-Bang, MD, PhD
Sebastian C. Holst, engineer, PhD
Vibeke N. H. Dam, psychologist, PhD

PhD students
Agata C. Sainz, molecular biomedicine
Annette Johansen, MD
Camilla B. Larsen, MD
Cheng T. Ip, psychologist (H. Lundbeck A/S)
Giske F. Opheim, neuroscientist
Gjertrud L. Laurell, medical nuclide techniques
Kristin Forsberg, MD (Psychiatric Center Copenhagen)
Kristian H.R. Jensen, MD (Psychiatric Center Copenhagen)
Lene L. Donovan, medicine with industrial specialization
Martin K. Madsen, MD
Nakul Raval, medical nuclide techniques
Sagar S. Aripaka, biochemistry
Sara Marie Larsen, MD
Sophia Armand, psychology
Stinne Høgh, midwifery
Søren V. Larsen, MD

Research assistants
Arafat Nasser, pharmacology
Dorte B. Zilstorff, MD
Drummond McCulloch, pharmacology

Emily Beaman, human biology
Ida Marie Brandt, molecular biomedicine
Josefine Sørensen, psychology
Louise F. Nielsen, psychology
Maja R. Marstrand-Jørgensen, medicine
Miriam R. Demattia, neuroscience & neuroimaging
Natasha D. Christiansen, neuroscience & neuroimaging
Sebastian E. Ebert, MD

Technical research personnel

Ajla Sabitovic, MRI-student assistant
Asta Kongsgaard, project nurse
Cecilie L. Nordberg, MRI-student assistant
Cecilie F. Skovsen, MRI-student assistant
Christina C. Schnohr, MRI-student assistant
Clara Madsen, molecular biomedicine
Ditte B. Christensen, MRI-student assistant
Ditte B. Nielsen, project nurse
Gunild Vulpius, medicine
Kristoffer Brendstrup-Brix, MRI-student assistant
Line N. Buchwald, MRI-student assistant
Lone I. Freyr, project nurse
Lucas K. Andreasen, HPLC-student assistant
Lærke V. Kristiansen, medicine
Minna H. Litman, project nurse
Nadia Taghavi-Larmaei, biology
Nanna Svart, MRI-student assistant
Simone Pleinert, psychology
Svitlana Olsen, medical technologist
Thomas W. Jørgensen, IT-support

Visiting professors

Adriaan Lammertsma, professor, VUmc, Netherlands
Barbara Sahakian, professor, Univ. Cambridge, UK
Graeme F. Mason, professor, Yale School of Medicine, USA
Todd Ogden, professor, Columbia University, USA
Trevor Robbins, professor, Univ. Cambridge, UK

Visiting scientists

Burcu Azak Pazarlar, physiology, PhD student from Izmir Katip Celebi Univ., Turkey
Ida Ivek, MD, ERASMUS intern from Univ. Zagreb, Croatia
Ida Vang Andersen, pharmcy, PhD student from Univ. Copenhagen, Denmark
Júlia Tolrà Azor, biomedical sciences, ERASMUS intern from Univ. Barcelona, Spain
Natalie Beschorner, PhD, post doc from Univ. Copenhagen, Denmark
Nídia Fernandez Ros, biotechnology, ERASMUS scholar from Universitat Autònoma de Barcelona, Spain
Silas Haahr Nielsen, MD from Department of Neurosurgery, Rigshospitalet

Pregraduate students

Aksel Berg, medicine
Albin Arvidsson, medicine
Anders Lykkebo-Valløe, bioinformatics
Anders S. Olsen, engineer
Andreea-Veronica Vascan, computer science
Ane G. Kloster, medicine
Anna Søndergaard, medicine
Annesofie Videbæk, cellular biology & physiology
Catharina Messell, music therapist
Cecilie A. Poulsen, medical technology
Charlotte H. Nykjær, medicine
Daniel Burmester, medicine
Ella Hedeboe, molecular biomedicine
Elisabeth B. Pedersen, medicine
Emma S. Høgsted, medicine
Emilie H. Mortensen, medicine
Frederik Gudmundsen, neurosicence & neuroimagning
Hannah Eichhorn, physics
Harald Schiønning, medicine
Ida L. Klausen, psychology
Inger Marie M. Sørensen, medicine
Katrine Kiilerich, biochemistry
Laura Fonnesbech-Sandberg, medicine
Liis Kivistik, bioinformatics
Line B. S. Knudsen, pharmacy
Malthe B. Scharff, biochemistry
Marcus A. Hansen, computer science
Maria Grzywacz, psychology
Martin Prener, medicine
Michael K. D. Nguyen, computer science
Niels Lorenzen, molecular biomedicine
Nizar Hamrouni, medicine
Oliver Overgaard-Hansen, psychology
Ottilia Wyon, medicine
Philip Fink-Jensen, medicine
Sophia K. Weber, psychology
Tina Segerberg, psychology
Tobias Fjeld, medicine
Tobias Mathiesen, psychology
Veronica Drejer, biology

Visiting professors

In 2020, NRU has had the pleasure of hosting two highly esteemed international visiting professors, namely Adriaan A. Lammertsma, professor of Nuclear Medicine at VU University Medical Center (Amsterdam, The Netherlands) and R. Todd Ogden, professor of Biostatistics at Columbia University (New York, NY, USA), enabled through two visiting professorship grants from the Lundbeck Foundation. Professors Lammertsma and Ogden have throughout their respective careers made remarkable impressions on the PET field by pioneering the development of pharmacokinetic models and other methodologies advancing neuroimaging as a research tool.

During their respective visits at NRU, Professors Lammertsma and Ogden are involved in a multitude of research projects, including e.g.:

- development of pharmacokinetic models describing radioligand displacement during on-going PET scans,
- estimation of errors arising in PET acquisitions and development of tools to use these errors when making statistical inference,
- estimation of the level of background signal in a PET image,
- development of statistical tools to improve the reliability of target engagement studies,
- development of statistical tools to minimize the number of research participants exposed to radioactivity as part of a PET scan,
- determination of a lower limit for the injected radioactivity without sacrificing quality of the data,
- hosting of seminars and course-lectures of state-of-the-art PET methodology.

Professors Lammertsma (left) and Ogden (right).

Professors Ogden and Lammertsma's contribution to NRU has, to date, resulted in 2 accepted publications.

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

PhD Degrees 2020

Kristin Köhler-Forsberg, Medicine

On April 4th, 2020, Kristin Köhler-Forsberg submitted her PhD thesis entitled "The serotonin 4 receptor binding as a novel imaging marker in major depressive disorder and the association to antidepressant treatment response" to the Graduate School of Health and Medical Sciences, University of Copenhagen. Dr. Köhler-Forsberg was supervised by professor Martin Balslev Jørgensen from Psychiatric Center Copenhagen and Institute of Clinical Medicine, University of Copenhagen. Primary co-supervisor was associate clinical research professor Vibe G. Frøkjær, NRU and professor Gitte Moos Knudsen from NRU and post doc Anders Jørgensen from Psychiatric Center Copenhagen were co-supervisors.

The aim of the thesis was to: 1) study differences in 5-HT4R PET binding in patients with major depressive disorder (MDD) compared with healthy controls, 2) predict treatment response in MDD after 8 weeks of serotonergic treatment, based on baseline 5-HT4R PET binding, 3) study changes in 5-HT4R PET binding after 8 weeks of serotonergic antidepressant treatment. The data suggests that depressed patients who remit to SSRI treatment have higher serotonin levels before treatment compared to healthy controls, perhaps as an indicator of a disturbance in the serotonin system. Alternatively, or in addition, these patients could be characterized by low capacity for 5-HT4R agonism. This study provides novel insights and point to PET neuroimaging of the 5-HT4R as a potentially useful biomarker to aid in the identification of distinct subtypes in MDD, which ultimately may facilitate future strategies for precision medicine.

Dr. Köhler-Forsberg successfully defended her thesis on June 26th, 2020, with professor Sidse Marie Hemmingsen Arnfred, Department of Clinical Medicine, University of Copenhagen, as chair and professor Brenda W.J.H. Penninx, Department of Psychiatry, Amsterdam Public Health Research Institute, Amsterdam University Medical Center, The Netherlands and Dr. Henricus G. Ruhé, Department of Psychiatry, Radboud University Medical Center, The Netherlands, as opponents.

Lene Lundgaard Donovan, Medicine with industrial specialization

Lene Lundgaard Donovan completed her PhD at NRU under the supervision of professor Gitte Moos Knudsen from NRU and co-supervision by associate professor Jacob M. Hooker, Massachusetts General Hospital, Massachusetts, USA, and PhD Hanne D. Hansen, NRU. Her PhD thesis entitled "Epigenetic and pharmacological investigations of the pig brain. *In vivo* and *in vitro* studies of [11C]Martinostat and psilocybin" was submitted to the Graduate School of Health and Medical Sciences, University of Copenhagen, on March 1st, 2020.

The aim of the thesis was to: 1) evaluate the PET radioligand [11C]Martinostat in the pig brain, including the regional distribution, suitable kinetic modelling and the correlation between *in vivo* and *in vitro* measured HDAC1-3 levels, 2) establish a large animal model for acute psilocybin administration and characterize the porcine reaction to psilocybin, including determining the 5-HT2AR occupancy of the dose eliciting behavioural changes, 3) investigate genetic mechanisms underlying the sustained effects induced by acute psilocybin administration. Her work provides the first cross-validation of the [11C]Martinostat radioligand and found that the *in vivo* SUVR correlates well with *in vitro* levels of HDAC1-3, making it a useful tool for epigenetic investigations of the living brain. Although psychedelics have been shown to promote synaptic plasticity and epigenetic alterations, such changes were not observed in the pig brain following a single dose of psilocybin. However, multiple unexplored targets could still be investigated, e.g., regulation of the mGluR2 gene expression (Grm2) and other synaptic markers like synaptophysin.

Dr. Lundgaard Donovan successfully defended her thesis on September 11th, 2020, with associate professor Birgitte R. Kornum from Department of Neuroscience, University of Copenhagen, as chair and associate professor Anne M. Landau, Department of Nuclear Medicine and PET, Aarhus University, Denmark and professor Charles D. Nichols, Department of Pharmacology and Experimental Therapeutics, Louisiana State University, New Orleans, USA, as opponents.

Martin Korsbak Madsen, Medicine

Martin Korsbak Madsen completed his thesis at NRU between October 2016 and June 2020 under the supervision of professor Gitte Moos Knudsen from NRU and co-supervision by senior scientist Dr. Patrick MacDonald Fisher, NRU. His PhD thesis entitled "Neurobiological effects of 5-HT2AR modulation" was submitted to the Graduate School of Health and Medical Sciences, University of Copenhagen, on June 1st, 2020.

Dr. Korsbak Madsen's thesis sought to improve the understanding of psilocybin's neuropsychopharmacology and the role of 5-HT2ARs through three studies: Study 1 evaluated relations between acute subjective effects, measured using subjective drug intensity (SDI) ratings, plasma levels of psilocybin's active metabolite psilocin (PPL) and 5-HT2AR occupancy, measured with [11C]Cimbi-36 positron emission tomography (PET). Study 2 assessed protracted effects of a single dose of psilocybin on personality and mindfulness and on 5-HT2AR binding measured with [11C]Cimbi-36 PET. Study 3 evaluated associations of PPL and SDI with functional magnetic resonance imaging (fMRI) resting state functional connectivity (RSFC). An important finding in Dr. Korsbak's work is that PPL correlates closely with 5-HT2AR occupancy, brain function and subjective experience, thus concluding that psilocin is a key determinant for psilocybin effects and also exemplified how a combination of molecular and functional neuroimaging methods coupled with measurement of plasma drug concentration and subjective experience can provide knowledge beneficial to drug development and the understanding of the brain.

