Neurobiology Research Unit

Annual Report 2021

Department of Neurology, Neuroscience Centre
Copenhagen University Hospital, Rigshospitalet

www.nru.dk

Cover page: The core of NRU is placed in the North Wing building at Rigshospitalet. Photo: 3XN.

REGION H Rigshospitalet KØBENHAVNS UNIVERSITET DET SUNDHEDSVIDENSKABELIGE FAKULTET

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Preface

It is a pleasure to present you with the 2021 annual report describing the activities of the Neurobiology Research Unit (NRU). Although the pandemic continued to affect the activities in some part throughout the year 2021, we were to some extent able to resume some of the scientific activities. When I write this, the number of new covid-19 infections continue to rise above what was ever seen before, but luckily the vaccinations have made it possible to keep many activities in the society open. After 1½ years with online meetings and congresses, we were able to join some of those physically. We have also adapted online possibilities as a handy measure to communicate with people, not only collaborators that we know well, but also to invite speakers from other continents to present their work at NRU journal clubs. This is the new normal - at least for a while.

NRU moved to the newly built North Wing in September 2020 and we have continued to install and improve the excellent and modern facilities, including completing the installation of the MR-mockup scanner with a new bed and a complete video and sound system. Moreover, the dedicated room for psychedelic interventions has undergone a profound remake and is now turned into a cosy and calming room, with only very remote resemblance of a traditional hospital room.

In 2021, we saw the largest ever number of new people at NRU. No less than 2 junior faculty members, 2 junior scientists, and 5 technical-administrative staff members and 46 pregraduate students had their first day at work at NRU in 2021, bringing the number of NRU-affiliated people to a total of 127. On top of this, 7 new visiting scientists were at NRU for shorter or more extended stays. Three new larger projects were funded: Grants focusing on neuroimaging for investigation of longevity and ageing (Drs. Svensson and Plaven-Sigray, the longevity impetus, Capital Region and Hjärnfonden), a grant for investigating the effect of music during a psychedelic experience (Dr. Stenbæk, DFF-Inge Lehmann Grant and Helsefonden) and a grant to cover running costs for a neuroplasticity project (Rigshospitalet). Many other smaller grants were successfully achieved; these will all be helpful in achieving our mission which is to investigate neurobiological aspects.

NRU continued to generate a substantial research output in 2021. Two PhD students successfully defended their theses and obtained their PhD degree (page 16-17) and another 3 got enrolled. Many NRU-affiliated researchers presented their work at international congresses, conferences, and meetings. In total, NRU published 67 peer-reviewed scientific publications (page 56). Notably, in recognition of how scientific news are disseminated and read nowadays, we have in this annual report begun to encounter peer-reviewed and accepted publications the year that they become available as pre-print online, rather than starting to count them from the year they are printed.

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 20) and the funding agencies that support our work (page 68). These have all been essential factors to ensure that 2021 was another very successful year for NRU.

I hope that you will enjoy reading this 2021 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 NRU

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

Our Mission & Activities

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

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

The activities within NRU fall in ten different categories:

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

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

Facilities

NRU facilities cover more than 1,400 m2, mainly situated at fifth and sixth floor of the North Wing building, sections 8057 and 8067 of Rigshospitalet (RH). At fifth floor, we span 822 m2, including 15 offices with space for 57 desks, a conference room with kitchen, a regular meeting/conversation room, a science lounge, two smaller quiet rooms for video calls, a laboratory for handling human specimens, a storage room, two sound-proof rooms with facilities for neuropsychological and -physiological testing, a calm sleep/intervention room, and an EEG-room 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, of the North Wing, we have a Siemens mock-up MR scanner installed, 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.

At sixth floor, the NRU experimental laboratory has 167 m2 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 m2) 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.

The calm and nice NRU sleep/intervention room where, e.g., psychedelic interventions or sleep-related research can take

In Building 93, RH section 9302, we have two dedicated laboratories for our *in vivo* studies, including small animal storage facilities and facilities for testing animal behaviour. These rooms cover 46 m2 and both are approved as isotope labs with an S1 permission. Furthermore, we have access to a storage room equipped with three -80 degrees freezers, shared with the other research groups in the building.

The SPECT laboratory of NRU is located on the ground floor in the North Wing. The facility is used both diagnostically and for research purposes. The laboratory consists of an office, a type B approved isotope laboratory, waiting room facilities for patients, and a scanner room equipped with a newer 3-headed dedicated brain SPECT/CT scanner (Mediso AnyScan) with unique multi-pinehole collimator. The SPECT laboratory also has a dedicated storage room in the basement and thereby occupy in total 130 m2.

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 m2 state-of-the-art facilities.

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.

The NRU neuroimaging facilities include a Siemens 3T Prisma MR scanner (above) and a 3rd generation high-resolution AnyScan SPECT-CT Mediso scanner (to the right).

Staff in 2021

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

Chief technologist
Gerda Thomsen

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

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

Post docs
Cheng T. Ip, PhD
Giske F. Opheim, PhD
Martin Nørgaard, PhD
Martin Schain, PhD
Mette Thrane Foged, MD, PhD
Pontus Plavén-Sigray, PhD
Sofi da Cunha-Bang, MD, PhD
Vibeke N. H. Dam, PhD
Vincent Beliveau, PhD

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

NRU staff members participating in "Mini-NRU day" in June 2021.

Research assistants
Anders S. Olsen, engineer
Ane G. Kloster, MD
Catharina Messell, music therapist
Christel Bormann, MD
Drummond McCulloch, pharmacologist
Emily Beaman, human biologist
Frederik Gudmundsen, neurosicence & neuroimagning
Gunild Vulpius, MD
Hannah Eichhorn, physicist
Jennifer Jacobsen, human physiologist
Kat Kiilerich, biochemist
Lise Berg, psychoanalyst
Martin Prener, MD
Niels Lorenzen, molecular biomedicine

Technical staff
Ajla Sabitovic, MRI-student assistant
Amalie B.E. Nielsen, EEG-student assistant
Anders Buch-Larsen, psychology
Asta Kongsgaard, project nurse
Asta Vølund, MRI-student assistant
Caroline Lund, psychology
Christina C. Schnohr, MRI-student assistant
Clara Madsen, molecular biomedicine
Ditte B. Nielsen, project nurse
Ella Hedeboe, molecular biomedicine
Emilie S. Engdal, EEG-student assistant
Emilie L. Henriksen, radiographer
Emma Balsby, psychology
Emma S. Høgsted, medicine
Erik Mogensen, psychology
Kathrine S. Christensen, psychology
Kristoffer Brendstrup-Brix, MRI-student assistant
Lars Hansen, senior researcher, PhD, biochemistry
Line N. Buchwald, MRI-student assistant
Lone I. Freyr, project nurse
Lucas K. Andreasen, HPLC-student assistant
Lærke V. Kristiansen, MRI-student assistant
Maria S. Christiansen, psychology
Maria Grzywacz, psychology
Marie Linneberg, psychology
Minna H. Litman, project nurse
Nanna Svart, MRI-student assistant
Oliver Overgaard-Hansen, psychology
Robert D. Pedersen, EEG-student assistant
Sandra N. Madsen, HPLC-student assistant
Sarah Bargmeyer, HPLC-student assistant
Sif G. Kaad, biomedical & molecular biology
Simon G. Sabroe, MRI-student assistant
Sophia K. Weber, psychology
Svitlana Olsen, medical technologist
Theodor J.H. Labianca, EEG-student assistant
Thilde K. Nielsen, psychology
Thomas W. Jørgensen, IT-support
Thurid W. Madsen, project nurse

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

Visiting scientists
Ali Ebrahimifard, PhD student, Univ. Tehran, Iran
Anders S. Olsen, PhD student, Technical University of Denmark
Burcu Pazarlar, PhD student, Izmir Katip Celebi Univ., Turkey
Ida Ivek, MD, ERASMUS intern, Univ. Zagreb, Croatia

NRU is a multi-national and -cultural work place.
In the 2021 staff list, 16 different nationalities are represented.

Ida Vang Andersen, PhD student, Univ. Copenhagen
Jes B. Madsen, DIS Copenhagen
Jonas Svensson, MD, PhD, Aleris psykiatri, Stockholm, Sweden
Ludovica S. Sirocchi, PhD student, Univ. Copenhagen
Marko Rosenholm, PhD, post doc, Univ. Copenhagen
Markus Hjorth, MD, Psychiatric Center Ballerup, Denmark
Martin Schain, PhD, Antaros Medical, Sweden
Natalie Beschorner, PhD, post doc, Univ. Copenhagen
Natasha S.R. Bidesi, PhD student, Univ. Copenhagen
Nicole Jakusevova, ERASMUS intern, Czech Republic
Nikolaj Daugaard, PhD student, Univ. of Southern Denmark
Sara Lopes van den Broek, PhD student, Univ. Copenhagen
Silas Haahr Nielsen, MD, Dept of Neurosurgery, Rigshospitalet
Sofi Atshemyan, PhD, ECNP intern, Armenia
Vladimir Shalgunov, PhD, Univ. Copenhagen

Pregraduate students

Alaa Alawadi, radiography
Allan Al-Dawaski, medicine
Anders Brammer, mathematics & technology
Anders Lykkebo-Valløe, bioinformatics
Anders S. Munch, psychology
Anna Søndergaard, medicine
Anni Gundersen, medicine & technology
Annika L. Rasmussen, medicine
Astrid Mikkelsen, medicine
Avneet Kaur, computer science
Bianca I. Pedersen, radiography
Cansu Gürel, radiography
Caroline E. Brugge, neuroscience
Cathrine Lind, quantative biology & disease modelling
Cecilie A. Poulsen, medical technology
Elisa Bouet-Garcia, neuroscience
Elisabeth B. Pedersen, medicine
Evangelos Vouros, medical physics
Hanaeli Hamzu, radiography
Haowen Lyu, neuroscience
Harald Schiønning, medicine
Ida L. Rasmussen, psychology
Inger Marie M. Sørensen, medicine
Jeppe S. Poulsen, psychology
Joan M.A. Gomez, medicine & technology
Josephine O. Thestrup, neuroscience
Kristian Larsen, neuroscience
Laura Fonnesbech-Sandberg, medicine
Lea L. Larsen, biotechnology & biology
Liis Kivistik, bioinformatics
Malene Ravn-Eriksson, medicine
Malthe B. Scharff, biochemistry
Martin R. Rassing, radiography
Mette Clausen, medicine
Naja S. Jessen, pharmaceutical sciences
Nina Fultz, neuroscience
Philip Fink-Jensen, medicine
Ramlah. S. Rehman, computer science
Silja M.P. Vange, quantative biology & disease modelling
Simon Chemnitz-Thomsen, mathematical sciences
Stine Mørup, human physiology
Tobias Mathiesen, psychology
William Reith, molecular biomedicine
Youssef Zeaiter, medicine

Visiting Professors

In 2021, NRU has continued hosting the two highly esteemed international visiting professors, Adriaan A. Lammertsma, from VU University Medical Center, Amsterdam, The Netherlands and R. Todd Ogden, Biostatistics at Columbia University, New York, NY, USA. This has been 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 for example:

- 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).

