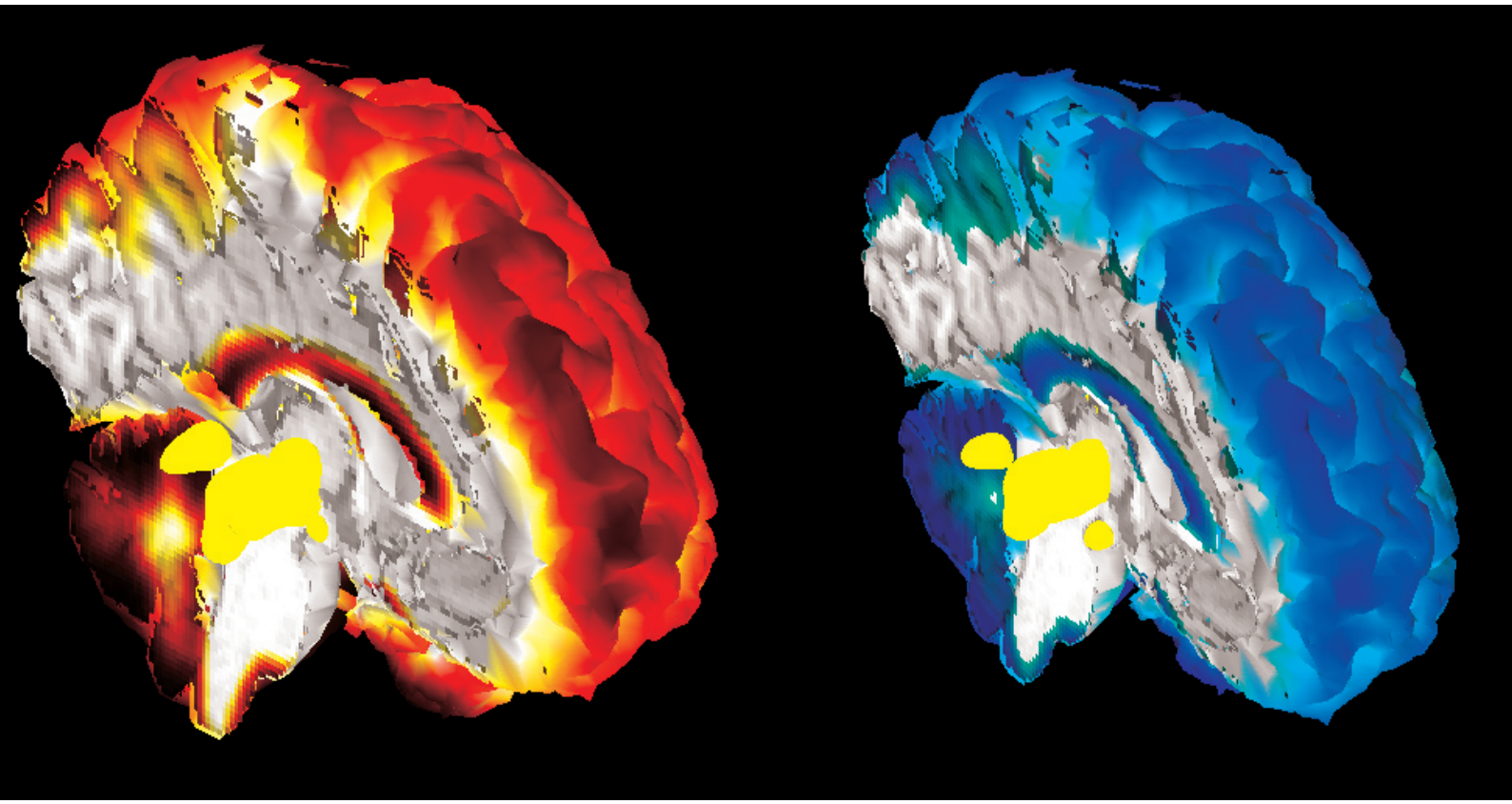
Neurobiology Research Unit

Dept. Neurology, Neuroscience Centre
Copenhagen University Hospital, Rigshospitalet

www.nru.dk

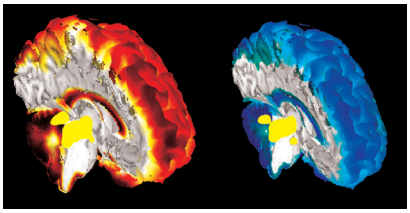
Annual Report 2016



Cimbi
Center for integrated molecular brain imaging

Innovation Fund Denmark
NeuroPharm
Center for Experimental Medicine Neuropharmacology

COGNITO
Det Strategiske Forskningsråd



[11C]DASB PET brain images of the serotonin transporter in a patient with seasonal affective disorder (SAD) from summer (left, warm colour scale) and winter (right, cold colour scale). The images illustrate the upregulation serotonin transporters in the winter. Courtesy of Brenda Mc Mahon.

Preface

Dear reader,

I am proud to present you with the 2016 annual report describing the activities of the Neurobiology Research Unit (NRU). I would like to take this opportunity to acknowledge and thank all of the NRU staff for their dedicated work as well as to thank our host institution, Rigshospitalet, and all our highly valued national and international collaborators and the funding agencies that support our work. These have all been essential factors to ensure that 2016 was another very successful year for NRU.

The past year has again been a year with substantial research output from the group. NRU-affiliated researchers have presented their work at a high number of international congresses, conferences, and meetings, and in total the group has published 47 peer-reviewed scientific publications and several book chapters. The full 2016 publication list can be found on page 30.

With respect to research training, we have in 2016 organized both pre- and post-graduate programmes with international speakers and well-attended programs. In terms of pregraduate training, one of our medical students defended his bachelor project and four of our medical research year students graduated after defending their research year reports (and Master's theses). Also, four of our non-medical students obtained their degree after a successful defence of their Master's theses in biochemistry and biomedical engineering, respectively. Further, three psychology students have been trained in internships at NRU, and we have hosted four FENS and YITP students in connection with the FENS meeting in Copenhagen in July 2016 as well as one ECNP research intern. In terms of postgraduate training in 2016, NRU senior staff members have supervised more than 20 national and international PhD students and post docs, and two courses were organized by NRU. This year, professor Olaf B. Paulson describes (on page 27) his 5-year teaching experience at The Sino-Danish Center for Education and Research where he and other NRU-staff members have taken part in the establishment and subsequent lecturing at the Master degree program 'Neuroscience and Neuroimaging' at the University of Chinese Academy of Sciences in Beijing.

2016 has indeed also been special in terms of anniversaries. In September, we first celebrated NRU project nurse Minna Litman's personal 25-year anniversary at Rigshospitalet with a reception and a week later the whole research unit's 20-year anniversary with a half-day event. The NRU 20-year anniversary was celebrated with a symposium with interesting talks from former and present NRU employees as well as with a celebration dinner in the restaurant of Sailing Club Sundet. Last but not least, in December we had the privilege to celebrate with a reception NRU founder professor Olaf B. Paulson's personal 40-year anniversary as consultant at Rigshospitalet.

The Center for Experimental Medicine Neuropharmacology (NeuroPharm), funded by the Innovation Fund Denmark has initiated its research projects. NRU is the coordinating partner in the Center and we collaborate with national partners from the University of Copenhagen, from university hospitals in the Capital Region of Denmark and from H. Lundbeck A/S as well as international partners from Massachusetts General Hospital, Imperial College London and the British-based small-medium sized enterprise Imanova Ltd. You can read more about NeuroPharm on page 22.

The funding period for the Center for Integrated Molecular Brain Imaging (Cimbi) is close to conclusion, but Cimbi continues to develop radioligands and the name of Cimbi will still be associated with the Cimbi Database and Biobank. A short summary of the 2016 research activities carried out in Cimbi is given on page 25.

Professor Jens D. Mikkelsen continued as part-time employee at NRU and as a leader of the Danish Strategic Research Council project COGNITO, described separately on page 24.

I hope that you will enjoy reading this 2016 annual report and encourage interested readers to stay tuned on our website (www.nru.dk).

On behalf of the NRU management group

Gitte Moos Knudsen
Professor, Head of Department

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About Neurobiology Research Unit

Mission & Activities

The mission of NRU is to conduct translational neuroscience research on brain neurotransmission at an internationally competitive level with the aim to promote preventive, diagnostic and therapeutic advances. We make use of behavioural in vivo molecular, structural, and functional brain imaging to uncover disease mechanisms and risk correlates as well as to determine drug effects. Also, 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 from cells and animals into healthy volunteers and patients as early as possible.

The activities within NRU fall in nine different categories:

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

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

NRU is a major training site for pre- and postgraduate students. We aim to attract physicians and people with other relevant educations to the neuroscience field and to educate and train research staff, in particular medical students, graduate students, PhD students and post docs. We organize PhD courses and regular meetings and seminars where the pre- and postgraduate students are expected to present their work.

Relative to the number of staff members NRU has an outstanding scientific output. 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. Together with the "Science Theatre", we have for more than a decade arranged a 2-hour session related to brain disorders. We also contribute with articles in popular journals, give public lectures, and participate in interviews for newspapers and TV.

Facilities

NRU has four separate locations on Rigshospitalet, Blegdamsvej, and has access to scanning facilities at additional three sites at the hospital.

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

The Rockefeller has since August 2013 been housing NRU on the 3rd floor.

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

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

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

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 MR-PET scanner facilities. NRU also uses MR-scanner facilities at the Department of Diagnostic Radiology, in close collaboration with the staff there.

About Neurobiology Research Unit

Staff in 2016

Head
Gitte Moos Knudsen, professor, MD, DMSc

Senior Researchers
Claus Svarer, chief engineer, PhD
Henrik B. Hansen, neuropharmacologist, PhD
Jens D. Mikkelsen, professor, MD, DMSc
Lars Pinborg, associate professor, MD, DMSc (half time at the Epilepsy Clinic, RH)
Olaf B. Paulson, professor, MD, DMSc
Patrick Fisher, neuroscientist, PhD
Vibe G. Frøkjær, MD, PhD (half time at Psychiatric Center Copenhagen)

Chief Technologist
Gerda Thomsen

Administration
Birgit Tang
Dorthe Givard
Peter S. Jensen

Junior group leaders (post docs)
Agnete Overgaard, human biologist, PhD
Hanne D. Hansen, molecular biologist, PhD
Mikael Palner, engineer, PhD

Post Docs
Brice Ozenne, biostatistician, PhD (half time at Section of Biostatistics, Univ. Copenhagen)
Dea S. Stenbæk, psychologist
Ling Feng, engineer, PhD
Melanie Ganz-Benjaminsen, computer scientist, PhD
* Sebastian Camillo Holst, engineer, PhD
* Stefanie Eriksson, MRI phycisist, PhD

PhD Students
Brenda Mc Mahon, MD
Cheng Teng Ip, psychologist (H. Lundbeck A/S)
Henrik Steglich-Arnholm, MD (Rigshospitalet-Glostrup)
Jo Henningsen, biochemist
* Kristin Forsberg, MD (Psychiatric Center Copenhagen)
Lene L. Donovan, Medicine with Industrial Specialization
Liv V. H. Brüel, psychologist
Louise M. Jørgensen, MD
Marie Deen Christensen, MD (Rigshospitalet-Glostrup)
* Martin Korsbak Madsen, MD
Martin Nørgaard, engineer
Mette T. Foged, MD
Per Jensen, MD
Sofi da Cunha-Bang, MD
Vincent Beliveau, neuroscientist

Research Assistants
Agnete Dyssegaard, pharmacist
* Camilla Borgsted Larsen, MD
* Shizhong Li, biologist, PhD
Vibeke N. H. Dam, psychology