Dr. Korsbak Madsen successfully defended his thesis on October 9th, 2020, with professor Steen Hasselbalch, Department of Neurology, Rigshospitalet and Department of Clinical Medicine, University of Copenhagen, as chair and professor Morten Kringelbach, Department of Clinical Medicine, Aarhus University, Denmark and Department of Psychiatry, University of Oxford, United Kingdom and associate professor Boris Quednow, Department of Psychiatry, University of Zürich, Switzerland, as opponents.

Vibeke Dam, Psychology

Vibeke Høyrup Dam completed her PhD at NRU under the supervision of professor Gitte Moos Knudsen from NRU. Primary co-supervisor was associate clinical research professor Vibe G. Frøkjær, NRU, and associate professor Dea S. Stenbæk, Department of Psychology, University of Copenhagen, was co-supervisor. Her thesis entitled "Shining a light on the black cloud of depression – A study of cognitive markers in Major Depressive Disorder" was submitted to the Graduate School of Health and Medical Sciences, University of Copenhagen, on December 15th, 2019.

The aim of the thesis was to implement and validate a Danish version of the EMOTICOM test battery and to investigate hot and cold cognitive markers in major depressive disorder (MDD). Overall, the EMOTICOM test battery exhibited satisfactory psychometric properties although select tasks, primarily from the Motivation and Reward domain, might benefit from modification to avoid issues with poor test-retest reliability and floor and ceiling effects in healthy individuals. Patients with MDD exhibited clear cognitive disturbances across both hot and cold cognitive domains relative to the healthy controls, and within the MDD patient group it was possible to detect the presence of three distinct cognitive profile clusters. The results emphasize that cognition should be viewed as a distinct symptom and treatment target in MDD and that cognitive profiles may be useful tools for stratifying patients in a precision medicine approach.

Dr. Høyrup Dam successfully defended her thesis on October 23rd, 2020, with professor Lars Vedel Kessing, Department of Clinical Medicine, University of Copenhagen, as chair and associate professor Vibeke Fuglsang Bliksted, Department of Clinical Medicine, Aarhus University, Denmark, and professor Catherine Harmer, Department of Psychiatry, University of Oxford, United Kingdom, as opponents.

Education

NRU is a major training site for pre- and postgraduate students. We aim to attract physicians and people with other relevant educations to the neuroscience field and to educate and train national and international research staff, in particular medical students, graduate students, PhD students and post docs. We organize pre- and post-graduate courses with prominent speakers and well-attended programs, including 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 programmes.

Basic Kinetic Modeling in PET and MR Imaging

In February 2020 we hosted our one-week PhD course on pharmacokinetics with participation by 19 national and international researchers (see photo to the right).

The Master's program in Neuroscience in Copenhagen

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

Master's in Neuroscience and Neuroimaging in Beijing

Lars Pinborg who is NRU senior researcher and associate professor at University of Copenhagen has again this year taken part in the lecturing at the Master's degree program 'Neuroscience and Neuroimaging' at the University of Chinese Academy of Sciences in Beijing as part of the Sino-Danish Center for Education and Research. As a consequence of the covid-19 pandemic, this year the lecturing was purely online. Dr. Pinborg has contributed to a course that provides an elementary overview of the structure and function of the nervous system, with special emphasis on the use of PET and SPECT tracers for the study of normal function and neurological, neurosurgical and psychiatric disease.

Danish Institute of Study Abroad

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

Preclinical Neurobiology

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

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

Radioligand Development

In the radioligand development group we combine biology, chemistry, radiochemistry and neuroimaging to develop radioligands for positron emission tomography (PET) imaging. As a multidisciplinary and translational group we work with different animal species before a potential clinical evaluation of the tracer.

Traditionally, testing of radiotracers begins in rats, however, the translational value of this species has been debated because of a higher amount and/or efficiency of efflux transporters in the blood-brain barrier of these animals. This effect was highlighted by Shalgunov et al. (**Figure 1**), in which eight different tracers were tested in both rats and pigs and results were subsequently compared [37].

Another example of our translational approach was the evaluation of the 5-HT_7 receptor tracer [^{11}C]Cimbi-701 in rats, pigs and baboons (**Figure 2**) in collaboration with the A. A. Martinos Center for Biomedical Imaging in Boston [23].

Our group has previously published evaluations of 5-HT_{2A} receptor tracer [^{18}F]MH.MZ in rats and pigs and these successful results have led to a clinical evaluation of the tracer as well. This project was conducted in collaboration with Dr. Vasko Kramer, Positronpharma in Chile [16]. Another target that we have been interested in is the α7 nicotinic acetylcholine receptor (α7 nAChR) where we have investigated two novel radioligands, [^{125}I]Iodo-ASEM and [^{18}F]ASEM both *in vitro* and *in vivo* [6]. Finally, we conducted the first *in vivo*/*in vitro* cross-validation of the novel PET radioligand [^{11}C]Martinostat in the pig brain and assessed its ability to measure histone deacetylase 1–3 (HDAC1-3) levels *in vivo* and found support that [^{11}C]Martinostat provides a good *in vivo* measure of the cerebral HDAC1–3 protein levels [7].

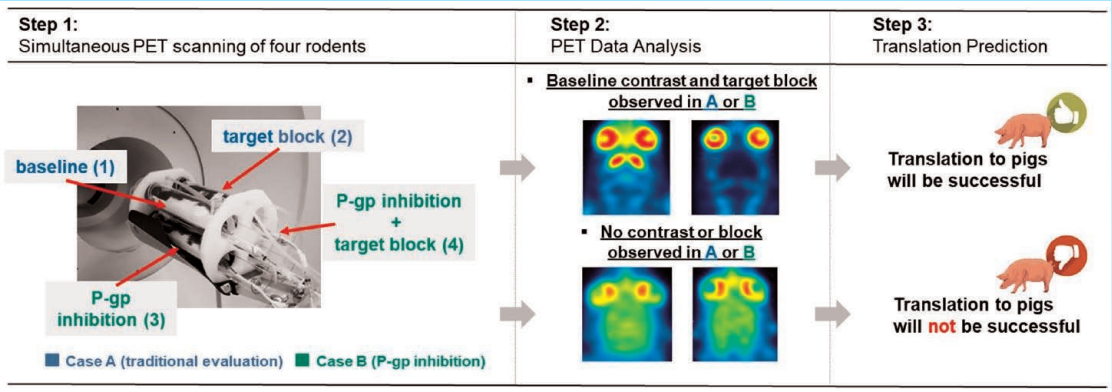


Figure 1: Tracer evaluation strategy. Step 1 and 2: Traditionally, specific binding can be determined by comparing tracer uptake at baseline and after target block (Case A). This work proposes to perform the same two experiments with simultaneous inhibition of P-gp (Case B). Step 3: If specific binding is observed in Case A or B, a successful translation from rodent to pig is predicted. From [37], Copyright © The Author(s) 2020.

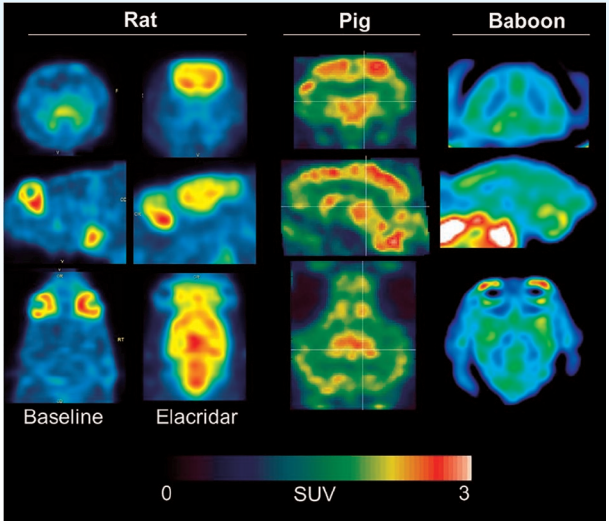


Figure 2: Summed PET images of [^{11}C]Cimbi-701 in the rat, pig and the baboon brain. For comparison, [^{11}C]Cimbi-701 in rats is shown before and after pretreatment with the P-gp efflux inhibitor elacridar (5 mg/kg). From [23], Copyright © 2019 John Wiley & Sons, Ltd.

Translational Neuroimaging and Behaviour

The research focus is to gain a functional and mechanistic understanding of neuropsychiatric diseases and functional clinical imaging. We use genetic tools to target selective brain circuits and correlate activation of these neuronal pathways to imaging outcomes and behaviour. In 2020 we secured a major grant from the Independent Research Fund Denmark, to gain a better understanding of the neurobiological pathways involved in compulsive behaviour and to compare effectiveness of a novel treatment regime with Psilocybin, a serotonergic agonist.

Measurements of synapses in the human brain

Synapses defines the connection between individual neurons and are key sites in neurotransmission and formation of neuronal circuits. Neurons can establish new contacts between each other, and they can lose them, dependent on whether they are used. The process named synaptic plasticity reflects adaptive changes in the wiring of neuronal connections under brain development and brain repair, and can be disturbed in disease. With the development of radioligands for imaging of the synaptic vesicle glycoprotein 2A (SV2A) it has now become possible to label presynaptic terminals and image these in the human brain. Our research aims to understand whether the SV2A density reflects synaptic plasticity.

Cerebral SV2A has been determined in patients with treatment resistant epilepsy. We make use of brain tissue that is resected during epilepsy surgery; this enables us to conduct biochemical and molecular analysis of SV2A in tissue from these patients. We have detected the gene expression and binding at the cellular level, and show that all cells in the human cortex express SV2A, and the level of both binding and expression is lower in patients compared to post-mortem age-matched controls (work in progress).

Pharmacological studies of microglia cells

We have been interested in the control of microglia function in the human brain; they play a main role in neuroinflammation. We use cellular models of human origin (both primary cultures and cell lines) to study inflammatory processes. We have also investigated the anti-inflammatory role of the α7 nicotinic acetylcholine receptor (α7 nAChR) in a stable cell line BV2 originating from microglia and we will see if this is the case also in primary microglia cell lines.

Gene effects

Homeostatically regulated EEG slow waves are a hallmark of deep non-rapid eye movement (NREM) sleep and have been implicated in the regulation of brain clearance. Since the astrocytic water channel aquaporin 4 (AQP4) is critically involved in brain-water homeostasis, their role in sleep-wake regulation could be essential. We investigated whether functional variants in the human AQP4 gene modulate human sleep, nocturnal EEG recordings and cognitive performance [41]. We found that a common eight-SNP AQP4-haplotype is associated with distinct modulations of NREM slow wave energy, strongest in early sleep and mirrored by changes in sleepiness and reaction times during extended wakefulness. The study provides the first human evidence for a link between AQP4, deep NREM sleep, and cognitive consequences of prolonged wakefulness.

Candidate gene studies have suggested that HTR2A single nucleotide polymorphisms including rs6311/rs6313, rs6314, and rs7997012 may influence risk for psychiatric disorders and mediate treatment response. Based on the Cimbi database, we assessed in 197 healthy adults if these genetic variants and the 5-HTTLPR predict neocortex 5-HT2AR binding, as measured with PET [38]. No variants were statistically significantly predictive of 5-HT2AR binding indicating that these variants do not significantly contribute to genetic load on human *in vivo* 5-HT2AR binding.

The NRU Neuroimaging Laboratory

By Gerda Thomsen
SPECT laboratory leader

SPECT-CT system

The NRU SPECT scanner facility in the North Wing of Rigshospitalet opened in September 2020, at the ground floor close to the main entrance. The 3rd generation high-resolution AnyScan SPECT-CT Mediso scanner was installed in the Fall of 2019. Clinical studies show really good results and expectations are high for the new scanner, both clinically and research-wise.