Furthermore, Professor Ogden is co-supervising PhD student Gjertrud Laurell and Professor Lammertsma is contributing with lectures at our annual one-week PhD course on pharmacokinetics.

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. Visiting professors continue to facilitate tight 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 in 2021

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

Cheng Teng-Ip, PhD

Towards personalized medicine: Effectiveness of pretreatment EEG biomarker in Major Depressive Disorder

The purpose of her thesis was to a) examine the test-retest reliability of an EEG battery in healthy males who were given different antidepressants, b) validate EEG candidate biomarkers that have previously shown some predictive value in a cohort of unmedicated patients with moderate to severe major depressive disorder, and c) explore the effect on EEG measures after 8 weeks of selective serotonin reuptake inhibitor/serotonin noradrenalin reuptake inhibitor (SSRI/SNRI) treatment.

Dr. Teng-Ip's PhD work was done in collaboration with H. Lundbeck, as an industrial PhD partly funded by the Innovation Fund Denmark. Dr. Teng-Ip was supervised by professor Gitte Moos Knudsen from NRU and Dept of Clinical Medicine, Univ. Copenhagen. Primary co-supervisor was senior scientist Søren Christensen from Dept of Experimental Medicine, H. Lundbeck A/S, and professor Sandor Beniczky from Dept of Clinical Neurophysiology, Aarhus University was co-supervisor. Associate professor Bastian Epp, Dept of Health Technology, Technical University of Denmark served as external assessor.

Dr. Teng-Ip successfully defended her thesis on Jan 29th, 2021, with professor Poul Jennum, Dept of Clinical Medicine, Univ. Copenhagen, as chair and assistant professor Martin Brunovský from Dept of Psychiatry and Medical Psychology, 3rd Medical Faculty of Charles University, Prague and associate professor Martijn Arns from Faculty of Psychology and Neuroscience, Maastricht University, Netherlands, as opponents.

Giske Opheim, PhD

Utilizing 7 Tesla MRI and automated segmentation - A new era in the presurgical evaluation of patients with severe epilepsy

The specific aims of the thesis were to: 1) assess automated 3T MRI hippocampal subfield segmentations for groups with hippocampal sclerosis type 1 and 2, 2) explore a set of radiomic MRI features in the hippocampi of radiologically diagnosed MTS patients, and compare the findings in clinical 3T and 7T MRI scans, and 3) provide a consensus-based set of guidelines on how to set up and evaluate a 7T MRI epilepsy scan protocol.

Giske Opheim completed her PhD at NRU under the main supervision of associate professor Lars H. Pinborg from NRU and Dept of Clinical Medicine, Univ. Copenhagen. Primary co-supervisor was professor Olaf B. Paulson from NRU and Dept of Clinical Medicine, Univ. Copenhagen, while associate professor Melanie Ganz-Benjaminsen, NRU and Dept of Computer Science, Univ. Copenhagen, Patrick M. Fisher, NRU, professor Henrik B.W. Larsson, Dept of Clinical Medicine, Univ. Copenhagen, and Ulrich Lindberg, Rigshospitalet, were co-supervisors.

Dr. Opheim successfully defended her thesis on February 5th, 2021, with professor Steen Hasselbalch from Danish Dementia Research Center, Rigshospitalet, and Univ. Copenhagen as chair, and associate professor Steffen Ringgaard, Dept of Clinical Medicine, Aarhus University, and professor Asta Haaberg from Norwegian University of Science and Technology and St. Olav's Hospital, Norway, as opponents.

Education

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

NRU faculty members are engaged in research-based teaching and education within their fields of expertise. Below are some of the major contributions to teaching programs. Due to the covid-19 pandemic, the one-week PhD course on pharmacokinetics was cancelled in 2021, but will be held February 2022.

The Master's program in Neuroscience in Copenhagen

Professor Jens H. Mikkelsen from NRU and Institute of Neuroscience, University of Copenhagen, is the study director of this two-year research-based education covering all aspects of the neurosciences. Courses are offered in cellular neuroscience, neural circuits, higher brain functions and experimental neuroscience, as well as elective courses. This is the second year of enrollment of 30 bachelor students in the Master's program in Neuroscience at the University of Copenhagen. Again, this year the program received enormous interest from all over the world, and we were only able to accept less than 15% of the qualified applicants for the program. The NRU faculty provide teaching in neuropharmacology, homeostasis, cognition, drug discovery 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 continued in 2021 to lecture 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 guest lectures for the following university-level courses at the Danish Institute of Study Abroad: "Neuroplasticity", "Neuroscience of Fear" and "Neurological Disorders and Disease".

PET Pharmacokinetics Course

Since the first international PET Pharmacokinetics Course was held by NRU in 1999, the course has rotated between virtually all continents. The approximately 12 faculty members are all internationally recognized experts in PET neuroimaging and they teach for free at this course which usually takes place annually in conjunction with either the Brain or Neuroreceptor Mapping meetings. Due to the covid-19 situation, the course was in 2021 held as a virtual course.

Strategic Collaborations

Strong collaborations are fundamental for excellent brain research to happen. We have for many years worked closely together with many different partners within Denmark and internationally. Listed below are some of our major strategic collaborations, which are particularly key for us. With respect to other collaborators within Dept of Neurology, please refer to page 40, and with respect to other neuroimaging collaborators, please refer to page 29.

PET and Cyclotron Unit, Rigshospitalet

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

Dept of Radiology, Rigshospitalet

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

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

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

Dept of Growth and Reproduction, Rigshospitalet

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

University of Copenhagen

Professor Jens Mikkelsen has become Faculty at the Institute of Neuroscience, University of Copenhagen, and in this role heads the new Master's program in Neuroscience.

Since the establishment of Cimbi in 2006, we have had a close collaboration on PET radioligand development with Dept of Drug Design and Pharmacology (Dr. Herth, professors Kristensen and Jensen). Likewise, we also appreciate our long-standing collaboration on biostatistics with Section of Biostatistics, Faculty of Public Health, with whom we share a biostatistician (Dr. Ozenne) and a PhD-student (Dr. Ziersen) through the *BrainDrugs* project, The Center for Translational Neuromedicine (professor Nedergaard), and with the Dept of Psychology with whom we share an associate professor (Dr. Stenbæk). Finally, we also highly appreciate our strategic collaboration with Dept of Computer Science, facilitated by a joint associate professor (Dr. Ganz) as well as cooperation in the *BrainDrugs* project.

Copenhagen Business School

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

Mental Health Services in the Capital Region of Denmark

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

As part of our joint study on habit forming where we include patients with obsessive-compulsive disorders, we collaborate with senior consultant Clas Winding Christensen and psychologist Sara Kerstine Nielsen (OCD). The project is jointly done with professor Trevor Robbins and colleagues, as described below. For our *BrainDrugs* project, we benefit greatly from our close collaboration with Allan Lohmann-Olsen and Eva Hundrup from CVD ('Center for Visitation og Diagnostik'), a unique central referral site for 'treatment packages', e.g., for patients with depression or obsessive-compulsive disorder who can be treated in outpatient settings.

Martinos Center, Massachusetts General Hospital, US

We have since 2011 had a fruitful collaboration with the Athinoula A. Martinos Center for Biomedical Imaging in Boston, US, which has pioneered brain imaging with MRI. The collaboration has so far included retreat meetings, the successful achievement of a joint 2-year NIH grant, the NRU-anchored *NeuroPharm* Center grant (2015-22) from the Innovation Fund Denmark, and funding from Lundbeck Foundation for instructor at Harvard University, Dr. Hansen, as well as bilateral exchange of scientists. Joint research areas include PET-MR of animals, PET data modelling and motion correction, and the collaboration has so far resulted in more than 20 publications.

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

The OpenNeuroPET project, funded through the BRAIN initiative and the Novo Nordisk foundation has been going on since 2019. You can read more about the project on page 32.

University of Cambridge, UK

We are collaborating with professors Trevor Robbins and Barbara Sahakian from University of Cambridge on two joint research projects funded by the Lundbeck Foundation; the collaboration includes bilateral secondments. The data acquisition for the project with Sahakian was completed in 2021 and we expect to complete data acquisition for the Robbins project in 2022.

Preclinical Neurobiology

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

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

We did the first direct comparison between [11C]UCB-J, a tracer targeting the synaptic vesicle protein 2A (SV2A), and [18F]FDG, a glucose derivate, for the detection of neuronal loss [54]. We used a rodent model for Parkinson's disease (the 6-OHDA model) and imaged the same animal with each PET tracer (**Figure 1**), on separate days. The experiment revealed, as expected, a greater effect size (better sensitivity to detect lesions) with [11C]UCB-J. But it also suggested that different mechanisms are at play in not directly affected regions in the frontal cortex.

At NRU we have the possibility and experience to work with larger animals such as pigs, and these are thought to have a greater translational value than, e.g., rodents. Donovan et al. showed that a dose of psilocybin which occupies 67% of the 5-HT2A receptors in the pig gives rise to behavioural changes such as head shakes (**Figure 2**). In a placebo-controlled pig study, we explored what genes were regulated 1 and 7 days after a single dose of psilocybin [20]. Gene Set Enrichment Analysis demonstrated that multiple immunological pathways were regulated 1 week after psilocybin exposure. This provides a framework for future investigations of the lasting molecular mechanisms induced by a single dose of psilocybin.

Brain tissue from the animals in the Donovan et al. project was used for an *in vitro* autoradiography study investigating the density of 5-HT2A receptors and the synaptic density as measured by the amount of the presynaptic SV2A (**Figure 3**). We found that a single dose of psilocybin increases the presynaptic marker, SV2A already after 1 day and that it remains higher 7 days after [53]. These data support the notion of increased synaptogenesis following psychedelic exposure, which is hypothesized to underlie the antidepressant effects observed in humans. We also showed a transient reduction in the hippocampus and prefrontal cortex 5-HT2A receptor density; it is reduced 1 day after intervention but not 7 days after.