Technical Research Personnel
* Daniel Burmester, MRI student assistant
Gunild Vulpius, MRI student assistant
Josephine Torp, HPLC student assistant
Lone I. Freyr, project nurse
Louise Nielsen, medical technologist
Minna Litman, research nurse
Stine Andersen, HPLC student assistant
Svitlana Olsen, medical technologist
* Søren Rønborg, MRI student assistant
Victor F. Hansen, IT-support

Visiting Scientists
Dan Peters, PhD, CEO at DanPET, Sweden
Leif Østergaard, professor, Århus, DK
Ulrich Lindberg, engineer, PhD, Glostrup, DK

Pregraduate Researchers and Students
* Adam Omari, medicine
* Agata Casado Sainz, molecular biomedicine
* Alexander Stark, medicine
* Anne-Sofie Thaulov Schneider, psychology
Annette Johansen, medicine
* Anna Maria Florescu, medicine
* Beatriche Henriksen, biomedicine
* Björg Vigfusdottir, engineer
Charlotte B. Mikkelsen, engineer
* Christa Koll Thystrup, psychology
Claudia G.K. Rasmussen, biochemistry
* Elizabeth Britt Landman, medicine
Emil Holm, medicine
Erik Perfalk, medicine
* Giske Opheim, neuroscience and neuroimaging (SDC student)
* Johan Skov Bundgaard, medicine
Jonas Villadsen, molecular biomedicine
* Katarzyna Chamera, biochemistry (ECNP intern)
* Keenie Ayla Andersen, engineer
* Kimberly Anne Go, psychology
Lars V. Knudsen, medicine
* Line Brogaard Pedersen, pharmacy
* Maja Højvang Sørensen, biochemistry
* Michelle Fussing Tengberg, engineer
Nanna Hansen, psychology
* Nimet Ocak, medical technologist
* Nizar Hamrouni, medicine
* Rana Al-Tayar, engineer
* Sana Ahmed, engineer
* Sara Kristiansen, psychology
* Siv Thorlund Peitersen, biology
* Sebastian Elgaard Ebert, medicine
* Simone Bærentzen, human biology
Sofie T. Pedersen, medicine
Terje Martens, medicine

All new faces in 2016 are marked with a *.

Positions of Trust

Gitte Moos Knudsen:

Chairman for the steering group for research laboratories at Rigshospitalet; Scientific Advisory Board Member of the Kristian Jebsen Foundation; Vice-president of the European College of Neuropsychopharmacology (ECNP); Field Editor at the International Journal of Neuropsychopharmacology; Board of Directors of the Brain Prize and of The Elsass Foundation.

Olaf B. Paulson:

Auditor for Danish Society for Neuroscience; Referee for several international journals; Member of the Research Ethical Committee of the Capital Region of Denmark.

Jens D. Mikkelsen:

Member of the Danish Medical Research Council for Health and Disease; Member of the chairman committee for external evaluations of medical educations in Denmark; Member of the Academy for Technical Sciences; regularly expert panel scientist for the EU commission, Brussels.

Vibe G. Frøkjær:

Member of The Young Academy of The Royal Society for Science and Letters.

About Neurobiology Research Unit

Some new NRU faces

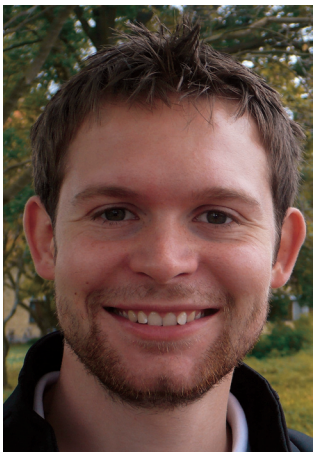
Post Doctoral Fellow

Sebastian Holst
Engineer, PhD

After completing a master degree in biomedical engineering from DTU and the University of Copenhagen in 2009, I moved to Switzerland to do a PhD in human neuroscience and sleep research at the University of Zurich. The main aim was to examine molecular underpinnings of human sleep need. To do so, I challenged sleep homeostasis by keeping volunteers awake for 2 days, while at the same time used pharmacological interventions such as caffeine, modafinil and tolcapone to modulate sleep drive.

In 2014 after having defended my PhD, I continued as a postdoc still investigating the biology of sleep. I ran a combined magnetic resonance spectroscopy (MRS) and PET sleep deprivation study, designed to measure molecular changes in the brain as a consequence of sleep loss.

It is with this experience that I in 2016 joined NRU, to setup and run a new MR study with Prof. Gitte Moos Knudsen in collaboration with Prof. Maiken Nedergaard from University of Copenhagen and Prof. Poul Jennum from Rigshospitalet-Glostrup. The study will investigate, manipulate and describe so called 'glymphatic flow' in humans, a mechanism proposed to clean the brain from metabolic waste products while we sleep. The project, which has received funding from the Lundbeck Foundation, aims to describe one of the remaining mysteries of science: Why we sleep, and whether sleep can be enhanced.



PhD student

Martin Korsbak Madsen
MD

I began my research career at NRU in 2011 as a pregraduate research year student under the supervision of Prof. Gitte Moos Knudsen and Dr. Patrick Fisher. Since then I have worked with different aspects of magnetic resonance imaging (MRI) of the human brain, including neural pathways associated with risk factors for affective disorders.

After graduating as a medical doctor from the University of Copenhagen in the summer of 2016, I joined the NRU as a PhD student in October 2016, again with Prof. Knudsen and Dr. Fisher as supervisors. My PhD project is an evaluation of the serotonin 2A receptor and its effects on brain function. We are combining pharmacological manipulation of the receptor with PET and functional MRI neuroimaging to evaluate the role of the receptor system in brain function and mood in healthy individuals. One of the pharmacological agents we are using is psilocybin, the active compound of magic mushrooms. It is currently the focus of intense scientific interest due to its beneficial effects in clinical populations and its profound effects on consciousness. This exciting multimodal neuroimaging project will provide important information about human serotonin 2A receptor neurobiology and may also indicate whether multimodal neuroimaging may be beneficial to novel drug development. My PhD project is an integral part of work package 2 in the NeuroPharm project (described on page 22).

NRU PhD degrees

Brenda Mc Mahon
Medical Doctor

In April 2016, Brenda Mc Mahon defended her PhD thesis entitled "Seasonal changes in cerebral serotonin transporter binding in individuals with or resilient to Seasonal Affective Disorder". Brenda graduates from the Faculty of Health and Medical Sciences at University of Copenhagen.

Supervisor:
Gitte Moos Knudsen, MD, DMSc, Professor, NRU, Department of Neurology, Copenhagen University Hospital, Rigshospitalet

Evaluation committee:
Professor Poul Videbech (chair), Glostrup Psychiatric Center and Faculty of Health and Medical Sciences,
University of Copenhagen, Denmark

Professor David J Brooks, Institute of Clinical Medicine, Department of Nuclear Medicine, Aarhus University Hospital, Aarhus, Denmark

Professor Nicole Praschak-Rieder, Department of Psychiatry and Psychotherapy, Medical University of Vienna, Vienna, Austria

Dea Siggaard Stenbæk
Psychologist

In January 2016, Dea Siggaard Stenbæk defended her PhD thesis entitled "*Sex steroid hormone manipulations and serotonergic neurotransmission in relation to verbal affective memory recall, simple reaction time, and mental distress*". Dea graduates from the Faculty of Health and Medical Sciences at University of Copenhagen.

Project supervisors:
Steen Gregers Hasselbalch (main supervisor), MD, DMSc, Professor, NRU and Danish Dementia Research Centre, Department of Neurology, Copenhagen University Hospital, Rigshospitalet

Vibe Gedsø Frøkjær, MD, PhD, Senior researcher, NRU, Department of Neurology, Copenhagen University Hospital, Rigshospitalet

Gitte Moos Knudsen, MD, DMSc, Professor, NRU, Department of Neurology, Copenhagen University Hospital, Rigshospitalet

Evaluation committee:
Lone Schmidt (chair), DMSc, PhD, Associate professor, Department of Public Health, University of Copenhagen, Denmark

Inger Sundström Poromaa, MD, PhD, Professor, Department of Women's and Children's Health, Uppsala University, Sweden

Rebecca Elliott, PhD, Senior research fellow in Cognitive Neuroscience, Institute of Brain, Behaviour and Mental Health, Manchester University, UK

Jo Beldring Henningsen
Biochemist

In May 2016, Jo Beldring Henningsen defended her PhD thesis entitled "*The roles of RFRP in the central control of reproduction: photoperiodic and sex-specific differences*". Jo graduates from the Faculty of Life Sciences, University of Strasbourg, France.

Principal supervisor:
Professor François Gauer, Dean of the Life Sciences Faculty, Neurobiology of Rhythms, Institute of Cellular and Integrative Neurosciences, University of Strasbourg, France.

Evaluation committee:
Dr. Frédéric Simonin, GPCRs, Pain and Inflammation, Department of Receptors, Membrane proteins and
Therapeutic innovation, University of Strasbourg, France

Professor Manuel Tena-Sempere, Department of Cellular Biology, Physiology and Immunology, University of Córdoba, Spain

Dr. Massimiliano Beltramo, Physiology of Reproduction and Behaviors, French National Institute for Agricultural Research, Nouzilly, France

Sofi da Cunha-Bang
Medical Doctor

In July 2016, Sofi da Cunha-Bang defended her PhD thesis entitled "*Multimodal Neuroimaging of Aggression in Violent Offenders*". Sofi graduates from the Faculty of Health and Medical Sciences at University of Copenhagen.

Principal supervisor:
Gitte Moos Knudsen, MD, DMSc, Professor, NRU, Department of Neurology, Copenhagen University Hospital, Rigshospitalet

Evaluation committee:
Professor Steen G. Hasselbalch (chair), MD, DMSc. Department of Clinical Medicine, University of Copenhagen, Denmark

Professor Jeffrey Meyer, MD, PhD, Research Imaging Centre, Centre for Addiction and Mental Health, Toronto, Canada

Professor Ulrike M. Krämer, Dr.rer.nat., PhD, Department of Neurology, University of Lübeck, Germany

Research at NRU

Experimental Neurobiology

Experimental neurobiological research is conducted at the Neurobiology Research Unit. Several researchers are working on research projects to study mechanisms in vitro and in vivo. Below are examples of three of these ongoing projects.