Clinical work

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

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

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

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

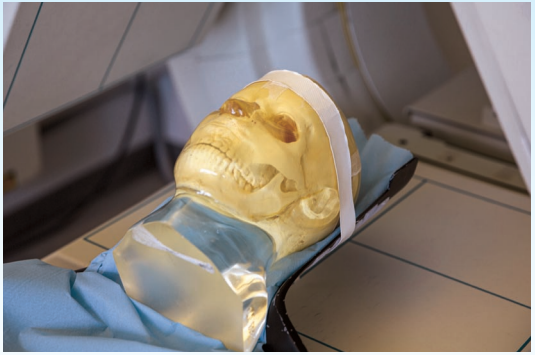
  This is a robust technique for early detection of dopaminergic deficits and is helpful when considering differential diagnoses in patients with movements disorder and/or dementias. The diagnostic report comes with a reference to a healthy age-matched population and is evaluated by a neurologist specialized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

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

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

Research projects

In two joint papers with the Glenthøj group at CINS examining antipsychotic-naïve schizophrenia patients, we describe first the relationship between the D2-receptors as measured with SPECT and the brain reward system [45]. The results indicate that salience abnormalities play a role in the reward system in schizophrenia and that in patients responding to a treatment-induced blockade of D2 receptors, the psychotic symptoms may be ameliorated by normalizing salience abnormalities. In a second paper [1], we find that antipsychotic-induced reduction in positive symptoms correlate significantly with the increase in striatal volume increase, driven by reductions in hallucinations. Our data demonstrate a clear link between antipsychotic treatment and striatal volume increase in antipsychotic-naïve schizophrenia patients.



The SPECT-laboratory is engaged in several ongoing research projects. As part of a collaboration project led by professor Anders Fink Jensen from the Psychiatric Centre Copenhagen, we have investigated glucagon-like peptide-1 receptor (GLP-1R) agonist stimulation changes dopamine transporters in the healthy human brain, to facilitate the interpretation of a parallel study in people with alcohol abuse. The GLP-1R agonist-induced modulation of striatal DAT activity previously reported *in vitro* in rats could not be replicated *ex vivo* in mice and *in vivo* in non-abusing humans [14]. Therefore, the underlying mechanisms of action for the GLP-1R agonists-induced efficacy in various addiction-like behavioral models still remains to be clarified.

3T MRI Scanner

By Patrick M. Fisher
MR group leader

Magnetic resonance imaging (MRI) is a central component of nearly all NRU research projects. We strive to both accomplish our own research goals and facilitate collaborative, high-quality clinical brain imaging research studies at Rigshospitalet. We acquire MRI data primarily on two Siemens 3T Prisma scanners located at Rigshospitalet: one located in the Department of Radiology, and MR001 which is NRU's research 3T Siemens Prisma MR scanner installed late 2019 in the newly opened North Wing building. MR001 is reserved for Department of Radiology for clinical investigations 50% of the daytime, leaving only 50% daytime capacity for NRU research. But thanks to our group of trained MR-assistants who are very flexible in terms of working hours, our scanner has been close to fully booked not only during normal working hours but also in the evenings and during weekends.

We are very pleased with our on-going collaboration with Siemens, especially the invaluable support we have received from Karen Kettless, MRI Applications Specialist. This collaboration clearly shortens the process from new ideas to implementation and test on the scanner. In spite of some pandemic-related unanticipated delays in the research activities during 2020, we managed to continue and even initiate new MR-related research projects. Below are some of the ongoing projects:

- Two projects in collaboration with Profs. Trevor Robbins and Barbara Sahakian from Cambridge University (UK). These studies examine selective serotonin-reuptake inhibitor (SSRI) effects on cognitive processing in healthy individuals and individuals with obsessive compulsive disorder.
- The REFORM project, in collaboration with Prof. Messoud Ashina from the Danish Headache Center at Rigshospitalet-Glostrup, aims to identify structural and functional brain markers of an antibody treatment for migraine.
- The Entrepreneurship project, in collaboration with Prof. 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, in collaboration with Prof. Christian Hassager from the Cardiology Department at Rigshospitalet-Blegdamsvej, aims to examine structural and functional imaging markers of cognitive recovery in patients following the experience of a cardiac arrest event.
- The CONNECT-ME, in collaboration with Assoc. Prof. Daniel Konziella from the Department of Neurology at Rigshospitalet-Blegdamsvej, aims to identify brain connectivity markers of consciousness in patients in, e.g., and markers that predict 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 NRU Sleep Study, an NRU-centered project, applies a novel MR imaging method, MR encephalography (MREG), to probe glymphatic flow in sleep and wakefulness.

The National 7 Tesla MR system at Hvidovre Hospital

By Professor Olaf Paulson

In collaboration with the Human Migraine Research Unit at the Danish Headache Centre, Rigshospitalet and the Danish Center for Magnetic Resonance at Hvidovre Hospital, we applied proton MR spectroscopy (1H-MRS) sequences tailored for pontine and thalamic investigations at 3T and 7T. Glutamate can be reliably measured in pons and thalamus at 7T. Spectral quality and variability of pontine and thalamic 1H-MRS was overall improved at 7T compared to 3T with a 3- to 4-fold shorter scan time. 7T provides the opportunity to improve spectral quality even more by extending scan durations [46].

In collaboration with the Danish Headache Centre, Rigshospitalet and the Danish Center for Magnetic Resonance at Hvidovre Hospital we investigated neurochemical changes across the lifespan *in vivo* with proton MR spectroscopy (1H-MRS), we found higher levels of glia related metabolites in all brain regions in older individuals and this was inversely correlated with working memory performance. No similar effect was found for the neuronal metabolites (tNAA and Glu) [22].

Neuropsychology

By Dea S. Stenbæk
Junior group leader

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

We have continued data collection and initiated several studies in collaboration with the Cambridge Cognition Group and Imperial College London, UK, the Heart Centre at Rigshospitalet, the Copenhagen Business School, and Psychiatric Centre Copenhagen. Four psychology master theses and one PhD thesis were successfully completed, and we were again fortunate to accommodate several talented students from University of Copenhagen and University of Southern Denmark. To strengthen the collaboration between NRU and Institute of Psychology at Copenhagen University, senior researcher at NRU Dea Siggaard Stenbæk was appointed associate professor at the institute.

In 2020, psilocybin research was again a major theme for the psychology group [26]. We undertook an investigation of the association between pre-drug levels of serotonin 2A receptors and acute psychedelic effects in healthy volunteers [Stenbæk DS, J Psychopharmacol, *Epub ahead of print*]. We found significant associations suggesting that lower pre-drug serotonin 2A receptor levels are coupled to more profound psychedelic experiences and with temporal unfolding of subjective drug intensity (**Figure 3**). In preparation for upcoming clinical psilocybin trials, we organized designated psychedelic intervention facilities at NRU. These facilities will be used for psychedelic therapeutic purposes in the coming years. In addition, we collected final data to study the synergy between effects of music and psilocybin in healthy volunteers, which will be analysed in 2021.

Another major theme was mental health factors in somatic [19,44] and psychiatric [12] patients where we found evidence of negative cognitive biases in depressed patients [Dam VH, Psychological Medicine, *Epub ahead of print*] and similarly evidence that negative cognitive biases are associated with depressive symptoms in healthy volunteers [39]. These results are consistent with results from other research groups and were part of validating the Danish version of a novel affective cognitive test battery EMOTICOM.

Clinically relevant papers involving the psychology group are also included in the section Clinical Neurology.

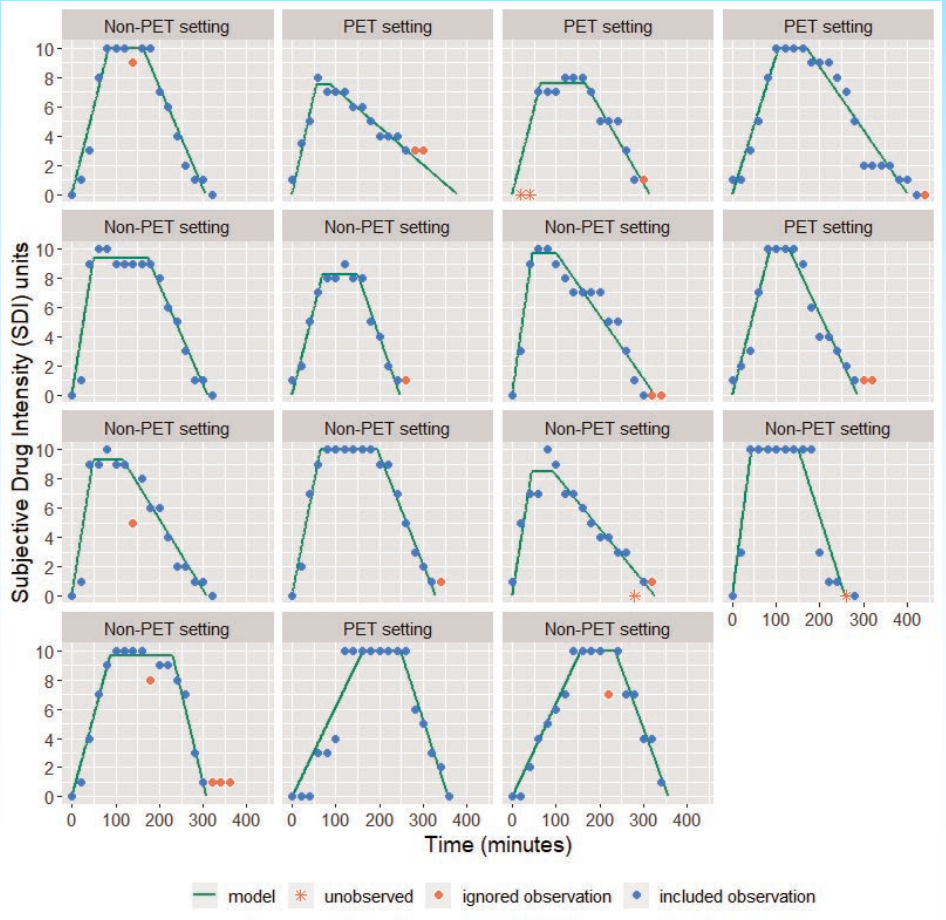


Figure 3: Subjective Drug Intensity (SDI) time courses. Illustration of the segmented two-breakpoint modeling of the SDI time courses for each participant. The green line represents our three primary model outcomes: 1) onset slope of psychoactive effects, 2) duration of peak plateau and 3) slope of decrease in psychoactive effects. From [Stenbæk DS, J Psychopharmacol, Epub ahead of print], Copyright © The Author(s) 2020.

Data Analysis

By Claus Svarer
Chief engineer

Methods for acquisition, analysis and sharing of data acquired in molecular PET imaging studies has been a focus area for the data analysis group this year.

Optimization of preprocessing strategies

There are many different steps and ways in which one can analyze neuroimaging data; this entire analysis process is referred to as a preprocessing pipeline. Researchers commonly apply different preprocessing pipelines and it is not clear how such preprocessing choices affect the study outcomes. In [30], we varied different pre-processing steps (**Figure 4**) to examine how these choices affect the outcome of the study. To evaluate this, we used data from one of our previous double-blind, randomized, placebo-controlled [11C]DASB-PET studies. We found that the two preprocessing steps that were most critical for the conclusions were motion correction and kinetic modeling of the dynamic PET data and only 36% of the applied preprocessing strategies replicated the originally reported finding ($p<0.05$). For preprocessing strategies with motion correction, the replication percentage was 72%, whereas it was 0% for strategies without motion correction. In conclusion, the choice of preprocessing strategy can have a major impact on the conclusions of a study.