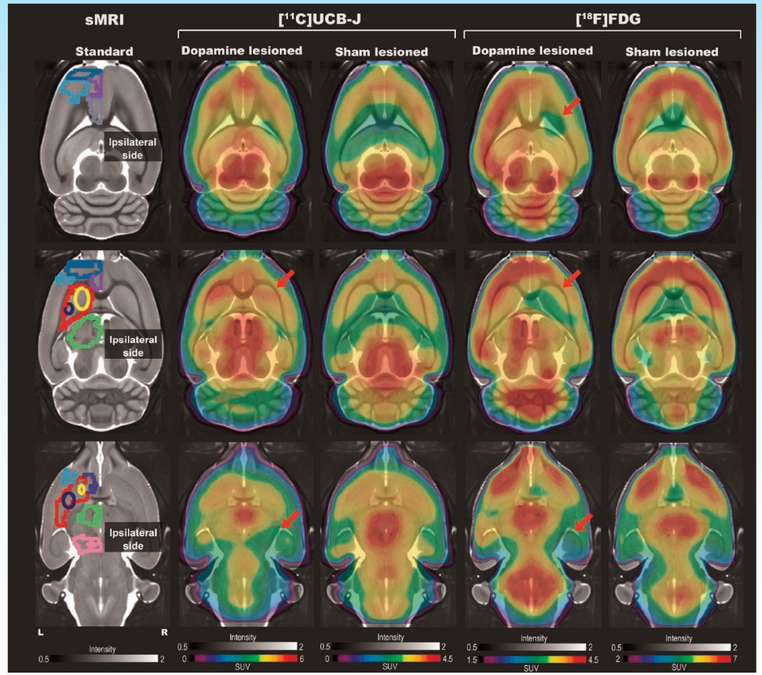


Figure 1: Representative [11C]UCB-J and [18F]FDG PET SUV horizontal brain slices from a dopamine and a sham lesioned rat. Standard structural MRI (for illustrative purposes) slices show the selected volumes of interest in one hemisphere; mPFC (medium blue), OFC (purple), motor cortex (light blue), ACC (grey), striatum (red), dorsomedial striatum (yellow), dorsolateral striatum (navy blue), thalamus (green), NAc (dark blue), and ventral midbrain (pink). For [11C]UCB-J, the SUV image represents the sum of 15-60 min; for [18F]FDG, it is the sum of all 45 min. The red arrow shows decreased tracer uptake in dopamine lesioned animals. From [54], Copyright © 2021 by the authors.

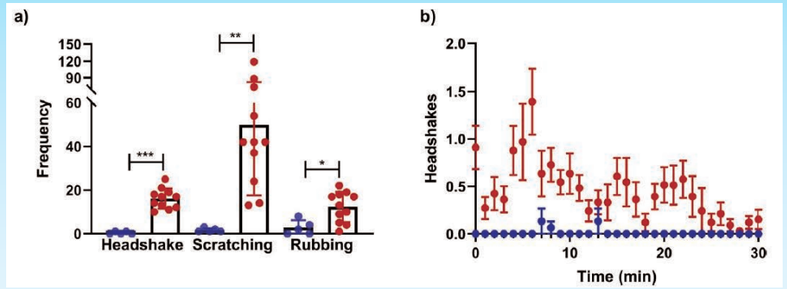


Figure 2: a) Behavioral changes in pigs after i.v. administration of either saline or psilocybin. b) Time-response curve of headshakes during the first 30 min after psilocybin injection. From [20], Copyright © 2021. Elsevier Inc.

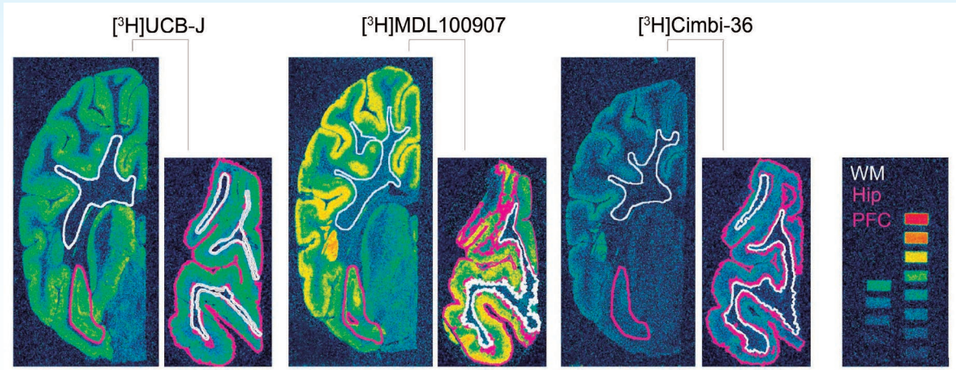


Figure 3: Representative autoradiograms of [3H]UCB-J binding to the SV2A protein and [3H]MDL100907 and [3H]Cimbi-36 which both bind to the 5-HT2A receptor. The purple delineations show the hippocampus and cortex of the pig brain. The white delineations show the white matter which is the reference region in these experiments. From [53], Copyright © 2021 by the authors.

Biomarkers for inflammation predict pain and quality of life in patients with low back pain

Together with Rachid Bech Azeddine and his team at Dept of Neurosurgery, Rigshospitalet-Glostrup, we have conducted a study on patients with low back pain [2]. Low back pain is the foremost cause of disability in the world, and it is estimated that about 80% of the population suffers from low back pain at some point in life. Some patients are diagnosed with a degenerative disc disease, and this condition can be very painful. The intervertebral disc absorbs and distributes applied loads and adds both stability and flexibility to the spine, and serves also as a back-movement controller. The disc is composed of the annulus fibrosus, which encircles the nucleus pulposus that is made of a primarily avascular, proteoglycan water-based gel. When degeneration occurs, some patients are offered neurosurgical treatment, where decompression and preparation of the disc space for placement of the intervertebral cage is conducted. At the exposure of the intervertebral disc during surgery for the involved patients, the spine surgeon harvested the annulus and the pulposus for research purposes before discectomy. Before surgery, patients were clinically evaluated, and pain and quality of life was subjectively scored by each patient. This allowed us to compare the expression of different genes and proteins in the discs with the pain expressed as visual analogue scale (VAS 0–100; where 0=no pain and 100=worst pain) and the disability due to back pain was assessed by the Oswestry Disability Index (ODI 0–100; which ranges from 0=no disability to 100 maximal possible disability).

We were able to show a strong and highly statistically significant positive correlation between pain intensity (VAS score) and the expression of tumour necrosis factor (TNF)-α in both the annulus fibrosus and the nucleus pulposus. We also detected that levels of the interleukins 1ß and 6 were correlated to pain intensity. In addition, we found significant positive correlation observed between disability score and expression of IL-6 in both tissue components of the lumbar disc.

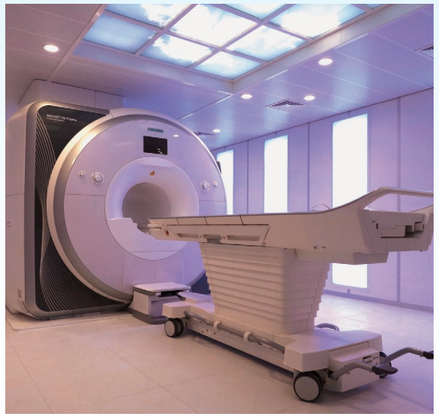
These results add to our understanding of the pathology of degenerative disc disease and lumbar pain. TNF-α is a protein known to be involved in inflammation. It can be concluded that the level of inflammation of the disc and not necessarily the level of degeneration is predictive for pain and disability.

The NRU Neuroimaging Laboratory

By Patrick M. Fisher
Group leader

3T MRI scanner

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



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

Despite continued corona-related delays, we remained active with on-going and new research projects, acquiring nearly 150 NRU-led scans in NRU 2021 and many more as part of collaborations. Below is a brief overview of collaborations in 2021:

- In collaboration with professors Trevor Robbins and Barbara Sahakian from Cambridge University (UK) we are evaluating selective serotonin-reuptake inhibitor (SSRI) effects on cognitive processing in healthy individuals and individuals with obsessive compulsive disorder.
- The NEAD group led by professor Kamilla Miskowiak from Psychiatric Center Copenhagen acquires structural and functional MRI to evaluate brain imaging markers associated with mood disorders including bipolar disorder as well as associated treatments and alterations in cognition.
- The REFORM project with professor Messoud Ashina from the Danish Headache Center at Rigshospitalet-Glostrup continues a large data collection endeavor to evaluate structural and functional brain markers of an antibody treatment for migraine.
- The Entrepreneurship project with professor Toke Reichstein from the Copenhagen Business School aims to identify distinguishing aspects of reward- and risk-related brain function in serial entrepreneurs.
- The REVIVAL project with professor Christian Hassager from the Dept of Cardiology at Rigshospitalet-Blegdamsvej is examining structural and functional imaging markers of cognitive recovery in patients following the experience of a cardiac arrest event.
- CONNECT-ME with associate professor Daniel Konziella from the Dept of Neurology at Rigshospitalet-Blegdamsvej aims to identify brain connectivity markers in patients with disordered consciousness and prognostic indicators of recovery.
- NeuroPharm Project 2, an NRU-centered project, aims to identify brain imaging markers of serotonin 2A receptor modulation, including a focus on the serotonin psychedelic, psilocybin.
- The EPOCH project with professor Rigmor Jensen from the Danish Headache Center at Rigshospitalet-Glostrup evaluates clinical and imaging effects of psilocybin administration to patients with Chronic Cluster Headache.
- 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.
- Two elements on the BrainDrugs center grant have started collecting MR imaging data in cohorts with depression and epilepsy.
- BIND (Brain Involvement in Dystrophinopathies) is a multi-site clinical research study with professor John Vissing from the Dept of Neurology at Rigshospitalet-Blegdamsvej with an arm that will acquire structural and functional imaging in Becker Muscular Dystrophy patients.
- OLF fMRI with professor Christian von Buchwald from Ear-Nose-Throat Surgery at Rigshospitalet-Blegdamsvej aims to evaluate brain imaging measures of smell in patients with impairment following Covid-19.
- The EU-funded R-Link project with professor Lars Kessing from Psychiatric Center Copenhagen aims to optimize response to Lithium treatment through personalized evaluation of individuals with bipolar I disorder.
- The KME project with professor Anders Fink-Jensen from Psychiatric Center Copenhagen uses MRS to investigate if a dietary supplement of a Ketone Mono Ester (KME) beverage reduces the use of benzodiazepines in alcohol withdrawal syndrome.
- The ECAC project with professor Tiit Mathiesen from the Dept of Neurosurgery at Rigshospitalet-Blegdamsvej aims to investigate correlations between arachnoid cysts and cognitive dysfunction, to elucidate the eventual role played by inflammation and glymphatic flow dysfunction and to identify the impacted functional networks.