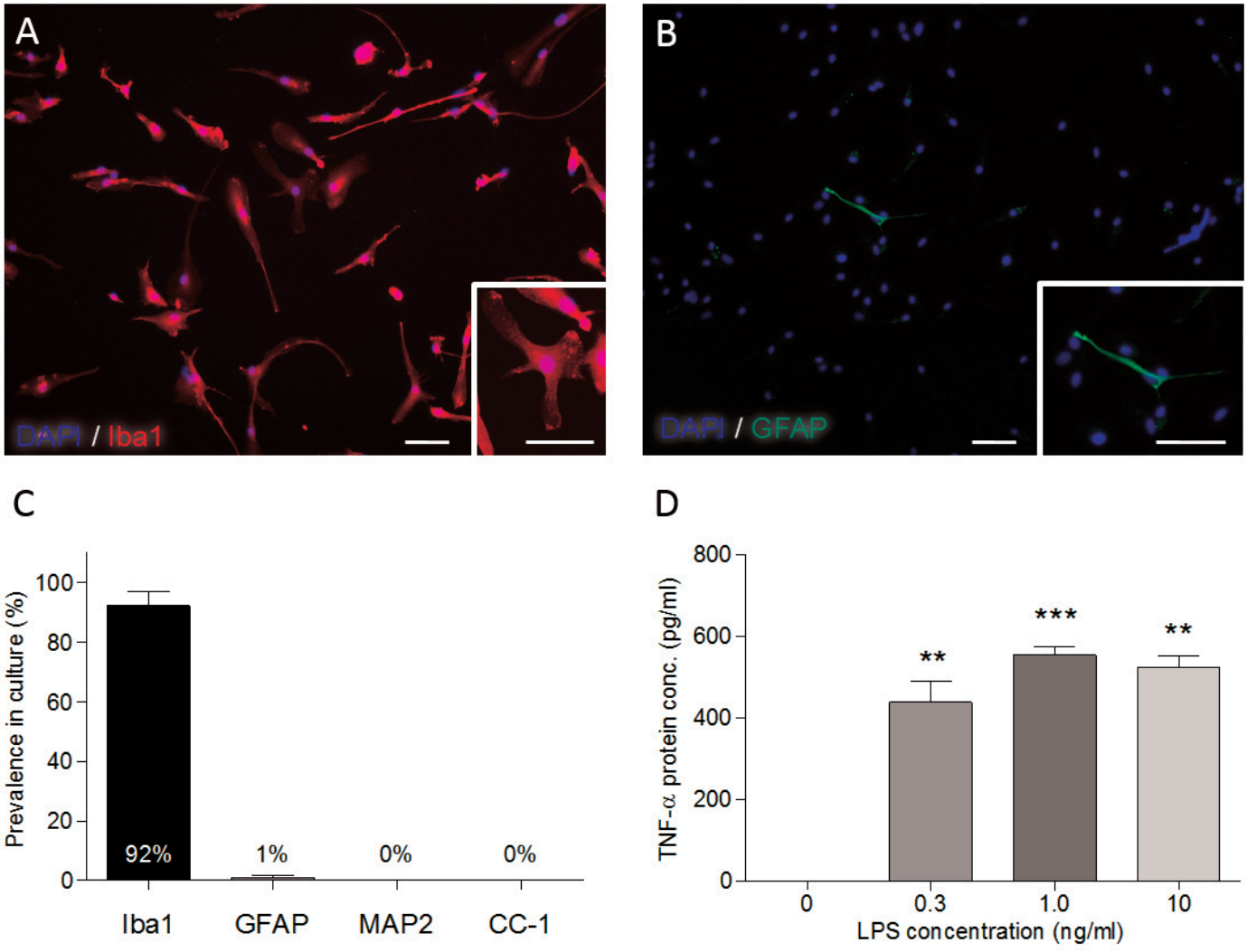
Group leader:
Jens D. Mikkelsen, Professor, MD, DMSc

Figure 1: Morphological and functional characterization of primary cultures of human microglia cells. The cells are isolated from resections of human neocortex and immunoreactive for ionized calcium binding adaptor molecule 1 (Iba1), a microglia/macrophage-specific calcium-binding protein (A, C). To a much lesser extent cells are immunoreactive for glial fibrillary acid protein (GFAP), as for neuronal markers. Functionally, these cells are capable of responding to lipopolysaccharide by secreting tumor necrosis factor (TNF)alpha to the medium. Modified from [5], Copyright © 2016 Wiley Periodicals, Inc.

Human primary microglia cell cultures

Microglia are the "immune" cells of the human brain serving important roles in the central nervous system (CNS) tissue. Microglia are activated by a range of cytokines and growth factors and thereby participate in inflammation processes in the normal brain and in several neurological pathologies. We have developed a method that allow culturing of primary glia cells from human temporal neocortex obtained from neurosurgical operations (**Figure 1**). Because the laboratory and the clinical department is under the same roof, it has been possible to facilitate this work.

These cells can be placed on petri dishes for electrophysiological recordings, and they can be kept in wells for biochemical analysis. We have been interested in studying the role of the nicotine alpha7 acetylcholine receptor (α7nAChR) in inflammation processes. This receptor is a penta-homomeric ligand gated receptor highly expressed in the brain, and considered to be a relevant drug target for a number of brain disorders. Neuronal α7nAChRs modulate neurotransmission and are considered to be the main target for those effects elicited by systemic administration of α7nAChR modulators. However, we have recently shown that α7nAChR may also be



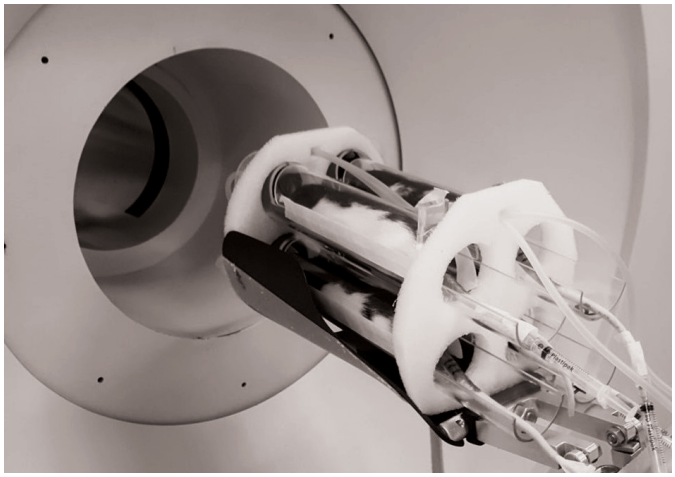
expressed in glia cells, and play an anti-inflammatory role. Rat microglia primary cultures secrete TNF-α when stimulated with a lipopolysaccharide as part of an inflammatory response, and we have previously shown that the α7nAChR partial agonists GTS-21 and NS6740 inhibit this effect. It is now our intention to reproduce these data in human microglia cells.

Translational Neuroimaging and Behavior

Junior group leader:
Mikael Palner, PhD

In 2016, Mikael Palner started as a new junior group leader in the experimental laboratory. His team is focused on translational neuroimaging and behavioral analysis of rats. The team uses Designer Receptors Activated Exclusively by Designer Drugs (DREADDs) to target single neuronal pathways and assess behavior and neuroimaging data following selective stimulation or inhibition.

The Palner team implemented the startle and prepulse inhibition behavioral model in the lab, and optimized open field analysis, with automatic measurements of locomotion, rearing and grooming. They also implemented Magnetic Resonance Spectroscopy (MRS) for in vivo detection of several brain metabolites in collaboration with Center of Basic and Translational Neuroscience at the University of Copenhagen and their Bruker 9.4 Tesla microMR. Furthermore, the team developed and tested a high-through-put "hotel" to scan 4 rats simultaneously in the HRRT PET scanner (**Figure 2**), in close collaboration with associate professor Matthias Hertz at University of Copenhagen and Sune Keller at the PET and Cyclotron Unit at RH. This "hotel" has been used with several PET tracers in 2016, including radiolabelled Cimbi-36, Cimbi-416, DASB, Fallypride and FDG, and proven to be a quick and reliable way to scan multiple subjects within a single tracer production.



Experimental Psychoneuroendocrinology

Junior group leader:
Agnete Overgaard, PhD

Agnete Overgaard returned to NRU in spring 2016, after one year postdoctoral fellowship in Professor Liisa Galea's laboratory at University of British Columbia, Canada, where she worked with the rat model of postpartum depression (PPD). Agnete has continued this work at the NRU in her post doc project which aims at understanding the neurobiological changes involved in PPD and dissecting contributions from different risk factors in these changes.

The experimental psychoneuroendocrinology team has investigated natural peripartum dynamics as well as the effects of the SSRI paroxetine in the PPD model, with endpoints including maternal behaviour, forced swim test, sucrose preference test, open field test, elevated plus maze, corticosterone stress response, serum estradiol, immunohistochemistry for hippocampal neurogenesis markers Ki67 and doublecortin. Autoradiography for 5-HT1A, 5-HT2A, and 5-HT4 receptors, and SERT as well as immunohistochemical identification of serotonergic fibers are ongoing. So far, the results show that the PPD model worked, but paroxetine failed to remediate depressive symptoms. Understanding how SSRIs work in the postpartum as well as investigating alternative treatment options will be the goals of future studies.

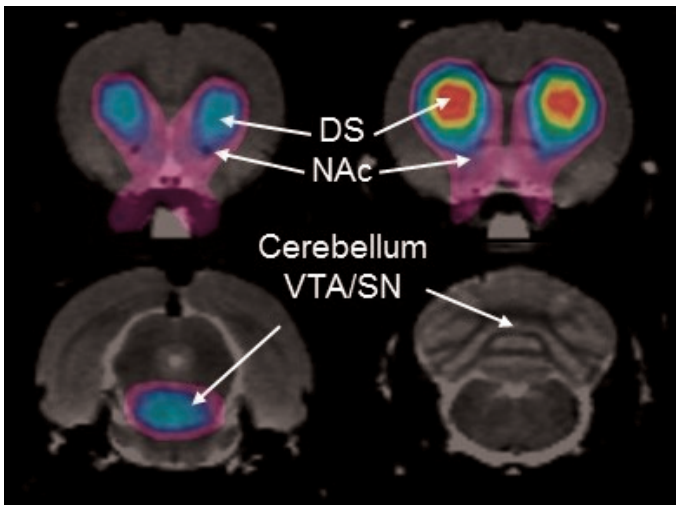


Figure 2: (Left) Picture of rat "hotel" with 4 rats ready for simultaneous PET scanning in the HRRT scanner and (up) the PET binding potential of 18F-Fallypride in rat brain superimposed on an MR structural image. Courtesy of Mikael Palner.

Research at NRU

Radioligand Development

Junior group leader:
Hanne Demant Hansen, PhD

In the radioligand development group we combine biology, chemistry, radiochemistry and neuroimaging to develop radioligands for positron emission tomography (PET) imaging. PET imaging allows us to quantify the receptors in the living brain of animal or humans and with novel and sensitive radioligands this imaging technique can measure changes in endogenous neurotransmitter levels in the brain.

In recent years, we have focused on the 5-HT2A receptor, for which we have developed a 11C-labeled radioligand, [11C]Cimbi-36. This ligand is currently being used in various preclinical and clinical studies. Furthermore, the ligand is being implemented as a research tool at both Imperial College in London and at Uppsala PET center in Sweden.

Parallel to the use and continuous evaluation of [11C]Cimbi-36, we are developing an 18F-labeled analogue of Cimbi-36. Because of the longer half-life of the 18F, it allows for longer scan time and distribution of the ligand to other PET centres in the vicinity of Copenhagen. In 2016, we have published two papers with a total of 8 unsuccessful radioligands [17,39]. Unfortunately, the ligands fail because of low brain uptake, defluorination or because of lack of specific binding to the receptors in the brain, as demonstrated in **Figure 3**.