Standardization of PET-data sharing archives

In order to standardize neuroimaging data acquisition and storage within and across research centers, the magnetic resonance (MR) neuroimaging community has over the last decade developed a consensus on how to organize and share MR data. Such efforts are important prerequisites not only for obvious quality control purposes but also for enabling data sharing between scientists and centers. Together with Prof. Innis at NIHM, NRU spearheaded the initiative to reach similar consensus for PET neuroimaging data; this was done over several NeuroReceptor Mapping meetings and resulted in a consensus paper establishing guidelines for the content and format of PET brain data in publications and archives [15]. To facilitate comparison of findings across studies, we first recommend publication standards for tracer characteristics, image acquisition, image preprocessing, and outcome estimation for PET neuroimaging data. The 42 co-authors of the paper, representing more than 25 PET centers worldwide, voted to classify information as mandatory, recommended, or optional. The initiative was subsequently awarded funding from the Brain Initiative and the Novo Nordisk Foundation in order to establish a database for PET data sharing, titled OpenNeuroPET, and NRU will

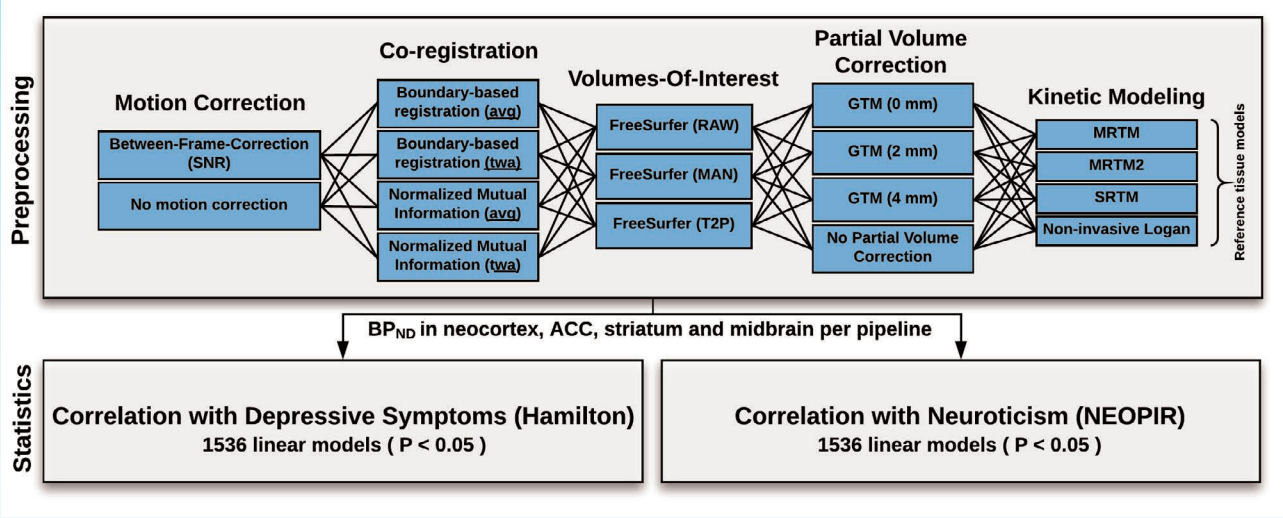


Figure 4: Schematic overview of the 384 preprocessing strategies applied for the [^{11}C]DASB quantification. The output from the preprocessing is BPND in the regions neocortex, anterior cingulate cortex (ACC), striatum and midbrain, which are subsequently entered into the statistical analysis, including the correlation with depressive symptoms (Hamilton) and the neuroticism (NEOPIR). This sums to a total of 384 preprocessing strategies x 4 regions x 2 dependent variables = 3072 linear regression models. avg: average; twa: time-weighted average; SNR: signal-to-noise ratio; GTM: geometric transfer matrix. From [30], Copyright © The Author(s) 2020.

play an important role in the roll-out of the platform. Assistant professor Melanie Ganz has continued to serve as a member of the BIDS steering committee since fall 2019 and has been acting as the lead of the PET BIDS extension since fall 2017. The BIDS PET extension got included and released with Brain Imaging Data Structure v1.6.0 in April 2021 (https://bids-specification.readthedocs.io/en/stable/).

Data sharing will make it easier to combine datasets from different centers to achieve larger sample sizes and stronger statistical power to test hypotheses. Combining of datasets from different centers may be enhanced by adoption of a common set of best practices in data acquisition and analysis (**Figure 5**).

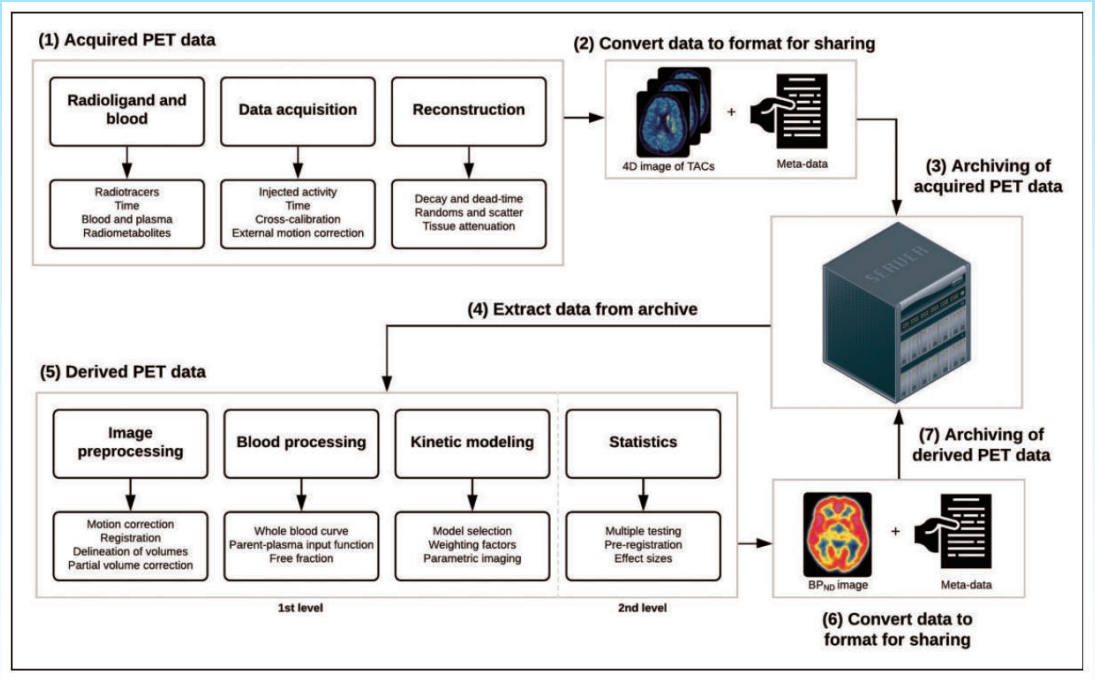


Figure 5. An overview of the data stream PET data. (1) Acquired data are composed of radiochemistry, blood, PET data acquisition and reconstruction data. (2) The data are converted into a suitable format, and (3) shared and/or stored in an archive. (4) The data can be extracted from an archive, and (5) analyzed at the subject level (first level), applying image preprocessing, blood data processing, and modeling for quantification. Quantified data may be used in a statistical analysis at the group level (second level) that should be accompanied by a correction for multiple testing and reporting of effect sizes. Ideally, approaches for generating acquired and derived data should be pre-registered before carrying out a study, in order to limit researcher degrees of freedom and false-positive results. The preprocessing, blood processing, kinetic modeling, and statistics constitute derived data in the form of binding and/or statistical estimates. (6) The derived data must be converted into a suitable format, and (7) shared and/or stored in an archive. BPND: non-displaceable binding potential; TAC: time-activity curve. From [30], Copyright © The Author(s) 2020.

Atlas of the structure of the serotonin system in the brain and relation to functional brain connectivity

Previous observations have revealed that the spatial distribution of serotonin (5-HT) receptors within the human neocortex does not conform with commonly used parcellations. This discrepancy indicates that a neocortical parcellation specific to the 5-HT system is needed. In [4] we first outline issues with an existing parcellation of the 5-HT system, and present an alternative view derived from brain MR- and high-resolution PET images of five different 5-HT targets from 210 healthy controls (**Figure 6**). We then explore how well this new 5-HT parcellation explains mRNA levels of all 5-HT genes. Overall, this characterization of the 5-HT system is found to be more stable and explains more variance of the underlying 5-HT molecular imaging data compared to other atlases, and may hence be more sensitive to capture region-specific changes modulated by 5-HT.

Atlas can be downloaded from: https://nru.dk/FS5ht-atlas/

The serotonergic neuroreceptor atlases that have been generated by us are now starting to provide a useful framework for understanding how, e.g., the 5-HT_{2A} receptor stimulation by the psychedelic drug psilocybin interacts functionally on a regional basis. This is the topic of [18] where a theoretical framework modeling the dynamical mutual coupling between the neuronal and the 5-HT_{2A} receptor is modeled. By combining diffusion MRI, functional MRI, and PET imaging of the 5-HT_{2A} receptor, the functional effects of psilocybin on the brain are explained.

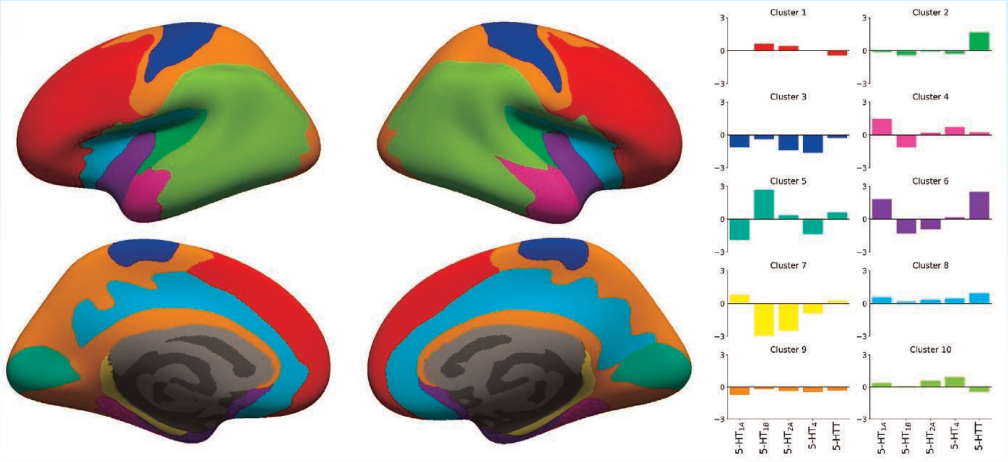


Figure 6. Parcellation obtained with K = 10 and the associated regional 5-HT profile for each region. The parcellation is presented on the inflated fsaverage surface medial (lower) and lateral (upper) for both hemisphere (left and right). From [4], Copyright © 2019 Elsevier Inc.

Clinical Psychiatry

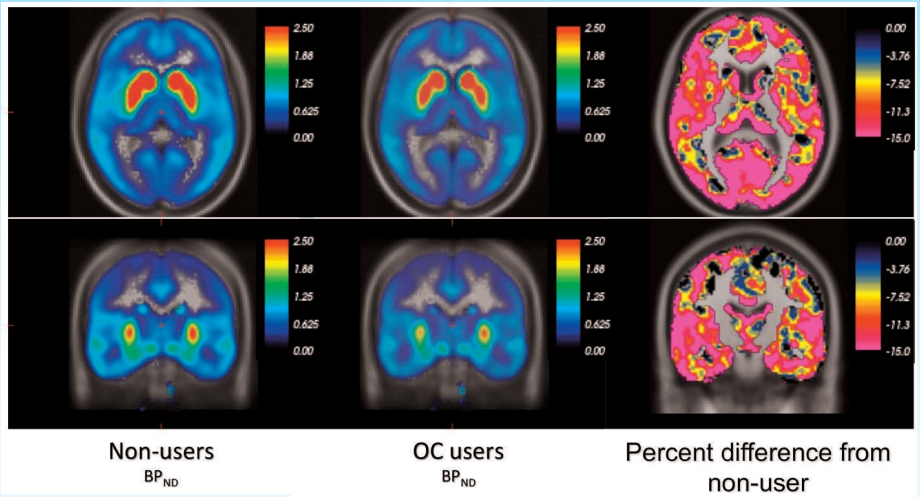
By Vibe G. Frøkjær
Group leader

We use imaging to map brain architecture in risk and resilience to mental disorders to provide a rationale for targeted prevention and treatment. We pursue clinical translations, e.g., precision medicine approaches to optimize treatment of Major Depressive Disorder [19]. We hold expertise in frontier molecular brain imaging of key features of the serotonin signaling system [4,8,30], which is profoundly involved in mood disorders, schizophrenia, neurodegenerative disorders and their treatments. In particular, we are interested in serotonin brain biology as a driver of healthy adaptation to, e.g., stressors, genetic make-up, sex-steroid hormones [20], personality [21], and appropriate navigation in social relations.