SPECT-CT system

The SPECT laboratory of NRU is located next to the Dept of Radiology on the ground floor in the new North Wing of Rigshospitalet. The facility is used both diagnostically and for research purposes. Our 3rd generation high-resolution AnyScan SPECT-CT Mediso scanner (see photo below) provides very good images, and we continue to develop new methodologies in collaboration with Mediso. We are currently completing the acquisition of a reference material for both HMPAO and FP-CIT.

By Gerda Thomsen
Chief technologist

Clinical work

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

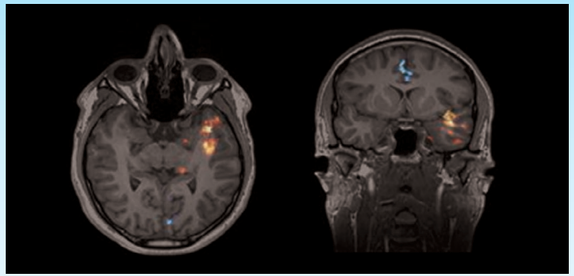
Regional cerebral blood flow with the SPECT ligand [^{99m}Tc]HMPAO

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) (**Figure 4**). 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 used diagnostically in patients with movements disorder and/or dementias of uncertain origin. The diagnostic report comes with a reference to a healthy age-matched population and is evaluated by a neurologist specialized in reading DAT-SPECT scan data.

Figure 4: Example of a SISCOM image clearly demonstrating an active epileptic focus (in the left temporal lope). The SISCOM image has been obtained by subtracting the ictal and interictal cerebral blood flow images and superimposing the difference image on the patient's structural MRI. Copyright © 2022 NRU.



Research projects

The SPECT-laboratory is engaged in several ongoing research projects.

- **Reduced acquisition time of [123I]FP-CIT DAT-scan with AnySan trio SPECT-CT with MPH collimators**

  The aim of this study was to investigate whether it is possible to reduce the acquisition time of [123I]FP-CIT DAT-scan with AnySan trio SPECT-CT with MPH collimators from the current acquisition time of 40 minutes, without affecting the diagnostic quality. Results of this project showed that it is statistically possible to reduce the acquisition time to 30 minutes without compromising optimal image quality and without affecting the diagnostic quality.

- **Arterial spin labeling MRI (ASL-MRI) versus HMPAO-SPECT can assess consciousness in acute brain injury**

  This is a proof-of-principle study which investigates if cerebral blood flow as measured by ASL-MRI or 99Tc-HMPAO-SPECT can serve as a proxy for global brain metabolism and reflect consciousness levels in patients with acute brain injury.

- **Striatal dopamine transporter (DAT): A head-to-head comparison between [123I]FP-CIT SPECT-CT and [18F]FE-PE2I PET-CT and establishment of an age adjusted normal healthy group**

  To perform a systematic evaluation of [123I]FP-CIT SPECT DAT scan with the new brain-dedicated pin-hole collimator AnyScan SPECT-CT, including establishing an age adjusted healthy population A 'head-to-head' comparison of [123I]FP-CIT SPECT-CT and [18F]FE-PE2I PET-CT and evaluation of the usefulness of adding MR based neuromelanin measurements.

Data Analysis

By Claus Svarer
Chief engineer

The data analysis section focuses on strategies for analyzing neuroimaging data for research as well as clinical purposes. This includes optimization and improvement of data acquisition methods, analysis pipelines, methods for PET quantification and multimodaltiy MR, EEG and PET data analysis. In 2021, the new data sharing initiative OpenNeuroPET, funded by the NovoNordisk Foundation and the US Brain Initiative, began. This transatlantic project respects GDPR rules for data sharing, and flexibly enables to securely share data between research groups.

The issue of inflated false positive rates in voxelwise neuroimaging with functional MRI has recently come to the attention of many scientists. Most brain PET studies use predefined brain regions rather than voxel-wise analysis, but we have now for the first time evaluated this issue within the field of PET and find very high rates of false positive findings (**Figure 5**), even exceeding the those seen in fMRI [23]. The false positive rate can, however, be remediated if pre-processing of the PET data and the statistical correction is properly done.

The PET ligand 11C-PBR28 binds to the 18-kDa translocator protein (TSPO) which is a biomarker of activated glia and neuroinflammation. In PET studies of TSPO, the ligand total distribution volume, V_T, is frequently the reported outcome measure. Since V_T is the sum of the ligand-specific distribution volume (V_S) and the nondisplaceable-binding

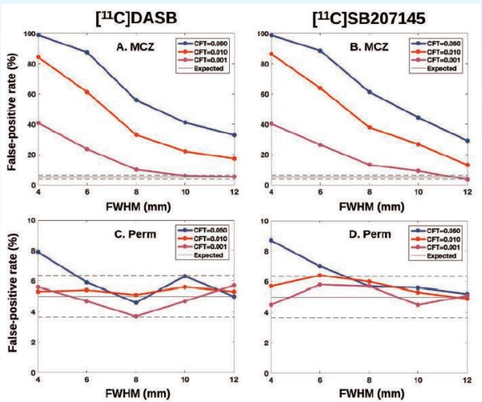


Figure 5: Clusterwise false positive rates (in %) versus applied smoothing level for the two radioligands 11C-DASB and 11C-SB207145 (10/group) and for either parametric Monte Carlo simulations (A-B, MCZ) or permutaions (C-D, Perm). Dashed lines are the 95% significance level. Abbreviations: Full-Width Half Maximum (FWHM). From [23], Copyright © The Author(s) 2020.

distribution volume (V_{ND}), differences in V_{ND} across subjects and groups will impact V_T. By means of a recently developed method for simultaneous estimation of V_{ND} to disentangle contributions from V_{ND} and V_S, and based on data from four previously published 11C-PBR28 PET studies, we found a difference in V_{ND} in individuals with alcohol-use disorder (AUD) and Parkinson's Disease and controls, but not in first-episode psychosis [31]. Consequently, differences in V_T cannot be interpreted as differences in TSPO if the V_{ND} has not been considered (**Figure 6**).

In another multi-site PET TSPO study, we examined differences in brain TSPO binding in patients with schizophrenia and healthy controls [51]. Contrary to the established hypothesis of increased TSPO in patients, this large data set shows significantly lower TSPO expression in the brain (**Figure 7**).

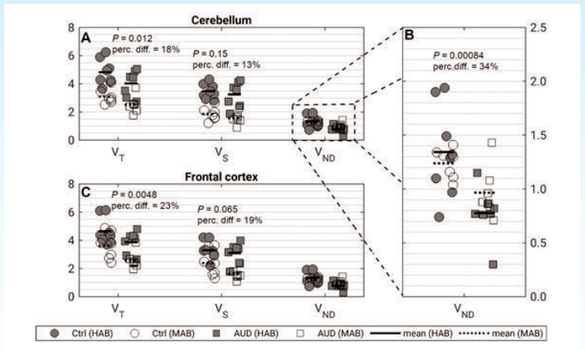


Figure 6: (A and C) Difference in outcome measures (V_T, V_S, and V_{ND}) between controls (Ctrl) and subjects with AUD in cerebellum (A) and frontal cortex (C). (B) Zoomed view of results for V_{ND}. P values and percentage difference (perc. diff.) between controls and patients are shown. HAB = high-affinity binder; MAB = mixed-affinity binder. From [31], Copyright © 2021 by the Society of Nuclear Medicine and Molecular Imaging.

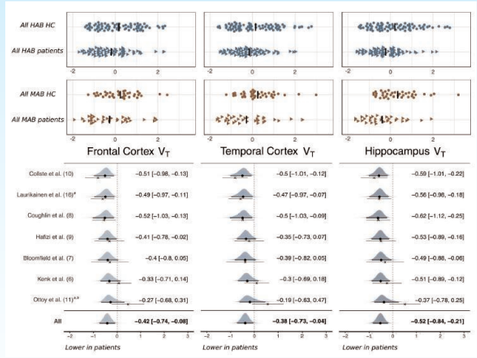


Figure 7: Differences (standardized) in total distribution volume (V_T) between patients with psychosis and healthy controls (HC). The top row shows the TSPO expression of all individual patients and healthy subjects, subdivided into high-affinity-binders (HAB) and mixed-affinity binders (MAB) genotype groups, respectively. The lower row shows the meta-analytical estimated standardized difference in V_T using a Bayesian linear effects model. From [51], Copyright © 2020 Society of Biological Psychiatry.

In 2021 we published a high-resolution in vivo atlas (**Figure 8**) of the $GABA_A$ receptor systems, as reflected by the benzodiazepine binding site [45]. The atlas was created based on PET [11C]flumazenil and structural MRI. On the basis of human brain autoradiography, the PET-based atlas was calibrated to protein densities and the association between protein concentration and mRNA from the Allen Human Brain atlas was established. The atlas is freely available at www.nru.dk.

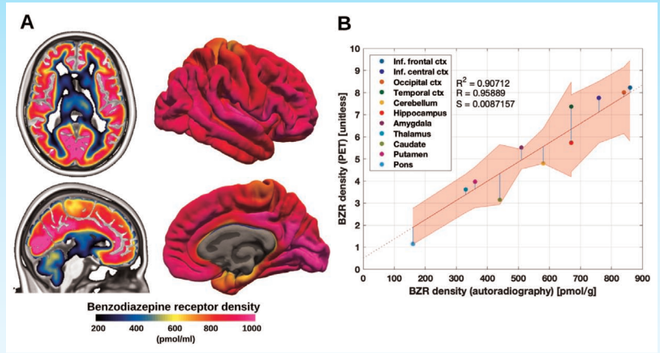


Figure 8: (A) High resolution human brain atlas of $GABA_A$ receptor density (pmol/mL) in MNI152 space (left) and on the surface (right). (B) Average regional benzodiazepine receptor density (from PET) and benzodiazepine receptor density (from mRNA, unit pmol/g). The regression is shown as the black line, and the intercept is the non-specific binding of the PET radioligand. The shaded area is the 95% confidence interval. From [45], Copyright © 2021 The Authors.

Also, we have examined the thalamic differences in dopamine D2-receptor levels between drug naive patients with first-episode psychosis and matched healthy control participants [52]. We show that patients show modestly lower thalamic D2-receptor binding, and most in a subregion with connectivity to prefrontal cortex (**Figure 9**). We also corroborate in a meta-analysis that thalamic D2-receptor binding is lower in patients with psychotic disorders.