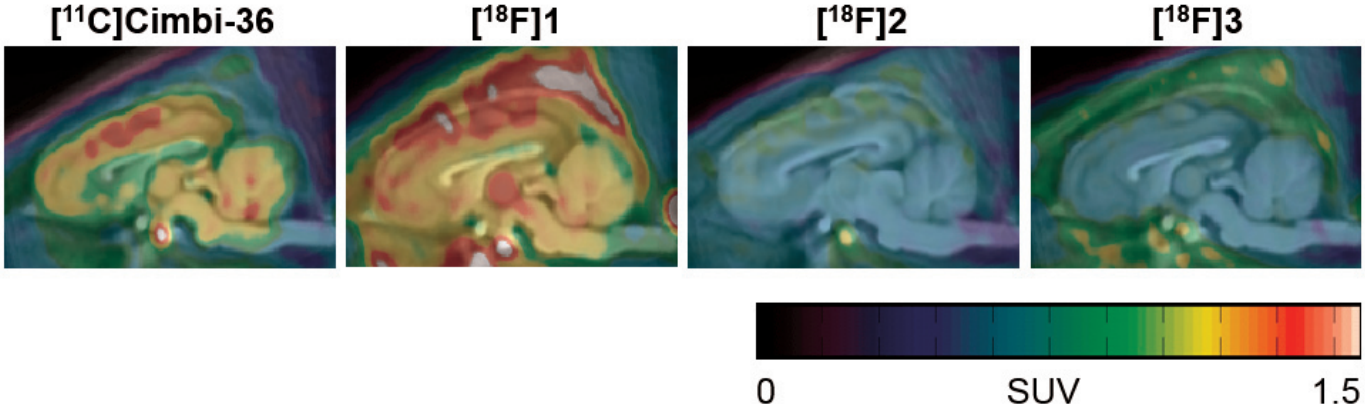


Figure 3: Sagittal PET images of three 18F-labeled radioligands and [11C]Cimbi-36 for comparison. Images are summed over 0–90 min and with a 3 mm Gaussian filtration and are overlaid with a standardized MR-atlas of the pig brain. [18F]**1** defluorinates over time resulting in excess radioactivity uptake in the bones of the animal, and [18F]**2** and [18F]**3** have low brain uptake. Furthermore, all three ligands failed to display specific binding to the 5-HT2A receptor and are thus not suitable as PET radioligands. Figure from [17], Copyright © 2016 Elsevier Inc.

Neuropsychology

Coordinating post doc:
Dea S. Stenbæk, PhD

The cognitive group at NRU (NRU-C) was established as a core facility to advance an interdisciplinary scientific approach to the understanding of risk and resilience factors in human health. We specialize in psychological effects of pharmacologically induced neuroendocrine changes and serotonergic neurotransmission in healthy volunteers. Furthermore, we specialize in pre- to post-treatment factors, e.g., changes in brain function, cognition, and affective symptomatology in depressed patients and in cancer- and cardiac arrest patients. We aim to integrate experimental and clinical research to accommodate the need for novel treatment strategies through pharmacology-assisted psychotherapy in the treatment of, e.g., depression, anxiety, and PTSD.

In 2016, we have continued to validate and improve our affective- and socialcognitive test-battery. This included a Danish psychometric validation of the first comprehensive three-hour test battery of affective and social cognition, EMOTICOM, in collaboration with the developers at Cambridge Cognition Group (**Figure 4**). It furthermore included an ongoing validation of our in-house developed extended version of the Verbal Affective Memory Test (VAMT-26) and of effects of intranasal administration of oxytocin on selected tests from EMOTICOM and VAMT-26.

Selected tests from our cognitive and affective-and social cognitive test-battery were also applied in a study investigating changes in affective processing in patients with Major Depressive Disorder in response to antidepressant treatment and in patients with Seasonal Affective Disorder in response to seasonal changes from summer to winter. Furthermore, they were applied in a study [44] investigating effects of GnRHa-induced sex-hormone changes in healthy women (**Figure 5**) and in a collaborative study with Kræftens Bekæmpelse Center for Cancer Research, Oncological and Hematological Clinic and Clinical Physiology, Nuclear medicine and PET departments at Rigshospitalet investigating changes in brain metabolism and cognition while undergoing chemotherapy in 30 patients newly diagnosed with Hodgkin's Lymphoma.

We collaborate with Babylab, which is an experimental research unit at UCPH and connected to "Center for Spæd- og Småbørn". In NeuroPharm we also collaborate with the Psychedelic Research Group at Imperial College, London, in preparing the first Danish study investigating psychological effects of the hallucinogenic drug psilocybin in healthy volunteers.

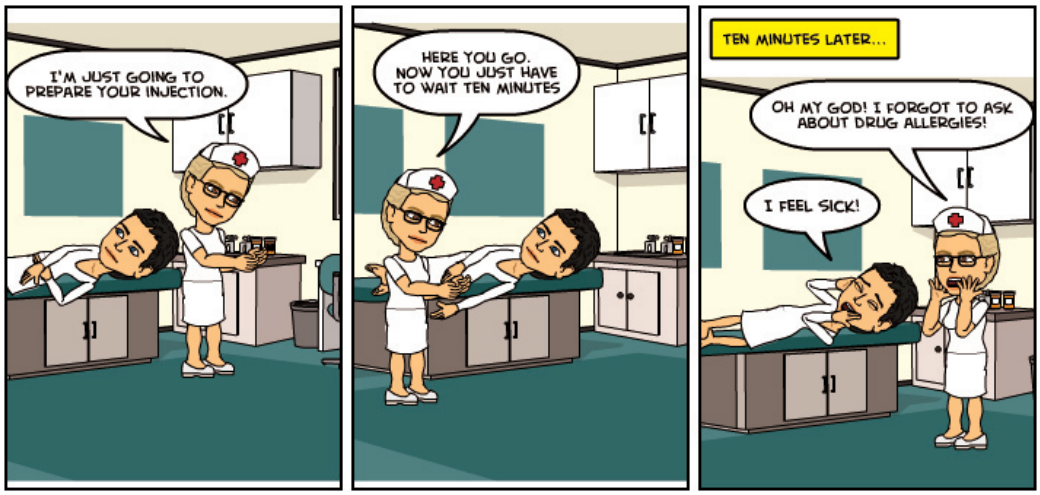


Figure 4: Example of moral scenarios from the Moral Judgement Task, EMOTICOM. The Moral Judgement task consists of moral scenarios depicted as cartoon strips. The test subject is asked to identify him/herself with either the "victim" or the "victimizer" and rate on a scale from one to seven how guilty, annoyed, shameful and bad he/she would feel if he/she had been in the character's shoes. Copyright © Cambridge Cognition Group 2016.

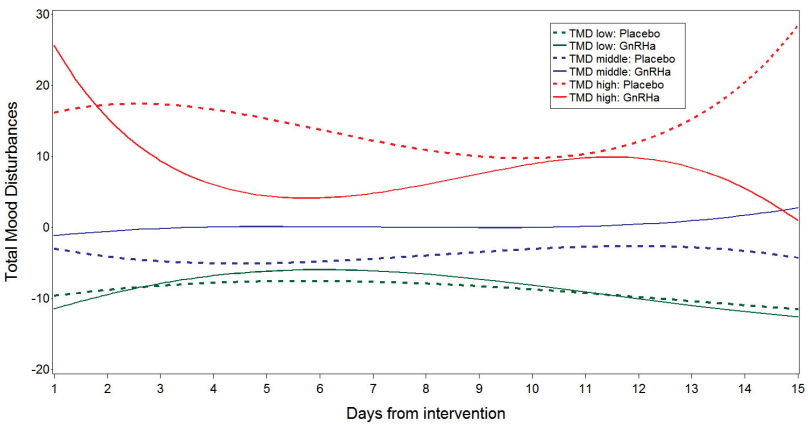


Figure 5: Interaction effect between intervention status and POMS (Profile Of Mood States) at baseline on the development of daily reported POMS during GnRHa (Gonadotropin-Releasing Hormone agonist) intervention. The figure shows the development of serial daily mood (POMS) as a function of intervention group and baseline POMS. Baseline POMS (baseline POMS groups, low: POMS<-8, moderate: -8<POMS<+8, high: POMS>8) significantly moderated the GnRHa intervention effect on POMS development (p=0.003). Specifically, GnRHa intervention significantly affected POMS development in women with high baseline POMS whereas there was no effect of intervention in women with moderate or low baseline POMS. Only for women undergoing GnRHa intervention with high POMS scores at baseline did the development of POMS during intervention deviate significantly from a straight line (p=0.016). Figure from [44], Copyright © 2016 Elsevier Ltd.

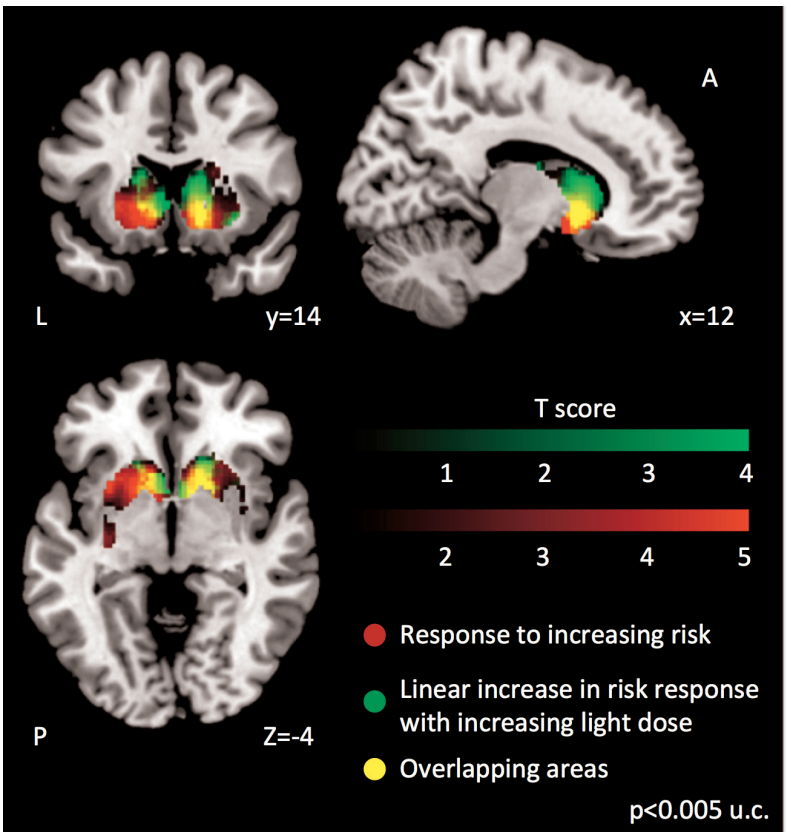
Functional MRI

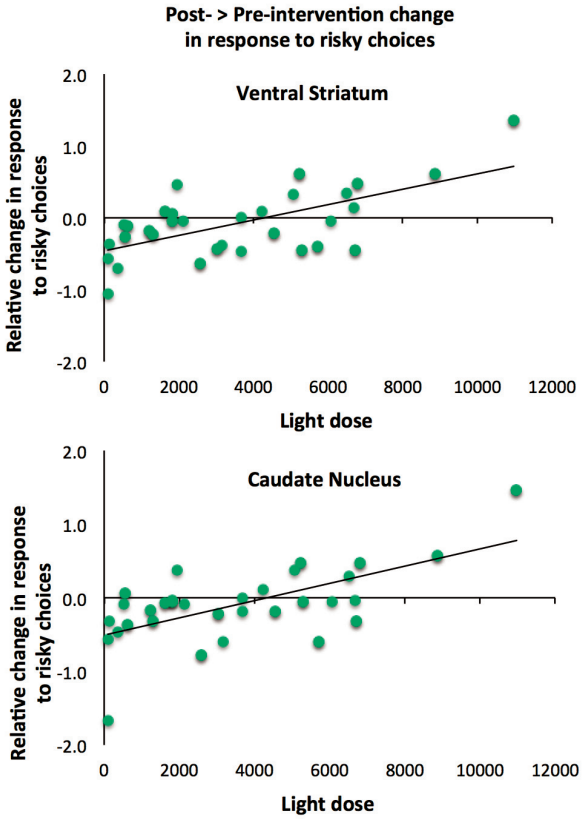
Group leader:
Patrick M. Fisher, PhD

At NRU, we use functional magnetic resonance imaging (fMRI) to assay features of brain function and connectivity that map onto relevant behavioral and molecular phenotypes and response to pharmacological or other intervention strategies.