Sex-Steroid Hormones

The dynamic interplay between brain biology and sex-steroid hormone systems represents a potent driver of risk and resilience for neuropsychiatric disorders, which we aim to understand better in order to illuminate targetable risk and disease mechanisms. We have previously shown how sex-hormone manipulations may trigger depressive symptoms in some women; this involves oestrogen sensitivity at the molecular level, which can be identified by gene transcript and DNA methylation profiles, changes in serotonergic signaling, functional brain connectivity, and emotion and reward processing [10]. We propose that sensitivity to hormone transitions, such as across pregnancy and the postpartum period, may represent a clinically relevant and distinct subgroup within the broad diagnostic category of depression. To enable future precision medicine approaches to targeted prevention and treatment we need to find ways to identify hormone sensitive women at high risk for, e.g., depression triggered by hormonal transitions. Sensitivity to hormonal changes may also play a role in the mechanisms by which use of oral contraceptives can trigger depressive episodes or subclinical depressive symptoms in certain women. Intriguingly, by leveraging data from the Cimbi database, we have demonstrated that women who use oral contraceptives differ markedly in serotonergic brain architecture from women who do not use oral contraceptives [20]. Specifically, we provide evidence for a 9-12% lower global brain serotonin 4 receptor binding in women who use oral contraceptives relative to non-users with the strongest effect in hippocampus (**Figure 7**). This is a highly interesting finding since it offers a plausible biological link between oral contraceptive use and increased risk of depressive episodes, which has important clinical implications.

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



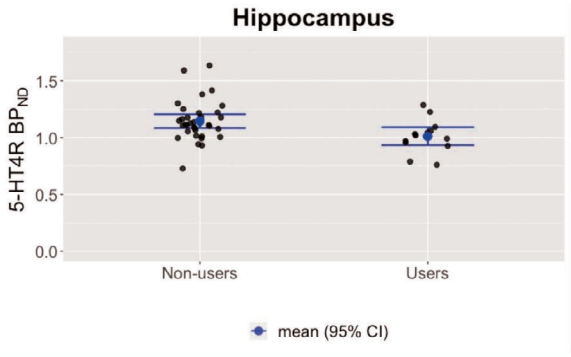
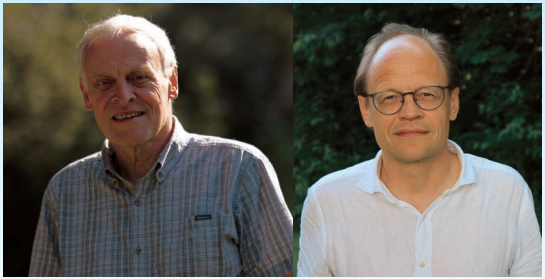


Figure 7: Serotonin 4 receptor brain binding is lower in OC users vs non-users. Upper: Illustration of the global effect of OC use on 5-HT4R BP_{ND} via voxel-based parametric images. The first two panels show the group's average non-displaceable binding potentials (BP_{ND}) (color bars represent BP_{ND} units). OC users appear paler both in subcortical and cortical areas. The third panel shows the percentage difference in BP_{ND} in OC users from non-users where the color bar scale illustrates percentage from 0 to 15%. Lower: Hippocampal 5-HT4R binding in OC vs non-OC users. Mean value and bars indicating the 95% confidence interval are shown. BP_{ND}'s are shown as unadjusted values. From [20], Copyright © 2020 The Authors.

Clinical Neurology

By Olaf Paulson & Lars Pinborg
Group leaders



Epilepsy surgery

Surgery aiming at curing drug-resistant epilepsy is centralized in Denmark at Rigshospitalet. We continue our efforts to leverage the standard use of MRI and EEG in the epilepsy surgery evaluation process: We assessed the added value of using high-definition EEG and source localization (**Figure 8**) using a prospective cohort design [9] and took lead in an international review on consensus recommendations on the future use of 7T MRI in epilepsy patients.

We use part of the tissue resected during the operation to test several interesting hypotheses, often with collaborators: With the Khodosevich group at BRIC, Univ. Copenhagen we demonstrated that multiple glutamate-signalling genes exhibit layer-wise dysregulation in epileptic cortex – in particular genes coding for AMPA receptor auxiliary subunits [35]. With the Bach group at Pharma, Univ. Copenhagen we described the possible role of cAMP in epileptogenesis and tested the role of cAMP in the action of well-known drugs against epilepsy [17,27]. Together with the Andersen group at BRIC and the Wellendorph group at Pharma, we demonstrated a large capacity for GABA uptake and metabolism in astrocytes from fresh human brain tissue implying a prominent role of astrocytes in human GABA homeostasis contrary to rodents [2].

Electroconvulsive therapy (ECT) of severe depression and brain structure

Data from one of our previous studies showing increased hippocampal volume following ECT was part of a major international multicenter study. In this, global as well as local variations in gray matter, white matter, and ventricle volumes were investigated and it showed cortical and subcortical gray volume increases in most parts of the brain. In contrast, white matter volume remained unchanged. The subcortical gray matter increase was negatively associated with total ventricle volume but there was no relation between gray matter volumetric enlargements and clinical outcome [31].

Traumatic post-concussion syndrome

We tested the feasibility and tolerability of transcranial pulsating low-frequency electromagnetic stimulation (T-PEMF) in treating post-concussion syndrome. T-PEMF has in other patient groups and studies shown promising results with proposed neuroprotective

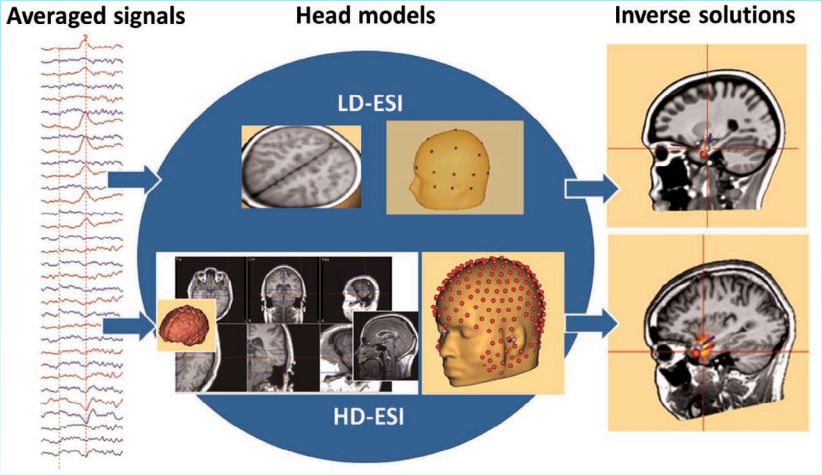


Figure 8: Flow diagram of electrical source imaging (ESI). Left: Interictal epileptiform discharges and ictal waves are averaged to increase signal-to noise ratio. Middle: For low density ESI, 25-electrode array is used, with an age-matched template head-model. For high density ESI, a 256-electrode array and individual head-model based on the patient´s own MRI is used. Right: Two different inverse solutions are used: equivalent current dipole and distributed source model (CLARA). From [9], Copyright © 2019 International Federation of Clinical Neurophysiology.

and anti-inflammatory effects. Compliance was high as all subjects completed the full treatment. The majority (n=5) had a reduction in overall symptoms but two patients experienced a worsening of their concussion symptoms during the course of treatment [28].

Cardiology and the brain

We are taking part in several studies with cardiologists, cardiac anesthesiologists and surgeons at Rigshospitalet.

The REVIVAL cohort study protocol describes the multi-center investigation of cognitive impairment and psychopathology in out-of-hospital cardiac arrest survivors in Denmark. The study aims to evaluate the efficacy of a novel screening procedure to predict risk of disabling cognitive impairment and psychopathology 3 months after cardiac arrest. It also aims to evaluate long-term prevalence of psychopathology in relatives [44].

In the PPCI trial, perfusion pressure and subsequent presence of cerebral infarcts was investigated in patients undergoing cardiac surgery with cardiopulmonary bypass. The patients were allocated to a mean arterial pressure of either 70-80 mm Hg (high-target) or 40-50 mm Hg (low-target). In a predefined secondary analysis, we compared selected cerebral metabolites using MR spectroscopy. We observed that a higher mean arterial pressure during surgery was associated with a postoperative decrease in GM N-acetylaspartate-to-total-creatine ratio, suggesting impaired cerebral metabolism [42].

Cimbi Database and Biobank

By Peter Steen Jensen, Database manager & Arafat Nasser, Biobank manager

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

The **Cimbi biobank** is the associated collection of biological specimens from the cohort, including saliva, blood, and in some instances, urine and hair samples, which allow for additional biochemical and genetic analyses. In 2020, the biobank was moved to new NRU freezers in the new dedicated freezer-core facility in the basement of the North Wing of Rigshospitalet.

The Cimbi database and biobank represent a unique and valuable research instrument serving the purpose of storing the wealth of acquired data in a highly structured and safe manner as well as providing a quality-controlled resource for future hypothesis-generating and hypothesis-driven studies. From an international perspective, the comprehensive nature and the sample sizes are exceptional. In 2020 a total of 25 official requests for data were approved. Further, the database provided aggregated data that were used in a total of 15 publications in 2020.

Innovation Fund Denmark

NeuroPharm

Center for Experimental
Medicine Neuropharmacology

Center director
Gitte Moos Knudsen

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.

The short-term goal of *NeuroPharm* is to answer pertinent and basic questions regarding human brain disease mechanisms and predict brain responses to categories of neuromodulatory interventions as well as treatment efficacy. The status of the research in the four *NeuroPharm* work packages (NP1-4) is described below.

NP1: Treatment outcome in Major Depressive Disorder

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

By Vibe G. Frøkjær
NP1 WP-leader

We have collected a rich deep phenotyping dataset in a population of 100 MDD patients and examined how different markers (neuropsychology, MRI, PET, EEG) relate to the outcome of a standard antidepressant treatment, i.e., escitalopram. Patients have been followed across a period of 12 weeks from treatment start. Neuroimaging was repeated at week 8 in a subgroup of 40 patients with variable antidepressant response [19]. We work now to disseminate our findings. In 2020, two NP1 affiliated PhD students defended their theses, namely Kristin Köhler-Forsberg, MD, PhD: "*The serotonin 4 receptor binding as a novel imaging marker in major depressive disorder and the association to antidepressant treatment response*" and Vibeke Dam, MSc in Psychology, PhD: "*Shining a light on the black cloud of depression - A study of cognitive markers in Major Depressive Disorder*". In the first original paper published we map baseline hot and cold cognitive profiles in MDD relative to a healthy reference and identify relevant clusters of cognitive profiles, which may represent critical strata and be useful in precision medicine approaches to MDD [Dam VH, Psychological Medicine, *Epub ahead of print*].

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 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 first and second subproject is completed. The third and final subproject evaluates psilocybin and ketanserin effects on brain connectivity and blood flow measured with MRI. Data collection for this subproject is on-going with 24 out of 30 datasets collected through 2020. We aim to finish data collection in early 2021.