In a longitudinal study [58] we show in patients with MDD depression that the cerebral serotonin transporter increases as symptoms are alleviated in response to internet-based cognitive behavioral therapy. This observation supports that previously reported cross-sectional molecular imaging findings of the serotonin transporter in depression most likely reflects the depressive state, rather than a permanent trait.

Two frequently asked questions in PET-studies are: What sample sizes should one aim for and how little radioactivity can you inject? In 2021, we have shown how sequential Bayes Factor testing can indicate when to stop scanning more individuals and that a study can be aborted early, while keeping the number of erroneous conclusions low (**Figure 10**). We show in an example on real PET data that support in favor of an effect can be obtained while simultaneously reducing the sample size by 30% [57]. Using this procedure allows researchers to reduce expense and radioactivity exposure for a range of effect sizes relevant for PET research.

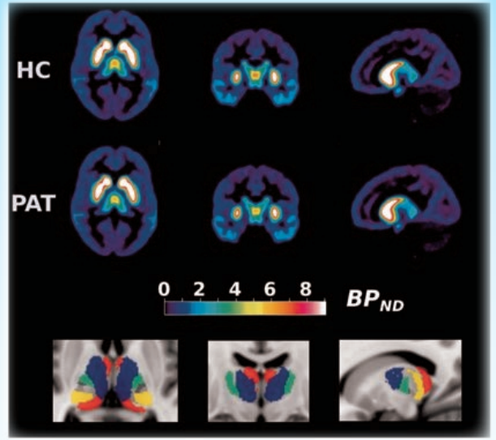
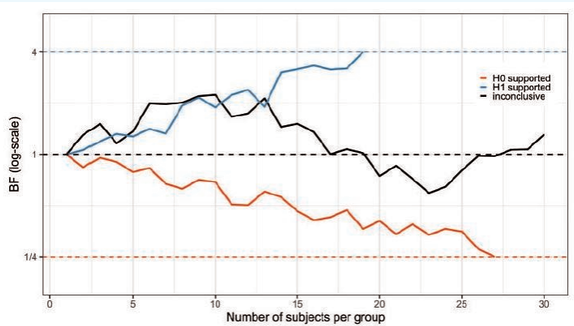


Figure 9: Average BP_{ND} values for healthy controls (HC) and patients with first episode psychosis (PAT), as well as subthalamic regions of interest based on a diffusion tensor imaging atlas; Blue = THA-PFC (connectivity projections to prefrontal cortex), red = THA-TC (temporal cortex), gray = THA-M1 (primary motor cortex), green = THA-PreMC (premotor cortex), orange = THA-PPC (posterior parietal cortex). From [52], Copyright © The Author(s) 2021.

Figure 10: Possible outcomes of sequential testing using Bayes Factor (BF). Three different studies have been initiated, all having N=30 as the maximum possible sample size. For the blue line, BF crosses the pre-specified threshold at N=19, triggering an early stop decision in favor of an effect. For the red line the pre-specified threshold is crossed at N= 27, stopping the study in favor of the null hypothesis. For the black line, BF does not reach either threshold before the pre-specified number of subjects have been reached, and therefore denotes an inconclusive stopping outcome. From [57], Copyright © The Author(s) 2021.



Neuropsychology

By Dea S. Stenbæk
Group leader

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

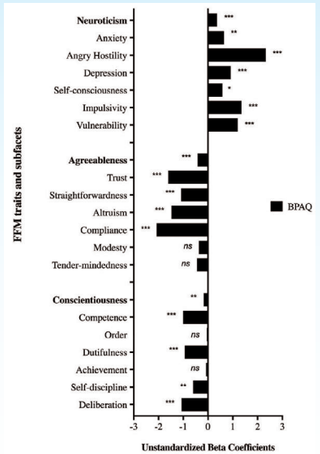


Figure 11: Association between trait aggression and FFM personality traits. From [18], Copyright © 2021 The Authors.

In 2021, psilocybin research was again a major theme for the psychology group [38,41,41]. We prepared and initiated data collection for a variety of different research projects on psychedelic effects and how music affects the acute psychedelic experience and a clinical trial of psilocybin for treatment of alcohol use disorder in collaboration with Psychiatric Centre Copenhagen. In collaboration with Imperial College London, we prepared a study of cognitive mechanisms of treatment with psilocybin for OCD which will run at the London site CIPPRes clinic (https://www.imperial.ac.uk/brain-sciences/research/psychiatry/cippres/).

Another major theme was mental health factors in somatic patients [4,62,63] and factors related to women's health [25] and aggression [18] where we found evidence of an association between personality and levels of trait aggression (**Figure 11**).

We have continued fruitful collaborations with the Cambridge Cognition Group where we finalised data collection for a study of the effects of sub-chronic treatment with SSRI on brain activity and cognition, and are continuing data collection for a study of the effects of sub-chronic treatment with SSRI in patients with OCD.

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. We hold expertise in frontier molecular brain imaging and analysis of key features of the serotonin signaling system [23], which is profoundly involved in mood disorders, schizophrenia, neurodegenerative disorders and their treatments. In particular, we are interested in serotonin brain biology in the treatment mechanisms for depression and as a driver of healthy adaptation to, e.g., stressors, genetic make-up, sex-steroid hormones, personality [18,41], and appropriate impulse control and aggression management [15], (**Figure 12**).

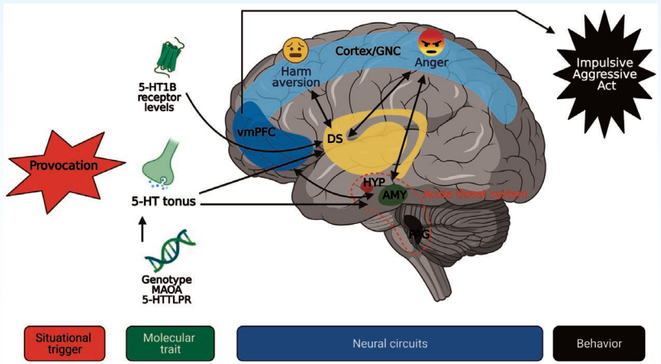


Figure 12: Model of the systems involved in impulsive aggression and their putative roles. A situational trigger activates a neural circuit comprising the amygdala (Amy), the general network of cognition (GNC), the dorsal striatum (DS), and the prefrontal cortex (PFC). Serotonergic tonus modulates Amy and DS reactivity, which may also be modulated by the PFC. Serotonin (5-HT) 1B receptors in DS facilitate heightened DS reactivity, which may modulate anger, harm aversion, and retaliatory motives. Activation of the GNC induces a subjective experience of anger, which may be modulated by Amy and/or DS, or vice versa: subjective experience of anger induces Amy and/or DS activation. This is integrated in the PFC, in particular, the ventromedial PFC that can evaluate and regulate the behavior accordingly by either inhibiting Amy/DS activity or by shaping representations of expected rewards and punishments associated with the action. From [15], Copyright © 2021. Elsevier Inc.

Major depressive disorder (MDD)

Building on data acquired in NeuroPharm, we continue to search for relevant biomarkers to define subtypes of MDD that respond differently to treatment, to predict the outcome. While we find that emotional faces fMRI paradigm-based predictors do not provide clinically relevant information to guide treatment choice [9], EEG-based predictors, in particular alpha asymmetry in women [26], maybe be more informative. With a comprehensive neuropsychological characterization, we have also directly compared the magnitude and patterns of impairment in hot and cold cognition between patients with MDD and healthy controls. We here find evidence of three separate clusters of distinct cognitive profiles in unmedicated depressed patients, which may prove useful as stratification tools in MDD [17] (**Figure 13**).

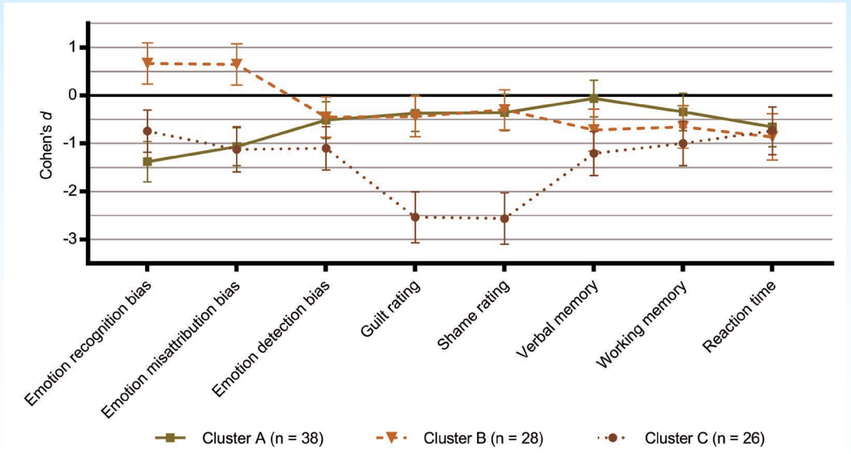


Figure 13: Clusters of cognitive profiles within the cohort of depressed patients (N = 92) based on the eight cognitive outcomes that showed a significant group difference between depressed patients and healthy controls (HC). Zero represent the HC group and differences are expressed as Cohen's d effect sizes. Error bars denote 95% Confidence Intervals (95% CI). From [17], Copyright © 2020 The Authors.

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 and a better understanding of this could identify 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 that repeatedly translates to clinical findings [43]. We therefore propose that sensitivity to hormone transitions, such as across pregnancy and the postpartum period and perimenopause, may represent a clinically relevant and distinct subgroup within MDD. This translates to premenstrual dysphoric disorder, which can be ameliorated by compounds that modulate sex steroid hormone signaling as shown in collaborative studies [30]. 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 their stress-hormone dynamics [25]. This is highly interesting because it offers a plausible biological link between oral contraceptive use that may be linked to serotonergic brain biology, and increased risk of mood instability [21] or depressive episodes.

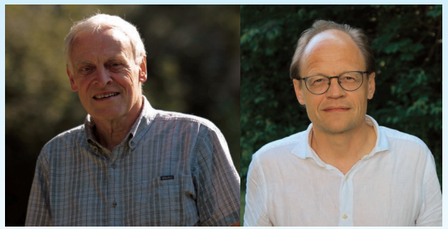
In collaborative and ongoing studies [7,8,11], Sapere Aude recipient Vibe Frøkjær and her group pursue opportunities to protect mental health across reproductive age, including mother and infant mental health across pregnancy and the postpartum in high-risk groups.