In 2016, a study in healthy individuals, led by NRU PhD-student Brenda Mc Mahon, evaluated how three weeks of bright-light intervention affects neuromolecular systems and brain function. NRU collaborator Julian Macoveanu and colleagues found that this effective treatment for seasonal affective disorder and other depressive disorders increased the response of ventral striatum to risky choices (**Figure 6**). The ventral striatum is a

Figure 6: Bright-light intervention increased ventral striatum response to risky decisions in a light-dose dependent manner. (Left) Brain areas responsive to task and intervention. (Right) Association between bright-light dose and change in brain responses. Figure from [31], Copyright © 2016 Elsevier Inc.





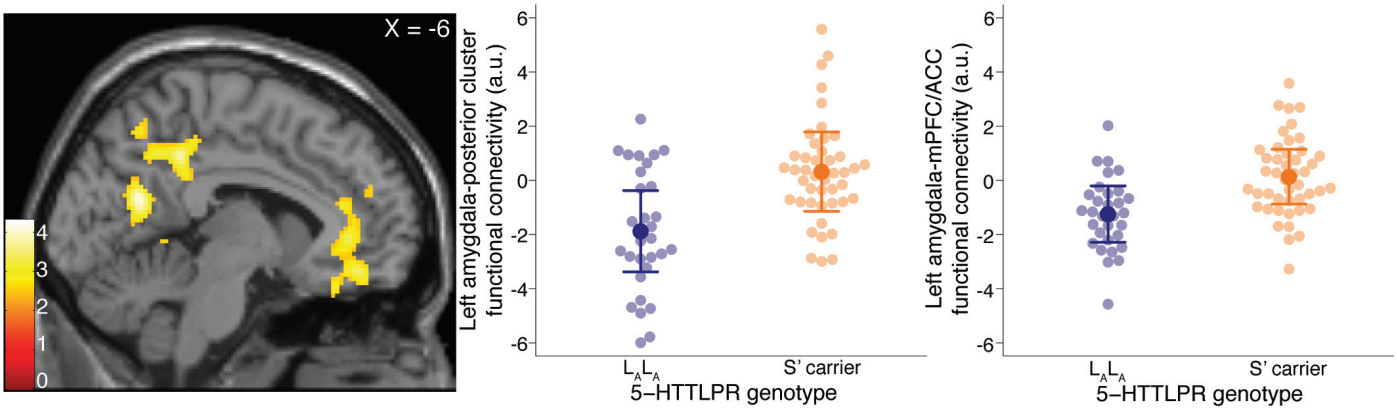


Figure 7: (Left) Prefrontal and occipital areas where communcation with the amygdala was predicted by 5-HTTLPR genotype status. (Center and right) Plots of the differences in amygdala communcation between 5-HTTLPR genotype groups. Figure from [32], Copyright © The Author 2015.

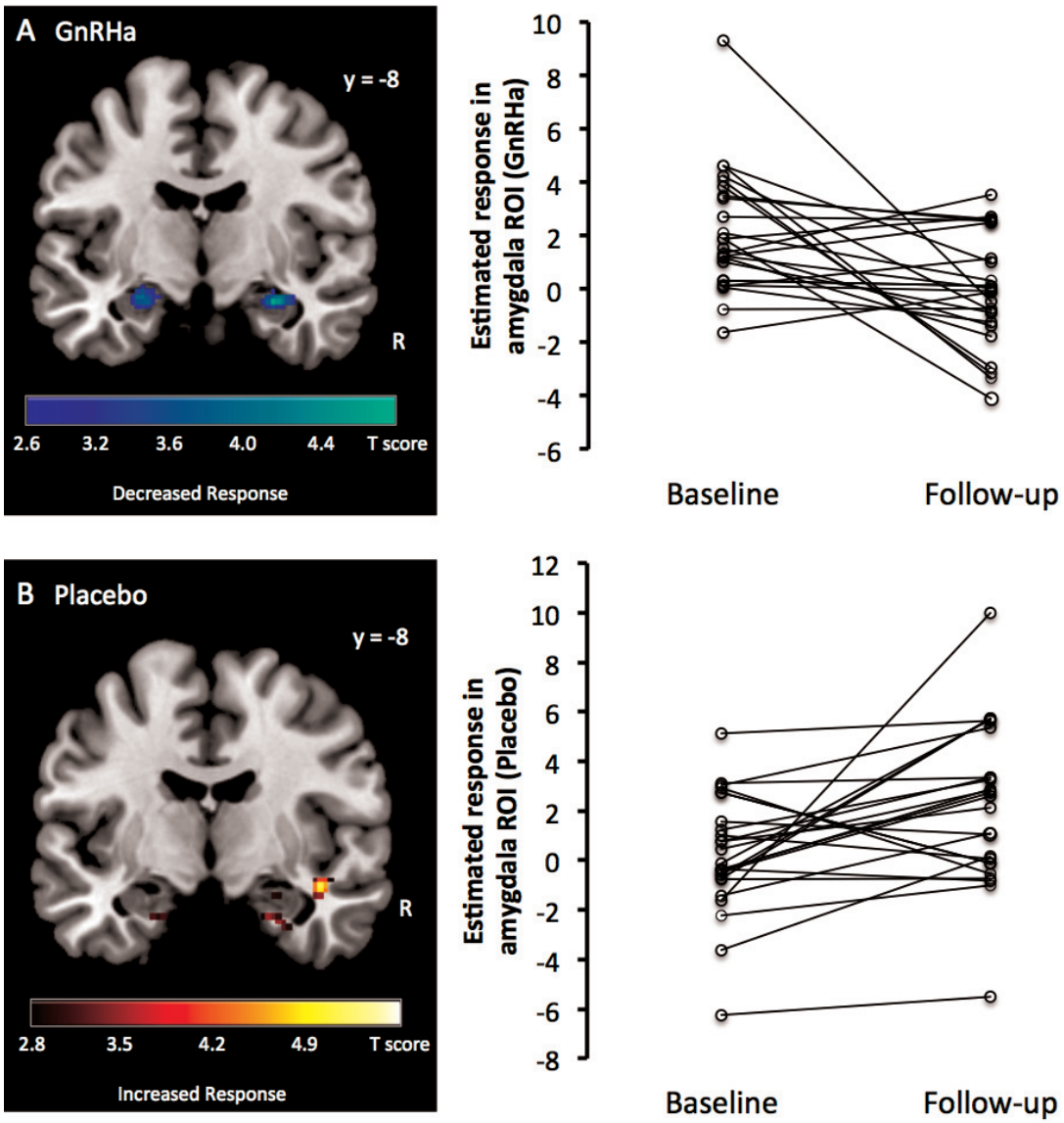


Figure 8: (A) Amygdala regions where sex-hormone manipulation significantly decreased the response to rewarding stimuli (B) Plot of decrease in amygdala response. Figure from [30], Copyright © 2016 American College of Neuropsychopharmacology.

key brain structure for processing reward-related stimuli and these findings suggest that bright-light therapy may be clinically effective by modulating the neural processes related to risky and rewarding decisions.

The amygdala is a central brain structure for processing emotionally salient information. Using the Cimbi Database, NRU PhD-student Martin Korsbak Madsen and colleagues evaluated whether a commonly studied genetic variant (5-HTTLPR) predicted amygdala communication with other brain areas during an fMRI task evaluating emotionally salient faces. The authors found that amygdala connectivity with behaviorally relevant brain areas such as the prefrontal and occipital cortex (**Figure 7**) was significantly predicted by 5-HTTLPR genotype status, and they also found that this association depended on neuroticism, a personality construct associated with risk for mood and anxiety disorders. These findings provide intriguing novel insight into how genetic variation shapes distributed neural communication in a manner related to personality.

The perception of risk and reward critically shapes how we navigate our environment and make decisions. Two studies this past year highlight how these neural systems are related to intervention. A study led by NRU senior researcher Vibe Frøkjær evaluated the behavioral and neurobiological effects of sex hormone manipulation in women to clarify how sex hormone fluctuations throughout the lifespan (e.g., during the menstrual cycle and menopause) shape risk for depression and other mood disorders. Julian Macoveanu and colleagues found that this manipulation decreased the amygdala response to reward using a gambling fMRI task (**Figure 8**). This suggests that a reduced neural response to positive experiences may underlie links between sex hormone fluctuations in women and increased risk for depression.

Data Analysis

Group leader:
Claus Svarer, PhD

The data analysis section optimizes molecular neuroimaging data analysis for research and clinical use. We are using novel multivariate data analysis techniques as well as more classical methods for optimization of quantification of, e.g., receptor binding data.

A commonly used method for quantification of positron emission tomography (PET) neuroimaging data is the reference tissue model. This model requires the presence of a proper reference region, i.e., a brain region where no specific radioligand binding is present. The most commonly used reference region is cerebellum but the reference tissue model assumes that the reference region is homogenous and behaves as a single tissue compartment which is not always the case. In a collaboration with researchers at MGH, we described a modification of the reference tissue model, the regularized full reference region model (rFRTM) and showed that the bias in parameter estimates by assuming that cerebellum is a one-tissue compartment can be ameliorated with rFRTM [33].

Reproducibility of neuroimaging data is important. We have in 2016 investigated the test-retest variability of our novel 5-HT2A receptor agonist [11C]Cimbi-36 PET and found an excellent test-retest reproducibility. This highlights the potential of [11C]Cimbi-36 for PET imaging of 5-HT2A receptor agonist binding in vivo. As illustrated in **Figure 9**, we also compared