Psilocybin is a serotonin psychedelic, the psychoactive constituent in *magic mushrooms*, and has perceptual effects that depend on 5-HT_{2A}R signaling. Recent clinical studies provide intriguing evidence that psilocybin has therapeutic effects across a range of brain-based illnesses, including depression. A single psilocybin session can evoke changes in clinical symptoms and personality that last for months. We sought to identify brain mechanisms mediating these effects in the first-ever study of psilocybin-induced changes in brain 5-HT_{2A}R levels [26]. Ten healthy and psychedelic-naive individuals completed a single psilocybin session. Before and one-week after the session, participants completed [^{11}C]Cimbi-36 PET scans. Before and three-months after the session, participants completed personality questionnaires. Novelly, we found that psilocybin significantly increased mindfulness and attentiveness. Although 5-HT_{2A}R levels did not change at a population-level (**Figure 9**), change in 5-HT_{2A}R levels correlated with change in mindfulness.

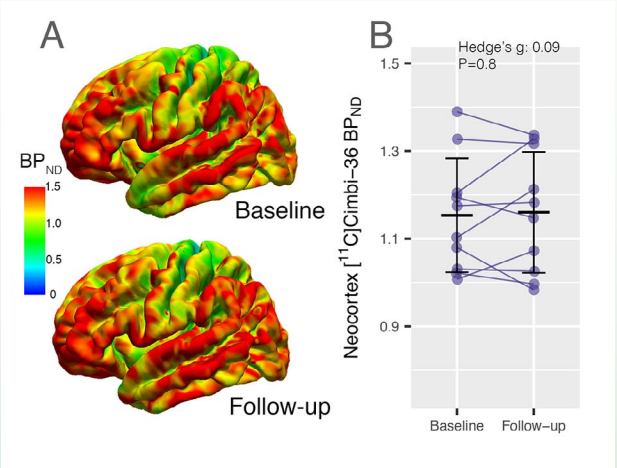


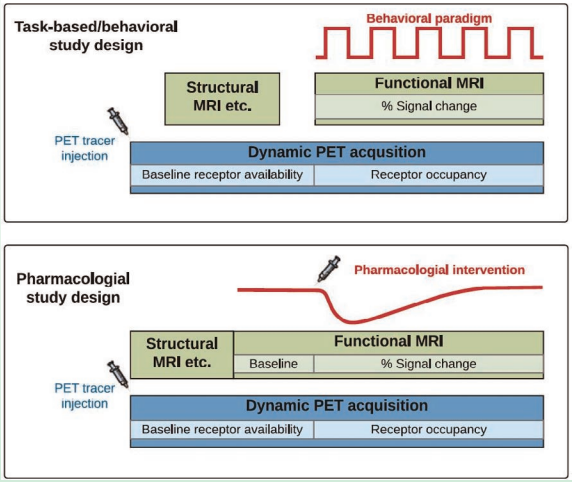
Figure 9: Effects of psilocybin on [^{11}C]Cimbi-36 BP_{ND}. (A) Mean vertex-level cortical [^{11}C]Cimbi-36 BP_{ND}, left hemisphere, at baseline and one-week follow-up. (B) Neocortical [^{11}C]Cimbi-36 BP_{ND} at baseline and one-week follow-up. Colored points: individual values; middle horizontal black line: mean; error bar: SD. From [26], Copyright © 2020 Elsevier B.V. and ECNP.

NP3: Novel neuroimaging methods for an experimental medicine approach

By Hanne D. Hansen
NP3 WP-leader

The ability to simultaneously measure receptor occupancy and brain reactivity with PET/MRI provides a completely novel approach to assess interventional effects (**Figure 10**). How simultaneous PET/MRI can be used to assess neuroreceptor function and how it can be used as a novel and translational tool in drug development was recently described in [36]. In a recent study, we also showed for the first time how a non-pharmacological intervention (autobiographical images) can change cerebral 5-HT levels in humans [11] **(Figure 11**). These findings provide a valuable, methodological proof-of-concept and insight into how 5-HT neurotransmission shapes visual processing.

Figure 10: Schematic representation of example task-based/behavioral or pharmacological study designs. Lighter colors are examples of outcome measures from each imaging modality for receptor-binding radiotracers. From [36], Copyright © The Author(s) 2020.



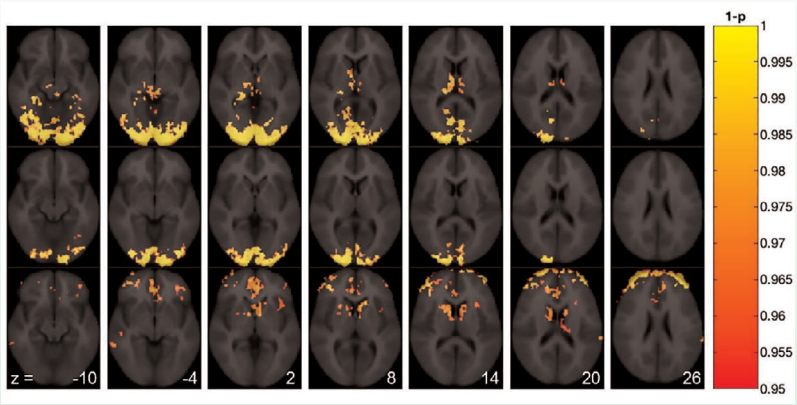


Figure 11: Significance maps showing voxels with changes in CBF in the stimulus session (upper row: 50-65 min > 35-50 min; middle row: 65-80 min > 35-50 min; lower row: 50-65 min > 65-80 min, n = 11). Numbers indicate z-axis in mm. CBF, cerebral blood flow. From [11], Copyright © 2020 The Authors.

NP4: Bioinformatics, statistical and predictive models

By Brice Ozenne
NP4 WP-leader

The main aim of NP4 is to adapt latent variable models (LVMs), a statistical modelling approach that can handle complex systems of variables, to the analysis of neuro-imaging data. Two methodological developments have been published this year: handling non-linear relationships between two latent variables [13] and bias-corrected maximum likelihood estimates along with Satterthwaite estimates of degrees of freedom for Wald test statistics in LVM [33]. The former can, for instance, be used to relate PET measurements from several brain regions to several psychological measurements without assuming a linear relationship, whereas the latter improves the reliability of conclusions drawn from studies involving small samples (typically n<50). Through a collaboration with colleagues from Hasselt University in Belgium, we also studied various approaches to quantify the uncertainty when assessing the benefit-risk balance of a treatment [43].

NP4 has also assisted other work packages with analysis of their data, providing or developing appropriate statistical methods. One study intended to assess, using data from the Danish registries, whether a treatment with greater blood-brain barrier penetrance (BBBP) would be associated with a larger risk reduction of a brain disease. We recently published a statistical approach for group comparisons in presence of competing risks (the risk of death was high, about 25% at 10 years), right-censoring (e.g., patients whose disease status is unknown after a certain time), and confounding (e.g., age, time of inclusion) [32]. We also optimized our software (R package riskRegression) and provided efficient adjustments for multiple comparisons over time and treatment. With this update, we could visualize the effect of BBBP on the risk over time with confidence bands that will, with probability 95%, contain the expected risk value for all times and level of BBBP.

In two non-human studies we assessed the effect of psilocybin on the brain serotonin system [Donovan LL, Neuropsychopharmacology, 2021] and on gene expression in the brain after 1 and 7 days [Raval NR, Int J Mol Sci, 2021]. Both studies involved a small number of pigs (6 in the control group and in the psilocybin group) and therefore we developed permutation tests for testing group effects on its temporal evolution, while adjusting for multiple comparisons when several brain regions or several genes are considered.

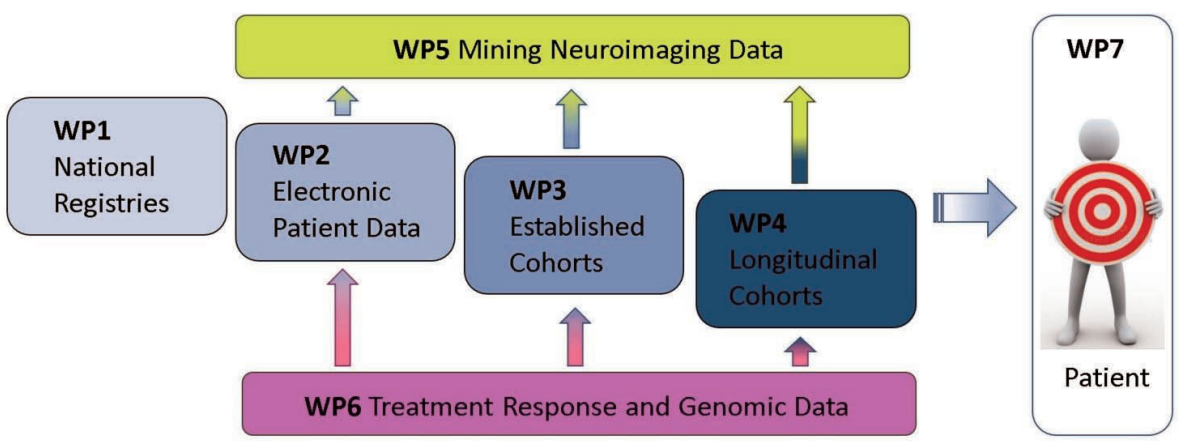
BrainDrugs

Center director
Gitte Moos Knudsen

In 2020 the wheels started turning for our strategic research alliance *BrainDrugs* which is our large-scale precision medicine project in epilepsy and depression (https://braindrugs.nru.dk). The alliance is a 5-year project funded by 40 mio DKK from the Lundbeck Foundation aiming at establishing which key features predict drug response in patients with epilepsy or depression. It is our hope that in the long run, *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 is supported by two European partners from Lausanne University Hospital, Switzerland and VU University Medical Center in Amsterdam, the Netherlands. The involved Danish institutions span several different departments at Copenhagen University Hospital, Rigshospitalet, 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 figure to the right.

In 2020 we hosted the first *BrainDrugs* annual meeting which was held as a hybrid online-physical meeting due to the covid pandemic (see photos below). Detailed plans for the work of the various WPs were presented and diligently discussed. Also, we succeeded to obtain the final signature of the overall collaboration agreement for *BrainDrugs* in July 2020, whereby the legal framework for the cooperation got in place.



WP1: National Registries

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. In 2020, we got formal access to all needed registry data and focused our efforts on extraction and curation of data as well as statistical analysis and interpretation of data in relation to the relevant research questions.

WP1-leader: Professor Lars Vedel Kessing

WP1 has a component in Copenhagen lead by Prof. Lars Vedel Kessing and a component in Aarhus lead by Prof. Jakob Christensen. Involved in the project are assistant Prof. Helene Charlotte Wiese Rytgaard and research assistant Simon Christoffer Ziersen in Copenhagen and senior researcher Julie Werenberg Dreier and PhD student Eva Bølling-Ladegaard in Aarhus.

WP2: Electronic Patient Data: Text mining and Machine Learning

The aim of WP2 is to use text mining methods to extract detailed, phenotypic features from free text in Electronic Patient Records (EPRs). We want to use EPRs from two sources; the Capital region and region Zealand from 2009-18 and from the specialized national epilepsy hospital, Filadelfia.

In 2020 we secured access to EPRs from the Capital Region and Region Zealand from 2009-16. This includes journal text for 57.406 patients with epilepsy and 127.648 patients with Major Depressive Disorder (MDD). These patients have been identified using the National Patient Registry (NPR), thus all of them have a diagnosis of epilepsy or MDD in the registry. We have applied Sundhedsdatastyrelsen for a list of CPR-numbers for patients with either a diagnosis of epilepsy or MDD based on NPR or patients that receive drugs for epilepsy or depression based on the National Prescription Registry. This list of CPR-numbers will enable us to update the EPRs to also include records from 2016-18 and to update the list of epilepsy and MDD patients based on the additional two years of EPRs and patients identified based on drug information from the Prescription Registry. The application to receive EPRs from Filadelfia has been approved and we are currently awaiting a plan for the delivery of the Filadelfia patient records. Furthermore, we are awaiting the final approval to merge the patient records we receive from Filadelfia with NPR data.