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 two major international multicenter study. The first study demonstrated that higher body mass index (BMI) was associated with a significantly lower increase in subcortical grey matter volume following ECT as compared to non-obese patients [46]. The other study compared psychotic major depression (PMD) with nonpsychotic major depression (NPMD). Compared with NPMD, PMD showed lower GMV in several region before ECT and following ECT there was no significant group-by-time interaction [59].

Clinical Neurology

By Olaf Paulson & Lars Pinborg
Group leaders



Epilepsy surgery

Surgery aiming at curing drug-resistant epilepsy is centralized in Denmark at Rigshospitalet. At NRU we continue our efforts to leverage the standard use of MRI and EEG in the epilepsy surgery evaluation process together with national and international partners: As part of Giske Opheims PhD (page 17), she took the lead on an international review on the current status and future consensus recommendations on the use of 7T MRI in epilepsy patients [47], we contributed to the first publication from the MELD consortium (https://meldproject.github.io) demonstrating how a data-driven atlas of focal cortical dysplasias and predictive models can be used as a precision medicine tool when counselling future epilepsy surgery candidates [64]. In another collaboration, we showed the feasibility of an automated analysis pipeline for localizing the seizure onset zone in epilepsy surgery candidates [5].

Magnetic resonance studies in migraine

We are taking part in several studies with the Headache Clinic at the Department of Neurology at Rigshospitalet. Two studies investigated the changes in the brainstem in relation to migraine without aura. Outside attacks using a proton magnetic resonance spectroscopy (MRS) at 3 Tesla revealed normal glutamate levels but increased total creatine levels as compared to controls suggesting that disequilibrium in the pontine energy metabolism could be an important feature of migraine pathophysiology [66]. During attacks, provoked by calcitonin gene-related peptide or sildenafil, glutamate levels in the pons remained unchanged while total creatine levels increased. Further cerebral blood flow also increased in pons, ipsilateral to pain side during attacks [65]. Another MR study revealed that intradural middle meningeal artery and the middle cerebral artery are dilated during migraine induced by calcitonin gene-related peptide as well as by sildenafil [14].

The National 7 Tesla MR system at Hvidovre Hospital

In collaboration with the Danish Headache Centre, Rigshospitalet and the Danish Center for Magnetic Resonance at Hvidovre Hospital we investigated neurochemical changes related to low-grade systemic inflammation and normal cognitive ageing and related it to in vivo with proton MR spectroscopy (1H-MRS) [35]. We found that the plasma concentrations of the proinflammatory markers C-reactive protein and interleukin 8 were higher in older age groups which is consistent with inflammation. These systemic proinflammatory markers were associated with elevated 1H-MRS glia-related metabolite levels in older individuals, possibly reflecting neuroinflammation. The CRP concentrations also correlated with visuo-spatial working memory score.

Glucocorticoid treatment for non-cerebral diseases in children

Previous studies from our groups have shown that glucocorticoid treatment for non-cerebral diseases in children may lead to changes both in mental function and in brain structure. The present study is a follow up, demonstrating alterations in the microstructure of the uncinate fasciculus [60].

Hypoxia, cerebral blood flow, and metabolism

Exposure to moderate hypoxia leads to cerebral lactate production. The mechanism by which the lactate production is triggered was explored by MR in volunteers where the same degree of reduced arterial oxygen concentration was induced by inhaling hypoxic air and carbon monoxide. In both groups, cerebral blood flow increased and cerebral metabolic rate of oxygen remained unchanged, whereas lactate production only increased with inhalation of hypoxic air. These results point toward a mechanism of lactate production by upregulation of glycolysis mediated by sensing a reduced arterial oxygen pressure [61].

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 [62,63]. 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.

Cimbi database and biobank

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

Over the last 20 years, NRU has systematically acquired 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. These data have been collected along with a wide range of associated data including demographic, neuropsychological, biochemical, and genetic 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. The biobank is stored safely in the dedicated freezer-core facility in the North Wing of Rigshospitalet.

The Cimbi database and biobank represents 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 2021 a total of 21 new official requests for data access were approved and a number of papers based on data from the Cimbi database and biobank were published.

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 center is scheduled to close in 2022 and we are planning for a symposium to be held in 2023.

The 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 3 of the 4 *NeuroPharm* work packages (NP1, NP2 and NP4) is described below. Work package 3 (NP3) was completed before 2021.

NP1: Treatment outcome in major depressive disorder

By Vibe G. Frøkjær
NP1 WP-leader

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

We have collected a rich deep phenotyping dataset in a population of 100 MDD patients and examined how different markers (neuropsychology, MRI, PET, EEG, biochemistry) relate to the outcome of a standard antidepressant treatment, i.e., escitalopram. Patients have been followed across a period of 12 weeks from treatment start. Neuroimaging was repeated at week 8 in a subgroup of 40 patients with variable antidepressant response. We work now to disseminate our findings. As mentioned on page 16, Cheng Teng-Ip defended her thesis on the EEG work. We also described the hot and cold cognitive profiles in MDD prior to treatment against healthy controls; based on this, we identified three clusters of cognitive profiles (**Figure 13**), which may represent critical strata and be useful in precision medicine approaches to MDD [17]. Further we have shown that while fMRI based single parameter predictors do not seem to provide clinically relevant information to guide treatment choice [9], EEG based predictors show more promise [26,27], in particular alpha asymmetry in female patients. Many more results are described in manuscripts under preparation. In particular, we are currently evaluating to what extent prediction models of treatment outcomes can be improved by integrating baseline deep phenotyping outcomes also collaborate in consortium structures to provide cross-validation resources for findings in related cohorts. The data generated in WP1 have established NeuroPharm as a center for this type of research, and we have initiated collaborations with the COORDINATE-MDD consortium led by Dr Fu, Imperial College London (UK).

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

By Patrick Fisher
NP2 WP-leader

NP2 applies an experimental medicine strategy coupled with human functional and molecular neuroimaging to elucidate the effects of 5-HT$_{2A}$ receptor (5-HT$_{2A}$R) modulation on brain function and mood in healthy individuals. We compare psilocybin (5-HT$_{2A}$R agonist) and ketanserin (5-HT$_{2A}$R antagonist) effects on brain function to identify neural mechanisms mediating the clinical effects of psilocybin and, more broadly, to establish this comparative strategy as a pathway for delineating pharmacological effects on the brain in humans. Data collection for the three planned projects was completed in 2021!

Former NP2 PhD student, Dr. Martin Korsbak Madsen, MD, PhD, published that psilocybin acutely modulates resting-state functional connectivity in a manner that is correlated with plasma psilocin levels and the subjective intensity of the experience [38] (**Figure 14**). Research assistant Anders S. Olsen has expanded on these data, describing how psilocybin acutely modulates connectivity dynamics in the brain. Associate professor Dea Stenbæk reported associations brain 5-HT$_{2A}$R levels and the temporal and mystical effects of psilocybin administration [56]. Examining lasting effects of psilocybin on resting-state connectivity with data from the second NP2 sub-project, research assistant Drummond McCulloch, reported a decrease in executive control network connectivity [42] (**Figure 15**). Related, we have spear-headed a collaborative review of psychedelic resting-state fMRI studies to inventory the field to date and promote good practice that can facilitate future data sharing. Although data collection for NP2 will wrap up in 2022, the rich data it has generated will be the backbone for additional hypothesis testing of 5-HT$_{2A}$R modulatory effects that we look forward to sharing with you next year!

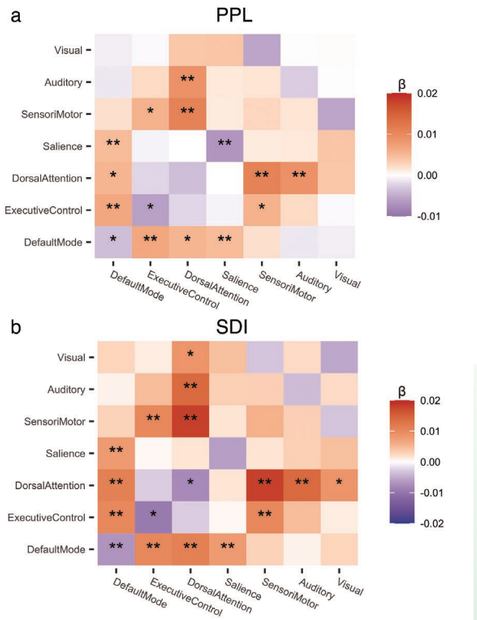


*Figure 14: Results of individual networks analysis. Correlation matrix of the association between plasma psilocin level (PPL) and functional connectivity (FC) (a) and between subjective drug intensity (SDI) and FC (b). The diagonal elements represent association within a network while the off-diagonal elements represent the between-network FC of a pair of individual networks. * p_{unc} < 0.05, ** p_{FWER} < 0.05. A graphical representation is shown of the slope estimates (β) for the correlation of region-to-region FC with PPL (67 connections) (c) and with SDI (138 connections) (d), respectively; only estimates are shown for which q_{FDR} < 0.05. Red links signify a positive association; blue signifies a negative association. Line thickness is proportional to β estimate for each analysis (within each circle). DMN=default mode network, ECN= executive control network, DAN=dorsal attention network, SAN=salience network, AN=audi- tory network, SMN=,sensorimotor network, VN=visual network. From [38], Copyright © 2021 The Authors.*

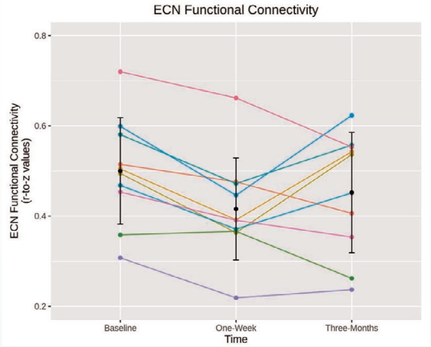


Figure 15: Executive control network (ECN) connectivity by participant. Spaghetti plot showing individual changes in mean ECN connectivity scores (y-axis) and time point (x-axis). Error bars represent mean ± standard deviation. Colours represent individual participants. ECN connectivity is significantly decreased at 1 week but not at 3 months. From [42], Copyright © The Author(s) 2021.