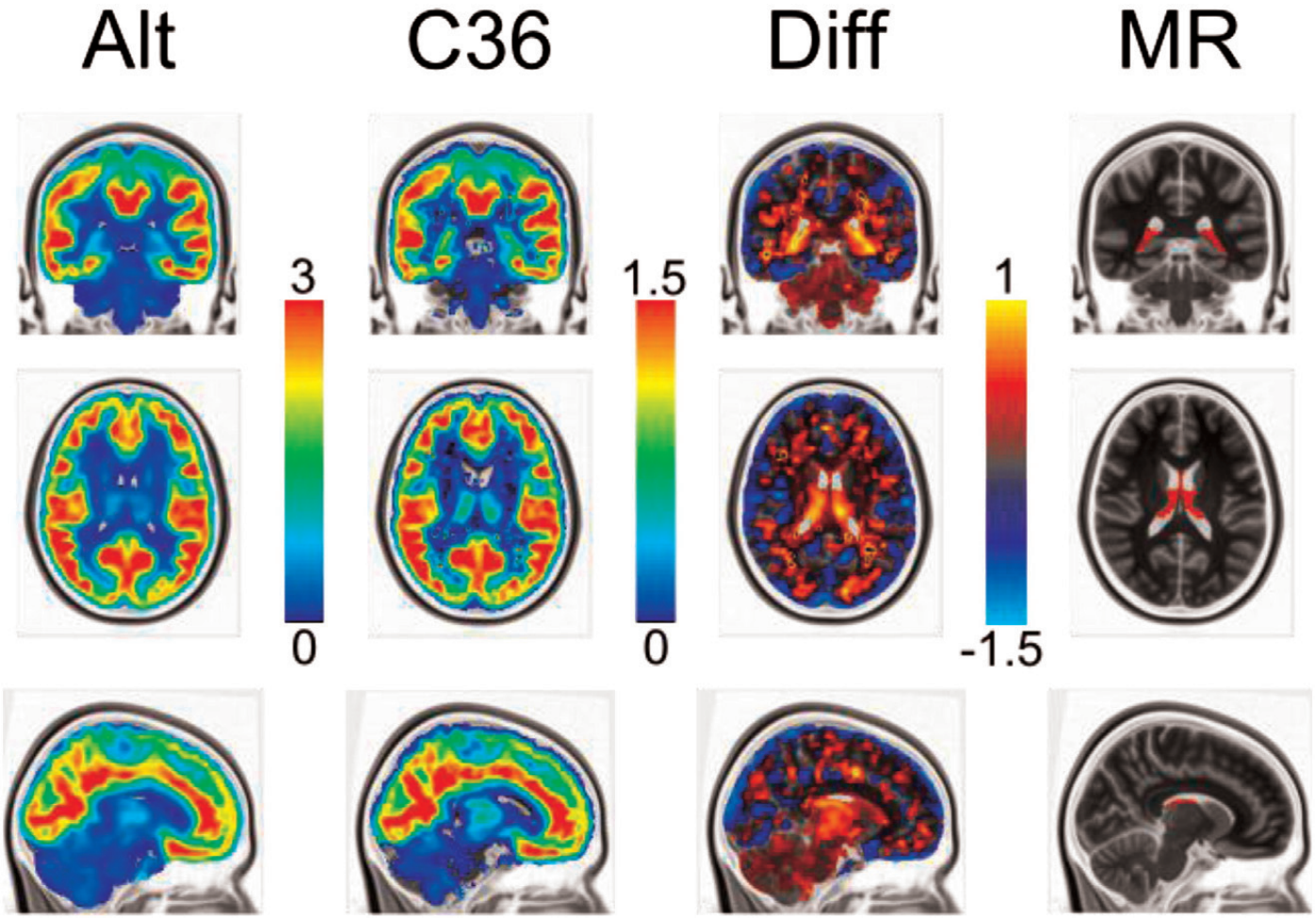


Figure 9: Parametric images of [11C]Cimbi-36 and [18F]altanserin in the human brain. Mean distribution over 8 subjects of the two PET radioligands is visualized in the first and second column in three views (top: coronal, middle: transversal, lower: sagittal). The third column (Diff) displays the average difference image between ([11C]Cimbi-36–[18F]altanserin) after applying similar scaling to the binding potential maps for each ligand to a distribution with zero mean and standard deviation of one. Corresponding structural T1-weighted MR-images overlaid with a choroid plexus region definition according to FreeSurfer in red are shown in the fourth column (MR). The colorbars from left to right represent [18F]altanserin BP_P, [11C]Cimbi-36 BP_{ND}, and normalized differences between BPs (standard deviations with yellow indicating relatively more [11C]Cimbi-36 binding and blue indicating relatively more [18F]altanserin binding). Figure from [12],

the brain binding of [11C]Cimbi-36 and the 5-HT2A receptor antagonist [18F]altanserin [12]. Our data suggest that Cimbi-36 and altanserin both bind to 5-HT2A receptors, but in regions with high 5-HT2C receptor density, choroid plexus and hippocampus, the [11C]Cimbi-36 binding likely represents binding to both 5-HT2A and 5-HT2C receptors.

In 2016, Ling Feng also developed and published a simulation system which pursuits the optimal design of infusion studies for attaining tracer steady-state conditions in brain and blood rapidly [13]. This system was constructed based on the tracer kinetics obtained from dynamic studies, and subsequently used to design inputs for bolus infusion (BI) or programmed infusion (PI) experiments assisted by an offline feed-back controller. Using the [11C]Flumazenil PET tracer as an example, steady-state was attained within 40 min using PI and 48 min using the optimal BI. Steady-state quantification is straight-forward with one short scan and a couple of venous blood samples, which is of particular interest for clinical studies. This simulation toolbox can be easily adapted for other PET-tracers.

With the recent trend towards Big Data analysis, neuroimaging datasets have grown substantially in the past years. While larger datasets potentially offer important insights for medical research, one major limitation is that many molecular neuroimaging studies not only apply different scanners, but also different data analysis pipelines. This severely hampers the possibility to share data sets across scientists and thereby to replicate previous findings. A primary goal for NRU PhD student Martin Nørgaard is to investigate the effects of using different data analysis pipelines. At the Neuroreceptor Mapping Meeting 2016, an international working group for standardization and PET data sharing was established under leadership of professor Robert Innis, NIH, and professor Gitte Moos Knudsen from NRU.

Clinical Neurology

Olaf B. Paulson, Professor, MD, MDSc

Lars H. Pinborg, Associate professor, MD, DMSc

Epilepsy surgery registry data

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

The construction of a prospective database for patients enrolled in the Danish Epilepsy Surgery program is essentially completed and will be up and running in 2017. The database is hosted at Rigshospitalet and the initiative is supported by the Danish Council for Independent Research. The database has been closely coordinated with European collaborators and implemented on the same software platform (REDCap) as the European Database for Epilepsy (eCRF, E-pilepsy) in order to optimize future data exchange and facilitate research initiatives on a European basis.

Modalities in epilepsy surgery

The implementation and integration of multimodal functional imaging techniques in the diagnostic workup of epilepsy surgery candidates is key for stepping forward both with respect to the number of patients we can offer surgery and the number of patients that surgery render free of disabling seizures.

NRU PhD student Mette Thrane Foged has in collaboration with Associate Professor Sándor Benickzy from the Epilepsy Hospital Filadelfia continued to record and analyse High density EEG (HD-EEG with 256 channels) in epilepsy surgery candidates. The patient's individual MRI scanning together with the exact location of the electrodes (from 11 different cameras) is used to perform a source localization (**Figure 10**). The aim is to estimate the added value of this new method in the epilepsy surgery evaluation process and compare results to the golden standard (the outcome of surgery). We took part in a study describing a novel method of reconstructing the MEG signals more feasibly in a clinical setting [4].

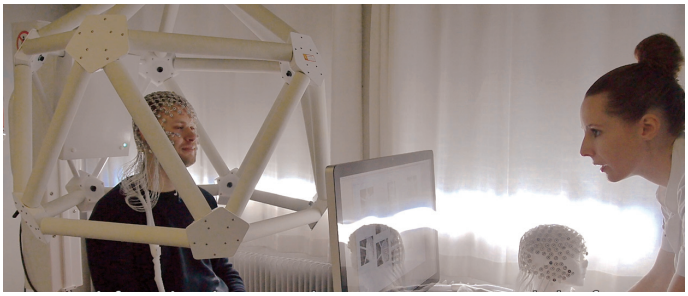


Figure 10: HD-EEG experimentl setup. Test person is wearing the 256 channels EEG cap on the head while sitting in the "cage" with the 11 cameras to record the position of the EEG electrodes. To the right Mette Thrane Foged.

Concurrent EEG and fMRI has been performed in a series of patients. The combination of the high temporal resolution of the EEG with the high spatial resolution of the fMRI is challenging. In order to improve the temporal resolution of fMRI, fast MRI sequences should preferentially be used, e.g. Multi-band EPI with short time to repetition (TR). Our results have shown that temperature increase beneath the electrodes are quite modest and not a concern. The fMRI signal is to some extend influenced by the electrodes, but do not affect the interpretation of the results. The EEG signal after clearing for MRI signal is poorer than outside the scanner. Further analysis will be performed.

Innovative treatment strategies for epilepsy

In 2016, we continued our collaboration with professor Merab Kokaia's group at Lund University and associate professor David Woldbye's group at the University of Copenhagen to pave the way for new innovative treatment strategies for drug-resistant

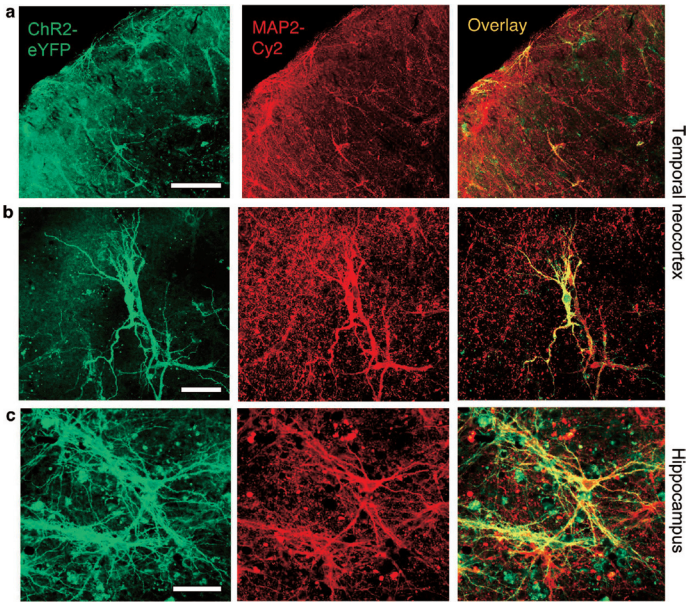


Figure 11: ChR2 expression in human organotypic brain slice cultures. Representative confocal images of enhanced yellow fluorescent protein expression (eYFP, green), neuron-specific microtubule associated protein-2 (MAP2, red) and the overlay of both channels. (a) Left, middle and right image from a cortical organotypic tissue culture (scalebar 200 µm) with a higher magnification image in (b) (scalebar 50 µm). (c) Left, middle and right image from a hippocampal organotypic tissue culture (scalebar 50 µm). Figure from [2], CC BY licence (Creative Commons Attribution v4.0 International License).

epilepsy patients. We contributed to a study demonstrating that viral vector-based optogenetic tools can be used to express opsins, such as ChR2 (**Figure 11**), in neurons from Danish epilepsy surgery patients to the level that enables functional manipulation of these neurons [2].

Imaging of neuroinflammation

Molecular imaging of neuroinflammatory changes in the brains of patients with neurological, neurosurgical and psychiatric disorders is a method of great potential for research and clinical application. As part of our involvement in the INMiND consortium supported by EU 7th framework programme, we have previously developed a SPECT method for imaging the 18-kDa translocator protein (TSPO) using the tracer [123I]CLINDE. In the brain, TSPO is preferentially present on microglia and less on other cell types like astrocytes. Microglia are the resident macrophage-like cells of the brain and are constantly scavenging the extra cellular environment for signs of damage to the brain. In the case of acute injury to the brain microglia are activated and TSPO is upregulated. Activated microglia are thought to contribute to functional recovery by removing damaged brain tissue and by pruning synapses and recruiting neurons and astrocytes. However, a number of recent studies suggest that the pro-inflammatory response orchestrated by activated microglia can initiate a number of processes that have a potential deleterious effect on brain function. Thus, microglial activation is believed to play a role in the pathogenesis of several brain disorders not usually considered to be neuroinflammatory. This concept opens new windows to understanding pathogenesis and recovery, early diagnosis, new treatment strategies and monitoring of treatment efficacy and brain diseases.

In 2016, recruitment of patients with MCA stroke came to an end. Twelve patients were clinically evaluated, [123I]CLINDE-SPECT and MRI scanned longitudinally approximately 2, 6 and 16 weeks after stroke. Data are part of the thesis of NRU PhD student Per Jensen which are to be handed in early 2017. We also finished a study on neuroinflammation in a rodent model of traumatic brain injury (TBI) where we demonstrated (**Figure 12**) that in response to brain injury TSPO binding is markedly increased in the contusioned area and in brain regions not directly affected by mechanical injury [11]. An upregulation was found in the contralesional cortex and at 28 days in the ipsilateral thalamus. We also demonstrated that most TSPO binding and most of the [123I]CLINDE binding could be attributed to microglia and macrophages. This rodent study has translated into a human study to test whether neuroinflammation after light head trauma is a predictor for development of post-concussion syndrome. NRU medical student Sebastian Ebert, supported by a scholarship from the Danish Council for Independent Research, is working on this project.