WP2-leaders: Professors Søren Brunak & Anders Søgaard

We have in collaboration with researchers from University of Cambridge and from Google and Deepmind submitted a paper for AAAI 2021 on improved language encoding. Language encoders encode words and phrases in ways that capture their local semantic relatedness, but are known to be globally inconsistent. In the paper we extract a large-scale multilingual, multi-word analogy dataset from Wikidata for diagnosing and correcting for global inconsistencies and implement a four-way Siamese BERT architecture for grounding multilingual BERT (mBERT) in Wikidata through analogy training. We have further improved the mBERT for Danish and implemented a negation scope resolution system for Danish, which will be made publicly available on Github.

In 2020, we have recruited several bright people for the project, namely post docs Mareike Hartmann and Isabella Friis Jørgensen and research assistant Sebastian Werge.

WP3. Deep Phenotyping Data from Established Research Cohorts

Whereas we can retrieve clinical and biochemical data from patient records, additional features can be identified from existing research databases and biobanks hosted in the Capital Region. Such inventories include the Lundbeck Foundation Center Cimbi database and data acquired by the Kamilla Miskowiak group. These databases will be exploited 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 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 2020, we have worked on the more detailed conceptualisation of the research questions as presented on the annual meeting. Permissions to work with ”deep phenotyping” data from the Cimbi Database in combination with data from relevant registers have been obtained. Once the final definition of desired register information has been determined, the data processing and analysis plan can therefore be made and the analyses can be initiated.

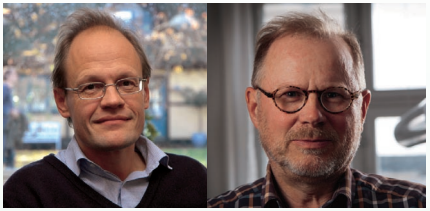
WP3-leaders: Assoc. professor Vibe G. Frøkjær & professor Kamilla Miskowiak

We have recruited two post docs and one PhD student for the further work with analysis, interpretation and publication. Post docs Vibeke Dam and Brice Ozenne will primarily work with long-term follow-up of healthy controls from the Cimbi Database in relation to register outcomes and short-term follow-up of a newer cohort of patients with depression with a view to predictors of prognosis after 12 weeks of treatment of a depressive episode. Simon Christoffer Ziersen will be a PhD student on a project that builds bridges between methods used in WP1 and WP3. In 2021 we will recruit an international post doc to work with data from the patient cohorts and existing fMRI data from Kamilla Miskowiak’s group. Furthermore, we will be expanding with a PhD student, funded through an EU Innovative Training Network grant, who will work with epigenetic data combined with neuroimaging data.

WP4. Deep Phenotyping Data from New Research Cohorts

To increase power to detect biomarkers and treatment response, we will use this WP to establish new cohorts of patients with epilepsy and MDD that we follow longitudinally. With the experience gained from the other WP's, such cohorts will enable replication of previous findings and empower additional research findings.

In 2020, we have defined a detailed study program and formulated ethics protocols for the epilepsy and the depression component of the work package. The protocol work has been coordinated by post doc Vibeke Dam, who is also participating in WP3. The depression protocol was submitted in December 2020 and we expect to submit the epilepsy protocol in Spring 2021.



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

In the depression part, an agreement regarding recruitment of relevant patients has been made with the Central Visitation of Psychiatry and selected Psychiatric Centres. We are currently investigating what data can be retrieved from Sundhedsplatformen in order for us to be able to conduct a long-term follow-up of the patients. MD Kristian Reveles Jensen was employed as a research assistant from July 1st, 2020, and he will be directly involved in all practical aspects of the depression project, expectedly as a PhD student from 2021.

In the epilepsy part, recruitment of new-onset drug-naïve patients and first-seizure patients has been agreed with the Department of Neurology and the Pediatric Clinic at Rigshospitalet. Also, we have made an agreement with the Belgian company Helpilepsy on the use of their smartphone app for collecting prospective data on epileptic seizures, epilepsy medication and seizure-provoking factors directly from the patients. These data will allow for close monitoring of the patients by WP4 project members. We have employed MD Maja Marstrand Jørgensen as a PhD student as of October 1st and Minna Litman part-time as a research nurse as of November 1st, 2020.

WP5-leaders: Assist. professor Melanie Ganz & professor Leif Østergaard

WP5. Mining neuroimaging data

The aim of WP5 is to implement new tools to facilitate regulated access to the large volume of neuroimaging data collected during routine clinical care and available in the institutional archives. Tools to identify, access and combine neuroimaging data with data extracted from the electronic healthcare records including the medical images will be implemented through a user-friendly portal that enables interactive analysis

and exploration of such valuable image repositories. Following this, the combined data will be validated by e.g., comparing automatically extracted image features with data extracted from the electronic healthcare records. Next, we will use image analysis and pattern recognition tools on the existing data to define characteristic features of poor drug responders compared to healthy controls. Finally, the neuroimaging data obtained in WP4 will be used to test and validate algorithms that are predictive of long-term outcome and drug treatment response.

In 2020, we have investigated different alternatives for how to best get access to the wealth of clinical neuroimaging data available in the hospital's official RIS/PACS system. We have identified an optimal solution with a bulk image export through AGFA who is the provider of the PACS system and are now in the process of getting the necessary approvals in place.

A new post doc position is hired to retrieve data from the PACS system and to validate automatically extracted image features (e.g., white matter signal abnormality burden) with data extracted from the electronic healthcare records. The task of the post doc will also entail using image analysis and pattern recognition tools on the existing data to define characteristic features of poor drug responders compared to healthy controls. Finally, the post doc is expected to provide image analysis support to the *BrainDrugs* research group, specifically WP3 and WP4.

WP6-leader: Professor Thomas Werge

WP6. Treatment Response and Genomic Data

With this WP, we aim to assess the (additional) effect of molecular alterations in selected relevant genes as well as amalgamated scores with discrete brain functions, clinical and biochemical features and treatment response of the patients. The work in this work package is awaiting relevant data from WP1-WP4 to become available.

WP7. Implementation in the Clinic

In this WP, we will strive to ensure a smooth and swift implementation of the research outcomes generated by this thematic alliance into the clinic, to generate a true precision medicine approach to future patients with epilepsy and/or MDD. The work in this WP will not be initiated before the end of the 5-year grant period.

WP7-leaders: Head of department Jesper Erdal & Chief medical officer Ida Hageman

Strategic Collaborations

Strong collaboration is fundamental for excellent brain research to happen. We have therefore for many years enjoyed working closely together with many different partners within Denmark and internationally. Listed below are some of our major strategic collaborations, which are particularly key for us. With respect to other collaborators within Dept. of Neurology, please refer to page 36.

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 eight years, the Dept. of Radiology has graciously provided NRU with key access to their 3T MR-scanner facilities, available after regular working hours. In the beginning of 2020, we moved most of our MR research projects over to our own newly-installed Siemens Prisma 3T MR scanner, but we are still enjoying a good collaboration with the Dept. of Radiology personnel. In particular, we highly appreciate the collaboration with Dr. Vibeke Andrée Larsen, professor Adam Espe Hansen, chief radiographer Bo Haugaard Jørgensen and project radiographer Christian Hammer Nielsen.

University of Copenhagen

Since the establishment of Cimbi in 2006, we have had a close collaboration on PET radioligand development with Dept. of Drug Design and Pharmacology, Faculty of Health and Medical Sciences. Likewise, we also appreciate our long-standing collaboration on biostatistics with Section of Biostatistics, Faculty of Public Health, with whom we share a biostatistician post doc and a research assistant through the *BrainDrugs* project, and with the Department of Psychology with whom we share an associate professor for supervision of PhD students with a psychology background. Finally, we also highly appreciate our strategic collaboration with Dept. of Computer Science, facilitated by a joint assisting professor position as well as cooperation in the *BrainDrugs* project.

Mental Health Services in the Capital Region of Denmark

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

Also, we have a collaboration with senior consultant Clas Winding Christensen and psychologist Sara Kerstine Nielsen for inclusion of patients with obsessive-compulsive disorders (OCD) as part of our joint study on habit forming with professor Trevor Robbins and his colleagues. For our *NeuroPharm* project, we have benefitted greatly from our close collaboration with 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.

We highly appreciate these collaborations and look forward to strengthening our joint research activities in the future. Together, this infrastructure and collaboration critically facilitates that large psychiatric patient populations can enter frontline clinical research projects and, ideally, will enable a fast translation of research results to optimize clinical mental health care.

Martinos Center, Massachusetts General Hospital, US

Since 2011, we have had a fruitful collaboration with the Athinoula A. Martinos Center for Biomedical Imaging in Boston, US, which has pioneered brain imaging with MRI. The collaboration has so far included retreat meetings, the successful achievement of a joint 2-year NIH grant, the NRU-anchored *NeuroPharm* Center grant (2015-22) from the Innovation Fund Denmark, and funding from Lundbeck Foundation for an international 3-year post doc position for Hanne Demant 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 15 publications.

University of Cambridge, UK

Since 2018 during their sabbatical as NRU, we have collaborated closely with professors Trevor Robbins and Barbara Sahakian from University of Cambridge with whom we are currently running two joint research projects funded by the Lundbeck Foundation. We appreciate the collaboration and expect to complete data acquisition in 2021.

Positions of Trust

Gitte Moos Knudsen:

President of European College of Neuropsychopharmacology (ECNP) since 2019, chair of the Scientific Advisory Board for The Human Brain Project since 2017, Member of the Brain Prize Council since 2017, board member of the Elsass Foundation since 2015, and member of the Scientific Advisory Board of the Kristian G. Jebsen Foundation, Norway, since 2014 and of the Hospital del Mar Medical Research Institute Foundation, Barcelona, Catalonia from 2020. Representing Professor for Neurology at Univ. Copenhagen. Field Editor at the International Journal of Neuropsychopharmacology. Honorary professor at University of Vienna, Austria, since 2016.

Olaf B. Paulson:

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

Jens D. Mikkelsen:

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

Lars Pinborg:

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

Vibe G. Frøkjær:

Appointed Danish representative in the management committee for the EU-based Riseup-Post Partum Depression (PPD) COST Action since 2019, and appointed member of the Neuroimaging Network of ECNP since 2017. Board member of Danish Society for Affective Disorders.

ECNP
european college of
neuropsychopharmacology

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.

Gitte Moos Knudsen, President of ECNP 2019-22

Dissemination 2020

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

NRU has in 2020 published a total of 4 PhD dissertations, 15 Master's or Bachelor theses, and 46 scientific peer-reviewed papers.

PhD dissertations

- Kristin Köhler-Forsberg. The serotonin 4 receptor binding as a novel imaging marker in major depressive disorder and the association to antidepressant treatment response. University of Copenhagen, Faculty of Health and Medical Sciences. Defended Jun 26, 2020
- Lene Lundgaard Donovan. Epigenetic and pharmacological investigations of the pig brain - In vivo and in vitro studies of [11C]Martinostat and psilocybin. University of Copenhagen, Faculty of Health and Medical Sciences. Defended Sep 11, 2020
- Martin Korsbak Madsen. Neurobiological effects of 5-HT2AR modulation. University of Copenhagen, Faculty of Health and Medical Sciences. Defended Oct 09, 2020
- Vibeke. Shining a light on the black cloud of depression – A study of cognitive markers in Major Depressive Disorder. University of Copenhagen, Faculty of Health and Medical Sciences. Defended Oct 23, 2020

Theses and reports

The following list of NRU-affiliated students have successfully defended their theses or research year reports during 2020:

- Aksel Berg. Health-related quality of life among Faroese PD patients based on motor, autonomic and cognitive symptoms. Master's thesis in medicine, University of Copenhagen.
- Albin Arvidsson. Stressful life events and serotonin 2A receptor binding in healthy subjects: a PET molecular brain imaging stydy. Master's thesis in medicine, University of Copenhagen.