NP4: Bioinformatics, statistical and predictive models

By Brice Ozenne
NP4 WP-leader

Based on data collected in NP1, NP4 is combining biomarkers from several modalities, e.g., PET, MR, EEG, and cognition, to predict recovery following SSRI prescription. Several biomarkers have missing values for some patients so we are adapting existing predictive algorithms to handle missing values. Assessment of the predictive performance is carried out using repeated cross-validation plus a permutation test to assess statistical significance, as recommended in the literature. This requires substantial computation time even for simple predictions models such as logistic regression, and model comparison is not straightforward. We are therefore investigating alternative approaches to quantify uncertainty and correct optimism based on asymptotic expansions, building upon previous work done in this work package.

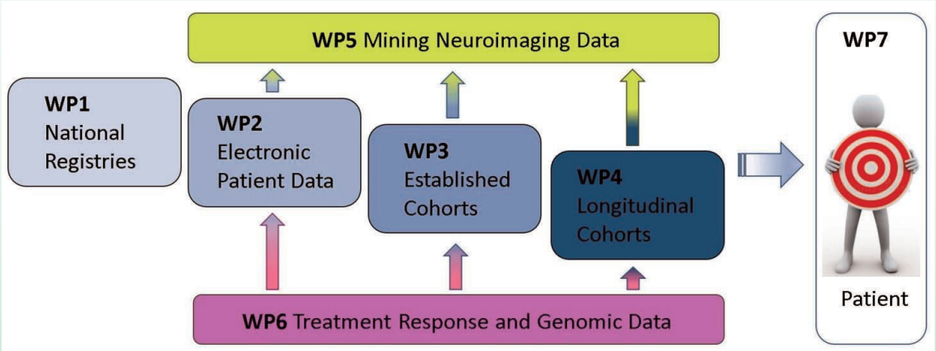
NP4 continues to assist other work packages with analysis of their data, providing or developing appropriate statistical methods. We have developed Latent Variables Models to study the effects induced by psilocybin in healthy volunteers, relating the intensity of the experience to the persistence of the psychological effects, or to relate EEG and PET signals. We currently are working on a statistical model to optimize the collection of cortisol saliva samples for estimating the cortisol awakening response.

BrainDrugs

Center director
Gitte Moos Knudsen

The strategic research alliance *BrainDrugs*, initiated in 2019, 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. The vision is that in the long run, *BrainDrugs* will serve as a model to be implemented internationally, and for other brain disorders.

The alliance builds on strong cross-disciplinary research environments within universities and hospitals in Denmark and by partners from Lausanne University Hospital, Switzerland and VU University Medical Center in Amsterdam, the Netherlands. The involved Danish institutions span several different departments at Copenhagen University Hospital, Rigshospitalet, Univ. Copenhagen, Aarhus University Hospital, and Aarhus University, as well as the Filadelfia Epilepsy Hospital and three different mental health centers from the Capital Region of Denmark: Psychiatric Center Copenhagen, Psychiatric Center Glostrup, and Mental Health Center Sct. Hans. The project consists of seven coherent work packages, as depicted in the diagram below.



In January, we initiated the BrainDrugs Early Career Forum (ECF) with the aim of further strengthening the coherence between BrainDrugs young scientists, e.g, post docs, PhD students and master students directly involved in data collection and analysis of BrainDrugs projects. The ECF has become a valuable inspiration for all participants for ways to improve or complement their own research and it also ensures maximal synergy between the work packages and campuses. In June we hosted the second *BrainDrugs* annual meeting which was a very productive full 1-day meeting where the status of the various work packages was presented and diligently discussed. While 15-20 people attended online, we managed to gather more than 40 people physically at Comwell Borupgaard outside Copenhagen, for many the first physical meeting since the beginning of the pandemic. Apart from the scientific discussions, the physical meeting was also an excellent opportunity for informal social interactions.

WP1-leader: Professor Lars V. Kessing

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.

WP1 has a component in Copenhagen lead by professor Lars V. Kessing and a component in Aarhus lead by professor Jakob Christensen. Involved in the project in 2021 have in Copenhagen been

assistant professor Helene Charlotte Wiese Rytgaard and PhD student Simon Christoffer Ziersen and in Aarhus, senior researcher Julie Werenberg Dreier and PhD student Eva Bølling-Ladegaard.

WP1 published a nation-wide population-based longitudinal register linkage study investigating long-term response to antidepressants in patients with depression with and without comorbid epilepsy [10.1016/j.jad.2021.11.046]. We found that the response to antidepressants was decreased in patients with comorbid epilepsy versus without comorbid epilepsy at all time points during a ten-year follow-up period. The study highlights the need for closely clinical monitoring and psychological support for patients with depression and comorbid epilepsy and emphasize the need for further long-term studies of effect of interventions.

WP2-leaders: Professors Søren Brunak & Anders Søgaard

WP2: Electronic patient data: Text mining and machine learning

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

We have now EPRs available for ~25,000 patients diagnosed with epilepsy in 2006-16 from the Capital Region of Denmark and Region Zealand. We are in the process of validating both the diagnosis of epilepsy and the subtype (generalized versus focal epilepsy) as given in the national patient registry (NPR) using text mining methods of EPRs. We have in 2021 created temporal disease trajectories for patients diagnosed with epilepsy in the NPR to showcase diseases that appear significantly more before and after the epilepsy diagnosis. We will stratify these disease trajectories by including text mined symptoms in the trajectories and thereby create disease-symptom-disease trajectories.

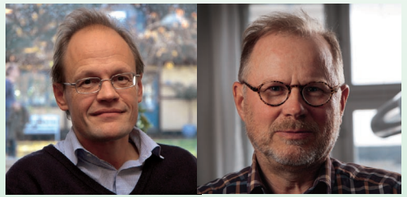
The application to receive EPRs from Filadelfia has been ethically approved and in 2021 we have finally received a list of CPR numbers for patients diagnosed with epilepsy from the Health Data Authority, which we will use together with Filadelfia to extract the relevant EPRs. Furthermore, we have received Health Data Authority approval to link the Filadelfia EPR data with NPR and the prescription registry data.

WP3. Deep phenotyping data from established research cohorts

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

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

Permissions to work with "deep phenotyping" data from the Cimbi Database and the NEAD database in combination with data from relevant national registers have been in place since 2020. Access to the National Health Register at Statistics Denmark has previously been granted, and in 2021 we succeeded in obtaining the approval to also use data from the drug prescription register. Many efforts have been spent on creating relevant data sheets for Statistics Denmark with Cimbi and NEAD data to be combined with register-based outputs, and these were submitted in Dec 2021. Also in 2021, data analyses and preparation of manuscript for the studies that are independent of the register outputs but rely on clinical follow-up have been undertaken.



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

WP4. Deep phenotyping data from new research cohorts

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

In 2021, we obtained ethics approval for conduction of both the epilepsy and the depression component of the work package, and patient recruitment and data acquisition was started. For the depression part, a trial paper was prepared and

submitted for publication. In the epilepsy part we have tested and implemented new protocols for the future MRI, PET and HD-EEG experiments. In addition, we have implemented new software for future data analysis in WP4, and tested specific aspects of EEG connectivity and MRI morphology in patients previously enrolled in the epilepsy surgery programme.

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

WP5. Mining neuroimaging data

The aim of WP5 is to implement new tools to facilitate regulated access to the large volume of neuroimaging data from routine clinical care which are 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.

We have in 2021 worked on several projects on both epilepsy and MDD. Firstly, we have in Philip Fink-Jensen's Master's project evaluated the volumetric differences in the brain in drug-resistant temporal lobe epilepsy patients prior to epilepsy surgery and compared patients who after surgery get a depression to those who do not. We have also evaluated brain volumetric differences in MDD versus healthy controls and MDD patients and the ENIGMA studies and the brain region-wise differences between drug treatment responders and remitters to determine if MRI volumetric features can predict treatment response.

We have now ethics approval to get access to neuroradiology reports and MRI images from several thousand epileptic patients in Denmark. Based on these data we will first establish a text-mining model that can automatically label the reports as MR positive or MR negative and identify the relevant abnormal features and then we will establish a deep learning model which is able to identify in the MR images structural abnormalities relevant to epilepsy. We have also explored deep learning methods in natural language processing (NLP) to automatically label radiology reports and corresponding structural MRI.

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.

WP6-leader: Professor Thomas Werge

WP7. Implementation in the clinic

The work in this WP will be initiated at the end of the 5-year grant period.

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

Positions of Trust

Professor Gitte Moos Knudsen:

President of European College of Neuropsychopharmacology (ECNP), chair of the Scientific Advisory Board for The Human Brain Project, Member of the Brain Prize Council, board member of the Elsass Foundation, and member of the Scientific Advisory Board of the Kristian G. Jebsen Foundation, Norway, of the Presidential Commission for the Max Planck Institute for psychiatry, Munich, 2019-21, and of the Hospital del Mar Medical Research Institute Foundation, Barcelona, Catalonia. Representing Professor for Neurology at Univ. Copenhagen. Field Editor at the International Journal of Neuropsychopharmacology. Honorary professor at University of Vienna, Austria. In 2021, reviewer for the Swiss National Science Foundation, and expert evaluator of a professorships at Uppsala University.

Professor Olaf B. Paulson:

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

Professor Jens D. Mikkelsen:

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

Associate professor Lars Pinborg:

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

Associate professor Vibe G. Frøkjær:

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

ecnp Neuroscience applied

For the science and treatment of disorders of the brain

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

Professor Gitte Moos Knudsen is president of ECNP in the period 2019-22.

Every year, NRU receives interns through the ECNP visiting scientists' program. NRU is involved in several of the ECNP Networks and in 2021, twenty NRU scientists were represented at the annual congress in Lisbon.

Dissemination in 2021

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

Since the beginning of 2021 NRU has published a total of 2 PhD dissertations, 14 Master's or Bachelor theses and reports, 2 book chapters, 2 multicenter studies without co-authorship and 67 scientific peer-reviewed papers, 2 preprints and 1 conference paper. All papers that have been printed or put online ahead of print during 2021 are included.

PhD dissertations

- Cheng-Teng Ip. Towards personalized medicine: Effectiveness of pretreatment EEG biomarker in Major Depressive Disorder. University of Copenhagen, Faculty of Health and Medical Sciences. Defended Jan 29, 2021
- Giske Opheim. Utilizing 7 Tesla MRI and automated segmentation– A new era in the presurgical evaluation of patients with severe epilepsy. University of Copenhagen, Faculty of Health and Medical Sciences. Defended Feb 5, 2021.