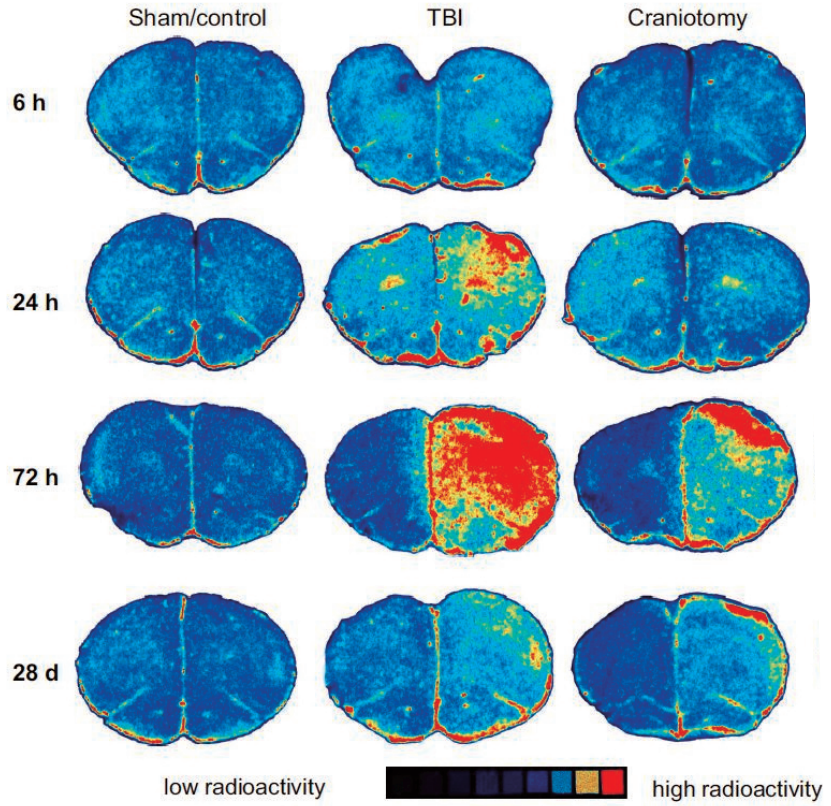


Figure 12: Focal traumatic brain injury (TBI) increases in vitro binding of the translocator protein 18 kDa selective radioligand [123I]CLINDE in the proximity of the contusion. Representative autoradiographs of the rat brain after sham operation (n = 5), controlled cortical impact-induced TBI (n = 5) and craniotomy (n = 3) at 6, 24, 72 h and 28 days post injury. Slice coordinates were: interaural 12.20 mm, bregma 3.20 mm. Red/yellow areas represent high; blue/black areas represent low binding of [123I]CLINDE. Figure modified from [11], Copyright © Springer Science+Business Media New York 2016.

Clinical Psychiatry

Group leader:
Vibe G. Frøkjær, MD, PhD

We use brain imaging methods to map brain architecture in risk and resilience to mental disorders to provide a rationale for targeted prevention and treatment. We hold an expertise in molecular imaging of key features of the serotonin signaling system, which is profoundly involved in mood disorders, schizophrenia [40], neurodegenerative disorders and their treatment. In particular, we are interested in serotonin brain biology as a driver of healthy adaptation to e.g. seasons, stressors, genetic make-up, personality, changes in sex-steroid hormone milieu and healthy navigation in social relations.

Anchored in our unique database of molecular and structural brain imaging, psychometrics and biomarkers [24], we found (**Figure 13**) that low serotonin tone (as indexed by higher serotonin 4 receptor binding) is associated with high trait aggression in males, but not in females [8]. We will pursue an interest in the role of serotonin in aggression in future studies, which may inform strategies for development of pharmacologic anti-aggressive treatments. Also, we have observed that higher serotonin tone (as indexed by lower serotonin 4 receptor binding) appears to support stress-hormone dynamics, which we speculate may support healthy navigation through natural environmental stressors [19]. Likewise, we have seen (**Figure 14**) that in seasonal affective disorder, depressive symptoms in winter appeared associated with a failure to downregulate serotonin transporter levels, which again suggests that dynamic brain changes that increase serotonin tone may compensate risk factors, i.e. may be necessary to overcome the stress of winter [34].

Further, in a human model of sex-hormone fluctuations, we have worked with the dynamic interplay between serotonin brain biology and steroid hormone systems as a driver of risk and resilience in an attempt to understand better how sex-steroid hormone fluctuations may trigger depressive episodes as frequently seen in the transition from pregnancy to postpartum and to the menopausal state in women. We have provided direct evidence for sex-hormone manipulation to provoke subclinical depressive symptoms in about 12% of healthy volunteers, which was coupled to markers of serotonin signaling, to the magnitude of sex-steroid (estradiol) decline, and to slower reaction time and labile mood [44]. In the same cohort, we have recently shown that sex-hormone manipulation reduces brain responses to reward, which reflects a reduced engagement in positive experiences [30]. If translating to disturbed serotonin signaling and social motivation in a cohort of depressed mothers this will be seminal in understanding mechanisms that mobilize natural maternal care capacities and promote social bonding of paramount importance to mother and infant health.

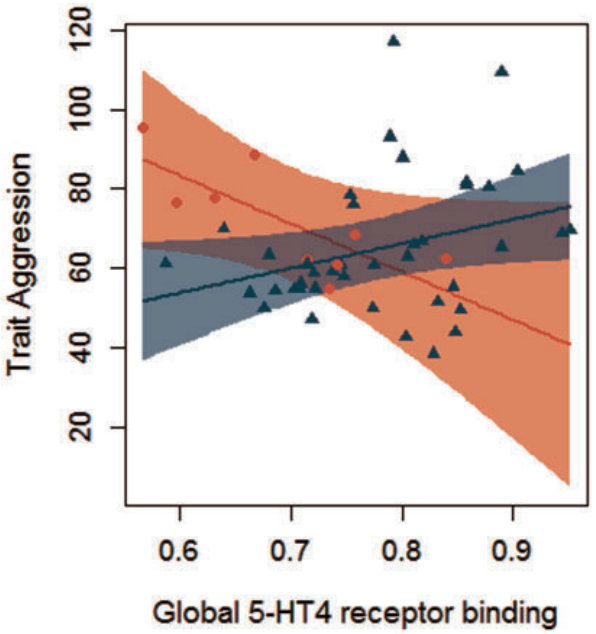
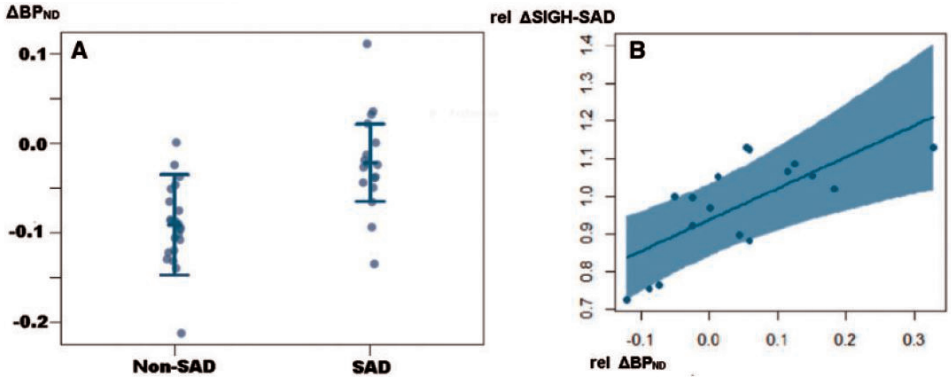


Figure 13: Association between global 5-HT4 receptor binding and trait aggression (BPAQ) in a sample younger than 50 years, adjusted for age, PET scanner type and 5-HTTLPR status. Gray triangles: men (n=40); orange circles: women (n=9). The difference in slopes is significant at P=0.02. Figure from [8], Copyright © The Author 2016.

Figure 14: (A) Cerebral 5HTT change across seasons between patients with seasonal affective disorder and healthy controls adjusted for sex, age, genotype and sex x group interaction effects. The ΔBP_{ND} (BP_{ND} winter - BP_{ND} summer) was significantly different between groups (P<.0001). (B) Relative change in symptom severity [SIGH-SAD scores winter-summer difference relative to winter (rel ΔSIGH-SAD)] was significantly associated with relative difference in global cerebral 5HTT binding (rel ΔBP_{ND} = $\Delta BP_{ND}/BP_{ND}$ winter) (n = 17, estimate = 0.83, R2 = 0.47, P = 0.01). Figure from [34], Copyright © The Author 2016.



The SPECT Laboratory

Chief medical technologist: Gerda Thomsen

In 2016, the SPECT-lab has been engaged in different NRU research projects and also been actively involved in some of the NRU publications from 2016. Two of these (see **Figures 15 and 16**) are based on data from the ENCDAT database of [123I]FP-CIT SPECT scans (European Normal Control Database of DaTSCAN) which we collected data for in the period 2008-10 together with several EU collaborators [1,7].

SPECT-lab is still actively engaged in the EU-funded INMiND project, and last year we contributed by performing several [^{123}I]CLINDE-SPECT investigations in both healthy subjects and in patients expected to show microglial activation. CLINDE data were presented at two congresses in 2016, namely the Annual Meeting for the Society of Nuclear Medicine and Molecular Imaging in San Diego, USA and the 3rd Congress of the European Academy of Neurology in Copenhagen.

Clinical work in the SPECT-laboratory

Patients with neurological disorders are referred to the NRU SPECT-laboratory for diagnostic SPECT-scanning, mostly from the Department of Neurology, Rigshospitalet, but also from Dianalund, Hillerød and other hospitals in Denmark.

NRU SPECT-lab conducts clinical DAT-SPECT which is striatal dopamine transporter (DAT) imaging with the SPECT ligand [^{123}I]FP-CIT. It is a robust and simple technique that can sensitively detect or rule out degeneration of presynaptic striatal dopaminergic nerve cells. It can differentiate presynaptic parkinsonian syndromes (PD, MSA, PSP) from essential tremor, drug-induced parkinsonism and psychogenic parkinsonism, but it cannot differentiate between these presynaptic parkinsonian syndromes. Furthermore, DAT-SPECT can also be used to differentiate dementia with Lewy bodies from other types of dementia, such as Alzheimer's disease. For each of these investigated patients, the SPECT-lab conducts the DAT-SPECT scan and performs a semi-quantitative analysis of the resulting scan based on an in-house developed method which correlates the actual scan to a database of age-matched healthy subjects. In 2016, the NRU SPECT-lab performed a total of 130 clinical DAT-SPECT investigations.

Another clinical scan performed by the NRU SPECT-lab is blood flow imaging with the SPECT ligand [^{99m}Tc]HMPAO. At present, we mostly use the technique for brain perfusion by SPECT in the presurgical detection of the epileptic focus in patients with complex partial seizures refractory to medical treatment. The technique is unique since after injection of [^{99m}Tc]HMPAO the lipophilic compound crosses the intact blood-brain barrier and distributes in proportion to cerebral blood flow with a peak brain activity within 2 min after injection. The SPECT-lab is highly specialized in presurgical epilepsy surgery work-up, since it is the only laboratory in Denmark to conduct ictal-interictal SPECT imaging with co-registration to MRI. The technique is called SISCOM (Subtraction Ictal SPECT Coregistered to MRI) and it has proven to be a highly valuable diagnostic tool to non-invasively localize the seizure-onset zone. The SISCOM technique also applies to investigations in children. In 2016, the SPECT-lab performed a total of 20 SISCOM-analyses.