- Anders Lykkebo-Valløe. Brain-state dynamics during psilocybin interventions. Acute effects of psilocybin on dynamic functional connectivity. Master's thesis in Bioinformatics.
- Andreea-Veronica Vascan. How do children move in the MR scanner with and without aneasthesia? Master's thesis in computer science, University of Copenhagen.
- Annesofie Videbæk. Expression of synaptic vesicle glycoprotein 2A in dopamine neurons in a preclinical animal model of Parkinson's disease. Master's thesis in biology, University of Copenhagen.
- Clara Madsen. Synaptic vesicle glycoprotein 2A (SV2A) radioligand binding as a measure of synaptic density in animal models of cerebral palsy and temporal lobe epilepsy. Bachelor thesis in molecular biomedicine, University of Copenhagen.
- Ella Hedeboe. Evaluating subcortical volumetric differences in major depressive disorder. Bachelor thesis in molecular biomedicine, University of Copenhagen.
- Emma Høgsted. Stress-hormone dynamics and working memory in women who use oral contraceptives versus non-users. Master's thesis in medicine, University of Copenhagen.
- Frederik Gudmundsen. Whole brain circuit dissection. A promising avenue for understanding the pathophysiology of OCD. Master's thesis in natural science in neurobiology, neuroscience and neuroimaging, University of Chinese Academy of Sciences.
- Katrine Kiilerich. Effects of chronic low doses of psilocybin on behaviour and receptor levels in Long Evans rat. Master's thesis in biochemistry, University of Copenhagen.
- Line Buchwald. Changes in the level of synaptic vesicle glycoprotein 2A in preclinical animal models of cerebral palsy. Master's thesis in human biology, University of Copenhagen.
- Louise Frederikke Nielsen. Clinical Utility of the Impact of Event Scale-Revised in Identifying ASD - An Empirical Study in Out-of-Hospital Cardiac Arrest Survivors. Master's thesis in psychology, University of Copenhagen.
- Martin Prener. Delineation of low-grade gliomas investigated by 7T MRI: An on-going inter-observer study. Master's thesis in medicine, University of Copenhagen.
- Nadia Taghavi-Larmaei. Changes in levels of synaptic vesicle glycoprotein 2A (SV2A) as a measure of synaptic density in animal models of cerebral palsy. Master's thesis in biology, University of Copenhagen.
- Ottilia Wyon. Affective cognition in DBS-STN treated patients with Parkinson's disease: a combined PET and EMOTICOM study. Master's thesis in medicine, University of Copenhagen.
- Tina Segerberg. Rumination in patients with major depressive disorder before and after antidepressant treatment. Bachelor thesis in medicine, University of Copenhagen.

Book chapters

B1. Paulson OB, Gjerris F, Sørensen PS, Waldemar G, Sørensen JCH, Sellebjerg F (eds.). Klinisk neurologi og neurokirurgi. 7. udg. København: FADL's forlag. 2020:1-773

Papers in peer-reviewed journals

1. Andersen HG, Raghava JM, Svarer C, Wulff S, Johansen LB, Antonsen PK, Nielsen MØ, Rostrup E, Vernon AC, Jensen LT, Pinborg LH, Glenthøj BY, Ebdrup BH. Striatal Volume Increase After Six Weeks of Selective Dopamine D2/3 Receptor Blockade in First-Episode, Antipsychotic-Naïve Schizophrenia Patients. Front Neurosci. 2020 May 20;14:484
2. Andersen JV, Jakobsen E, Westi EW, Lie MEK, Voss CM, Aldana BI, Schousboe A, Wellendorph P, Bak LK, Pinborg LH, Waagepetersen HS. Extensive astrocyte metabolism of γ-aminobutyric acid (GABA) sustains glutamine synthesis in the mammalian cerebral cortex. Glia. 2020 Dec;68(12):2601-2612
3. Baltzersen OB, Meltzer HY, Frokjaer VG, Raghava JM, Baandrup L, Fagerlund B, Larsson HBW, Fibiger HC, Glenthøj BY, Knudsen GM, Ebdrup BH. Identification of a Serotonin 2A Receptor Subtype of Schizophrenia Spectrum Disorders With Pimavanserin: The Sub-Sero Proof-of-Concept Trial Protocol. Front Pharmacol. 2020 Apr 30;11:591
4. Beliveau V, Ozenne B, Strother S, Greve DN, Svarer C, Knudsen GM, Ganz M. The structure of the serotonin system: A PET imaging study. Neuroimage. 2020 Jan 15;205:116240
5. Bratteby K, Torkelsson E, L'Estrade ET, Peterson K, Shalgunov V, Xiong M, Leffler H, Zetterberg FR, Olsson TG, Gillings N, Nilsson UJ, Herth MM, Erlandsson M. In Vivo Veritas: 18F-Radiolabeled Glycomimetics Allow Insights into the Pharmacological Fate of Galectin-3 Inhibitors. J Med Chem. 2020 Jan 23;63(2):747-755
6. Donat CK, Hansen HH, Hansen HD, Mease RC, Horti AG, Pomper MG, L'Estrade ET, Herth MM, Peters D, Knudsen GM, Mikkelsen JD. In Vitro and In Vivo Characterization of Dibenzothiophene Derivatives [125I]Iodo-ASEM and [18F]ASEM as Radiotracers of Homo- and Heteromeric α7 Nicotinic Acetylcholine Receptors. Molecules. 2020 Mar 20;25(6)
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Public lectures

Jun 18-20, 2020: Gitte Moos Knudsen - Bloom Science Festival: “Hjernen på svampe”: https://www.bloom.ooo/explore/hjernen-p%C3%A5-svampe-gitte-moos-knudsen.

Oct 2, 2020: Gitte Moos Knudsen - Psykedelisk Samfund: “Forskning i psilocybin og psilocybin-terapi”

Oct 27, 2020: Gitte Moos Knudsen – Videnskabernes Selskab: “Hvordan kan man måle lægemidlers effekt i hjernen?”: https://www.youtube.com/watch?v=5rEmyK4u6Tw.

Media attention

Jan 11, 2020: Dea S. Stenbæk in the podcast series ”24 spørgsmål til professoren”.
https://www.carlsbergfondet.dk/da/Nyheder/Formidling/24-Sporgsmaal-til-professoren/2020#q2

Jan 14, 2020: Gitte Moos Knudsen in DR TV-Avisen.
https://www.dr.dk/drtv/se/tv-avisen-21_00_-fuld-opbakning-til-venstres-formand_162641.

Apr 29, 2020: Louise Møller Jørgensen in the Berlingske magazine Life Science.

May 6, 2020: Martin Korsbak Madsen in the stetoskopet.nu podcast ”Din hjerne på svampe”.
https://stetoskopet.nu/podcast/082Psilocybin_b_edit_v2.mp3.

Jun 4, 2020: Melanie Ganz in Politikken.
https://politiken.dk/debat/debatindlaeg/art7805783/Algoritmer-kopierer-l%C3%A6gers-fordomme-om-race-og-k%C3%B8n.

Sep 7, 2020: Gitte Moos Knudsen in the radio4 program Kraniebrud.
https://www.radio4.dk/program/kraniebrud/?id=lykke_ep_07_09_20.

Sep 28, 2020: Gitte Moos Knudsen in the radio4 program Kraniebrud.
https://www.radio4.dk/program/kraniebrud/?id=psykedeliske-stoffer_ep_28_09_20.

Sep 28, 2020: Vibe G. Frøkjær in the podcast series ”24 spørgsmål til professoren”.
https://www.weekendavisen.dk/2020-39/24spoergsmaal/oestrogen-og-skarpe-hjerner.

Oct 1, 2020: Vibe G. Frøkjær in the radio4 program Kraniebrud.
https://www.radio4.dk/program/kraniebrud/?id=p-pillen_ep_01_10_20.

Nov 4, 2020: Sara Marie Ulv Larsen and Sebastian Holst in the magazine ‘Krop & Livsstil’ in the newspaper Jyllandsposten.

Nov 13, 2020: Gitte Moos Knudsen in the BrainStorm podcast.
https://videnskab.dk/krop-sundhed/kom-ud-i-lyset-og-andre-raad-mod-vinterdepression-saadan-hjaelper-du-din-hjerne-gennem.

Nov 14, 2020: Martin Korsbak Madsen, Dea Stenbæk, Ida L. Klausen and Tobias Mathiesen in a one-hour documentary, DR2 på syretrip med Peter Lund Madsen. The documentary can be seen (in Danish):
https://www.dr.dk/drtv/program/dr2-paa-syretrip-med-peter-lund-madsen_218280.

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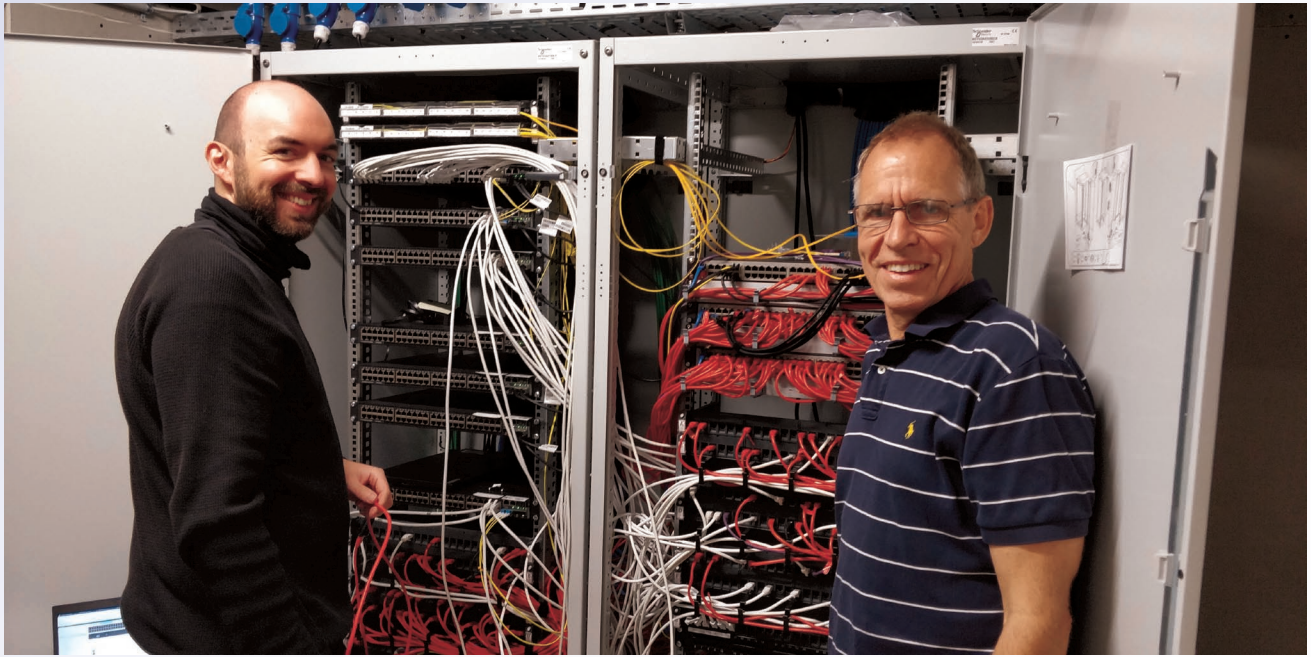
2020 - a year of many changes



NRU IT-supporter Thomas Wiklund Jørgensen and NRU chief engineer Claus Svarer reconnecting all the cables for the NRU IT-system after the big move to the North Wing building. Impressively, the disconnecting, moving and reconnecting of the system was mastered within a few hours.

Due to the covid-19 pandemic many physical meetings, conferences and seminars in 2020 had to be replaced by virtual events. The traditional NRU christmas symposium was no exception.

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