Master's and Bachelor theses and reports

The following list of NRU-affiliated students have successfully defended their theses or research year reports during 2021:

- Anders Stevnhoved Olsen - *Quantication of sleep states using dynamical modeling of functional neuroimaging data*. Master's thesis in science in engineering, biomedical engineering, Technical University of Denmark
- Cecilie Aston Poulsen - *Systematisk evaluering af skanningstid i forbindelse med [123I]FP-CIT DAT-skanning med ANYSCAN Trio SPECT-CT med hjernededikeret MPH-kollimator*. Bachelor's thesis in biomedical laboratory science, University College Copenhagen
- Clara Madsen – *Effects of in utero exposure to isoflurane on the levels of synaptic vesicle glycoprotein 2A (SV2A) in the developing rat spinal cord*. Master's thesis in molecular biomedicine, University of Copenhagen
- Frederik Gudmundsen - *Whole Brain Circuit Dissection. A promising avenue for understanding the pathophysiology of OCD*. Master's thesis in Neurobiology, Neuroscience & Neuroimaging. University of Chinese Academy of Sciences
- Gunild Vulpius – *Serotonin 4 receptor brain binding is positively associated with the cortisol awakening response in untreated patients with Major Depressive Disorder: A Neuropharm 1 study*. Master's thesis in medicine, University of Copenhagen
- Harald Arnaud Gangneron Schiønning – *Psilocybin-induced changes in functional brain network structure*. Master's thesis in medicine, University of Copenhagen
- Laura Fonnesbech-Sandberg - *The association between estradiol change and mental well-being in the peripartum period*. Master's thesis in medicine, University of Copenhagen
- Lea Lydolph Larsen - *Changes in the levels of synaptic vesicle glycoprotein 2A (SV2A) during development of the spinal cord in rats*. Master's thesis in biotechnology, University of Copenhagen
- Liis Kivistik – *Evaluating task- and resting-state functional connectivity differences in major depressive disorder and prediction of antidepressant treatment response*. Master's thesis in Bioinformatics, University of Copenhagen
- Malthe Scharff - *Does psilocin bind to the 5-HT$_7$ receptor? The effect of intermittent microdoses of psilocybin on 5-HT$_7$ receptor levels, and the role of 5-HT$_7$ in psilocin induced synaptic plasticity*, Master's thesis in biochemistry, University of Copenhagen
- Oliver Overgaard-Hansen - *Clinical treatment with psychedelic substances: a systematic review*. Bachelor's thesis in psychology, Southern University of Denmark
- Philip Fink-Jensen - *Orbitofrontal Cortical thickness is reduced in drug-resistant temporal lobe epilepsy patients and precedes the onset of depression in patients undergoing temporal lobe surgery*. Master's thesis in medicine, University of Copenhagen
- Sophia K. Weber - *Sexual function in patients with Major Depressive Disorder before and after treatment with Selective Serotonin Reuptake Inhibitor*. Master's thesis in psychology, Southern University of Denmark
- Stine Truel Mørup - *Synaptic vesicle glycoprotein 2A (SV2A) binding in major depressive disorder with and without psychotic symptoms and the potential of physical activity on synaptic density*. Master's thesis in human physiology, University of Copenhagen.

Book chapters

B1. Gade A, Knudsen GM. Metaboliske, endokrine og andre systemiske sygdomme. In: Gade A, Gerlach C, Starrfelt R, Pedersen PM (eds). Klinisk neuropsykologi. 2. udgave. København: Frydenlund Academic, 2021:379-390

B2. Knudsen G.M., Hasselbalch S.G. (2021) Imaging of the Serotonin System: Radiotracers and Applications in Memory Disorders. In: Dierckx R.A., Otte A., de Vries E.F., van Waarde A., Lammertsma A.A. (eds) PET and SPECT of Neurobiological Systems. Springer, Cham. https://doi.org/10.1007/978-3-030-53176-8_25.

Multicenter studies without co-authorship

M1. Gau R, Noble S, Heuer K, Bottenhorn KL, Bilgin IP, Yang YF, Huntenburg JM, Bayer JMM, Bethlehem RAI, Rhoads SA, Vogelbacher C, Borghesani V, Levitis E, Wang HT, Van Den Bossche S, Kobeleva X, Legarreta JH, Guay S, Atay SM, Varoquaux GP, Huijser DC, Sandström MS, Herholz P, Nastase SA, Badhwar A, Dumas G, Schwab S, Moia S, Dayan M, Bassil Y, Brooks PP, Mancini M, Shine JM, O'Connor D, Xie X, Poggiali D, Friedrich P, Heinsfeld AS, Riedl L, Toro R, Caballero-Gaudes C, Eklund A, Garner KG, Nolan CR, Demeter DV, Barrios FA, Merchant JS, McDevitt EA, Oostenveld R, Craddock RC, Rokem A, Doyle A, Ghosh SS, Nikolaidis A, Stanley OW, Uruñuela E; Brainhack Community. Brainhack: Developing a culture of open, inclusive, community-driven neuroscience. Neuron. 2021 Jun 2;109(11):1769-1775

M2. Veronese M, Rizzo G, Belzunce M, Schubert J, Searle G, Whittington A, Mansur A, Dunn J, Reader A, Gunn RN; Grand Challenge Participants#. Reproducibility of findings in modern PET neuroimaging: insight from the NRM2018 grand challenge. J Cereb Blood Flow Metab. 2021 Oct;41(10):2778-2796.

Papers in peer-reviewed journals

1. Alwassil OI, Khatri S, Schulte MK, Aripaka SS, Mikkelsen JD, Dukat M. N1H- and N1-Substituted Phenylguanidines as α7 Nicotinic Acetylcholine (nACh) Receptor Antagonists: Structure-Activity Relationship Studies. ACS Chem Neurosci. 2021 Jun 16;12(12):2194-2201
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Conference papers

Delorme A, Truong D, Martinez-Cancino R, Pernet C, Sivagnanam S, Yoshimoto K, Poldrack R, Majumdar A, Makeig S. Tools for Importing and Evaluating BIDS-EEG Formatted Data. 2021 10th International IEEE/EMBS Conference on Neural Engineering (NER), 2021, pp. 210-213, https://doi.org/10.1109/NER49283.2021.9441399.

Public lectures

June 18, 2021, Bloom festival, Søndermarken, Gitte Moos Knudsen og Niels Lyngsøe: Ti dages stilhed: Et essay om meditation og bevidsthed"

Jul 4, 2021, Science and Cocktails, Danish Radio Concert Hall, Vibe G Frøkjær: "Female sex hormones, brain function and mental health: How sex hormones shape our brain"

Sept 24, 2021, DOC1, Aarhus, Gitte Moos Knudsen and Dea Siggaard Stenbæk: Folkeuniversitetet: "Hjernen på psykedeliske stoffer"

Oct 25, 2021, København, Gitte Moos Knudsen and Dea Siggaard Stenbæk: Folkeuniversitetet: "Hjernen på psykedeliske stoffer".

Media attention

Jan 29, 2021: Zetland article about being test person in a psilocybin experiment at NRU:
https://www.zetland.dk/historie/s85E7EdR-ae2EpyRR-b0972

Mar 26, 2021: Gitte Moos Knudsen in "Klar Vikar på 4'eren" on Danish Radio P4 about the importance of cultural life for the brain

April 17, 2021: Gitte Moos Knudsen in Berlingske about "Vi prøvede en app, der angiveligt giver halvpsykedeliske oplevelser og sender dig på underbevidst opdagelsesrejse. Her er, hvad vi fandt ud af":
https://www.berlingske.dk/kultur/vi-proevede-en-app-der-angiveligt-giver-halvpsykedeliske-oplevelser-og

Jun 17, 2021: Gitte Moos Knudsen in "Kulturen" on Danish Radio P1 about how culture and science merge on the annual Bloom Under the Oak Festival

Jun 18, 2021: Gitte Moos Knudsen in Kristeligt Dagblad about "Den lyse tid giver lykke – hvis vi får vores søvn":
https://www.kristeligt-dagblad.dk/danmark/den-lyse-tid-giver-lykke-hvis-vi-faar-vores-soevn

Jun 18-20, 2021: Gitte Moos Knudsen in Bloom video on "Hjernen på svampe":
https://www.bloom.ooo/explore/hjernen-p%C3%A5-svampe-gitte-moos-knudsen

Jun 18-20, 2021: Gitte Moos Knudsen in the Bloom interview "Ti dages stilhed":
https://www.bloom.ooo/explore/ti-dages-stilhed-niels-lyngs%C3%B8-og-gitte-moos-knudsen

Jun 25, 2021: Vibe G. Frøkjær in "Sygt Nok" on Danish Radio P1:
https://www.dr.dk/lyd/p1/sygt-nok/sygt-nok-2021-06-25

Aug 26, 2021: Lars Pinborg in Sundhedspolitisk Tidsskrift about "Flere og flere opereres for epilepsi":
https://sundhedspolitisktidsskrift.dk/nyheder/5095-rigshospitalet-og-ouh-nedbringer-tiden-til-rette-epilepsibehandling.html

Oct 1, 2021: Gitte Moos Knudsen in Jyllands-Posten about "Musik er et vidunder-værktøj, når forskerne skal undersøge hjernen":
https://jyllands-posten.dk/nyviden/ECE13330692/musik-er-et-vidundervaerktoej-naar-forskerne-skal-undersoege-hjernen/

Oct 4, 2021: Dea Siggaard Stenbæk in ECNP congress news release, which subsequently received some reasonable international news coverage, including in Yahoo News:
Magic mushroom" anti-depressive psychedelic affects perception of music.

Oct 6, 2021: Interview with Dea Siggaard Stenbæk for Inverse:
Psychedelic therapy can work better if this element is in the mix.

Oct 13, 2021: Gitte Moos Knudsen and Dea Siggaard Stenbæk in the digital news media Vig&Sans:
https://vidogsans.dk/svampetrip-kan-blive-fremtidens-antidepressiver/

Nov 5, 2021: Gitte Moos Knudsen in Kristeligt Dagblad about " Psykedeliske stoffer kan være en vej til et sundt sind":
https://www.kristeligt-dagblad.dk/debat/psykedeliske-stoffer-kan-vaere-en-vej-til-et-sundt-sind

Nov 25, 2021: Martin Korsbak Madsen in Frederiksborg Amts Avis and Nordjyske Stiftstidende Aalborg about "Hjerneforskere sender patienter på syretrip":
https://avisendanmark.dk/artikel/hjerneforskere-sender-patienter-p%C3%A5-syretrip

Dec 18, 2021: Gitte Moos Knudsen in Universet Udenom about "Falling in love":
https://xn--videnskabsr22-yfb.dk/2021/december/18/.

Dec 20, 2021: Gitte Moos Knudsen in Universet Udenom about "Oxygen":
https://xn--videnskabsr22-yfb.dk/2021/december/20/.

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