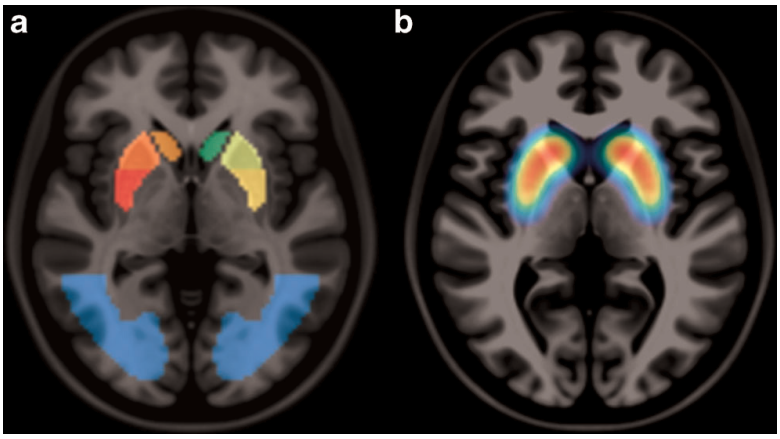


Figure 15: Implementation of new 3D VOIs for the semiquantitative analysis. (a) Newly implemented VOIs (caudate nucleus, anterior and posterior putamen, and the occipital cortex) adapted from the Automated Anatomical Labeling (AAL) atlas and coregistered to the MNI MRI template. (b) New healthy control [123I]FP-CIT SPECT template implemented in EARL-BRASS generated from 103 corrected scans obtained in healthy controls, which were normalized and coregistered to the MNI MRI template. Figure from [1], Copyright © Springer-Verlag Berlin Heidelberg 2016.

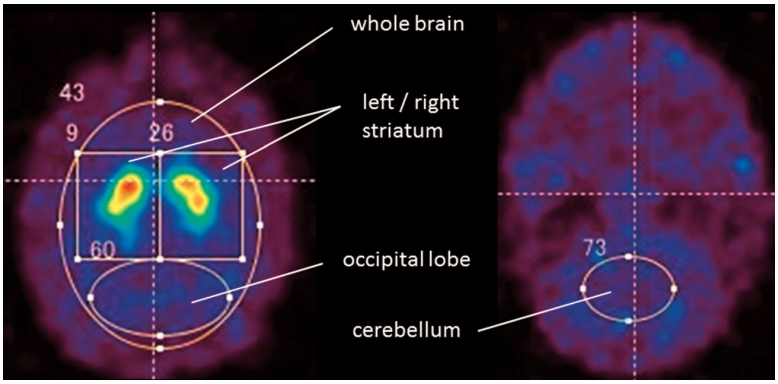


Figure 16: Manually delineated regions of interest (ROIs) for the left and right striatum, whole brain, occipital lobe and cerebellum. Figure from [7], Copyright © Springer-Verlag Berlin Heidelberg 2016.

NeuroPharm

www.neuropharm.eu

Center Director: Gitte Moos Knudsen

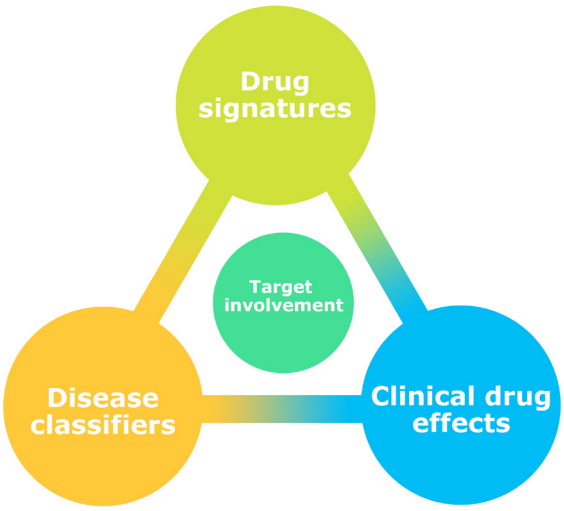
The Center for Experimental Medicine Neuropharmacology (NeuroPharm) is a research center under Rigshospitalet and University of Copenhagen (UCPH) funded by the Innovation Fund Denmark. NRU is the coordinating partner in the Center and the national partners include the pharmaceutical company H. Lundbeck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

The short-term goal of NeuroPharm is to answer pertinent and basic questions regarding human brain disease mechanisms and predict brain responses to categories of neuromodulatory interventions as well as treatment efficacy. We use PET and MR brain scanning to image brain receptors, receptor occupancy, and the brains regional interactions, i.e., functional connectivity. The ability to *simultaneously* measure drug occupancy and brain reactivity directly in humans provides a completely novel approach to assess interventional effects. We employ these brain imaging tools in patients with, e.g., depression and migraine. Also, we make use of existing data and biological samples in the context of a multivariate data analysis framework in order to generate predictive statistical models that will allow for a more informed use of data acquired within the Center and will provide a foundation for better study designs.

The research in NeuroPharm is divided into four work packages (WP1-4) which are described in detail below.

WP1: Treatment outcome in Major Depressive Disorder (WP leader: Vibe G. Frøkjær, NRU)

Major depressive disorder (MDD) most likely comprises a heterogeneous collection of different biological entities, which calls for studies that can inform a targeted treatment and potentially a new etiological classification. Most antidepressants act on the serotonin (5-HT) system but less than 50% of MDD patients respond successfully to 5-HT acting drugs. Identification of biological features that enables a relevant stratification of MDD patients would, importantly, allow for individualized treatment and can help facilitate more efficient clinical drug trials.



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 MDD and will, in the long term, provide a rationale for tailored treatment choice for MDD patients based on quantitative measures of brain function, rather than - as is the case today - rely exclusively on clinical assessment. The project is carried out in a close collaboration between NRU and Psychiatric Center Copenhagen and it includes a newly established PET-based marker of the brain serotonin system (5-HT4 receptor binding determined by 11C-SB207145 PET), various MRI techniques, EEG, neuropsychological testing, blood and saliva which enables genotyping and determination of cortisol awakening response, inflammatory markers and epigenetic variations across the study period.

We will enroll 100 MDD patients and examine how these markers relate to the outcome of a standard antidepressant treatment. Patients will be treated with standard antidepressant treatment, i.e., a selective serotonin reuptake inhibitor (SSRI), escitalopram, adjusted contingent on effects and side effects. They will have follow-up sessions at week 1, 2, 4, 8, and 12 where a trained psychiatrist will rate their depressive symptoms. Brain imaging with 11C-SB207145 PET, structural and functional MRI with resting state fMRI (rs-fMRI), and EEG will be conducted in all patients before pharmacological intervention is initiated and repeated at week 8 in 40 patients with variable antidepressant response.

In 2016, the project obtained all relevant approvals from the ethics committee and the Danish Medicines Agency and the data acquisition phase was initiated in August when the first MDD patient was successfully enrolled in the study. At the end of 2016, a total of 9 patients have been enrolled.

WP2: 5-HT_{2A}R modulation effects on neurobiology, cognition and mood (WP leader: Patrick Fisher, NRU)

Serotonin 2A receptor (5-HT_{2A}R) agonists, which have hallucinogenic properties, have emerged as an intriguing novel treatment for MDD and other mood and anxiety disorders. 5-HT_{2A}R agonists such as psilocybin result in both acute and lasting improvements in well-being. Psilocybin has been found to produce sustained antidepressant-like effects in patients and well-being in healthy volunteers and changes in brain activity that are consistent with effective antidepressant interventions. Thus, a better understanding of psilocybin's brain effects with PET and MRI will advance our understanding of serotonergic mechanisms implicated in depression and treatment. Comparing 5- HT_{2A}R agonist effects against drugs with opposing pharmacological actions (e.g., ketanserin, a 5- HT_{2A}R antagonist) would further elucidate the role 5-HT_{2A}R in these processes.

In this work package, we will with PET (^{11}C-Cimbi36) and rs-fMRI investigate healthy individuals to establish dose-dependent drug effects of psilocybin and pimavanserin on cerebral 5-HT_{2A}R binding and determine if psilocybin and ketanserin have

opposing effects on brain connectivity. Also, we will determine the neurobiological effects of the interventions and relate those to effects on cognition and mood. This will generate important insights into aspects of the neuromodulatory effects of 5- HT_{2A}R on cognition and mood and will provide a direction for the development of this and other potential future treatments.

The project is a clinical trial and in Fall 2016, the study protocol obtained all needed approvals from the ethics committee, the Danish Medicines Agency and the good clinical practice (GCP) unit at Bispebjerg Hospital, and hence data collection could finally be initiated at the very end of 2016.

WP3: Novel neuroimaging methods for an experimental medicine approach (WP leader: Hanne D. Hansen, NRU)

In non-human primates (NHPs), we have previously found that targeted binding of an antagonist to dopamine D2 receptors elicits a hemodynamic response that is coupled to receptor occupancy. However, the hemodynamic response is not only dependent on receptor occupancy but also on the functionality of the drug, i.e. whether the drug is an agonist or an antagonist. Together with our collaborating partner at the Martinos Center in USA, we have shown that the 5-HT1BR partial agonist AZ10419369 elicited a dose-dependent biphasic hemodynamic response that was related to the 5-HT1BR occupancy. By contrast, injection of the antagonist GR127935 did not elicit significant hemodynamic responses, even at a 5-HT1BR cerebral occupancy similar to the one obtained with a high dose of AZ10419369 (**Figure 17**). These results suggest that simultaneous PET-MRI opens for the possibility of testing novel drug compounds for their blood-brain-barrier passage, their brain occupancy and their functionality, based upon the hemodynamic response.

In our investigations of cerebral spatial and temporal response to triptans following experimental induction of migraine, we have completed the data collection and are now analysing the data. In this project, all patients have got three PET scans with 11C-AZ10419369: an interictal baseline scan and two scans after provocation of migraine.

Last but not least, we will settle a long-debated issue, namely to establish if migraine patients without aura (MO) symptoms have reduced brain serotonin levels. For this purpose, 16 MO patients will be scanned and compared to 16 matched healthy controls. The data collection and the data analysis is now finalized and a manuscript has been drafted of the results.

WP4: Bioinformatics, statistical and predictive models (WP leader: Klaus K. Holst, UCPH)

In order to meet the clinical need of robust diagnostic and prognostic classifiers for the individual at risk or with a manifest brain disorder, we will in this work package make use of existing data either from our Cimbi database or from collaborators to be analysed in the context of a multivariate data analysis framework and subsequently test the identified key variables for their predictive value in new data sets. We will use machine-learning techniques and seek to define a set of parallel biomarkers that can optimize the prediction of treatment response with high validity. In addition, statistical assistance for the other three work packages will be provided, both in terms of study design and optimal statistical analyses. We hypothesize that generation of predictive statistical models will allow for a more informed use of data and will provide a framework for optimized study designs in the future.

For this purpose, recent advances in high-dimensional statistics and machine-learning are employed. Depression and certain other brain disorders are characterized by differences in functional brain connectivity as determined by rs-fMRI; this approach may offer a sensitive measure for disease classification. Data acquired in WP1-WP3 will be used to extract resting-state brain networks and we will use multivariate statistical analysis applied to discover networks that, e.g., predict recovery from depression before initiation of drug intervention. A validated prediction model may serve as an important step in translating the knowledge gathered from WP1-WP3 into directly clinically applicable tools.

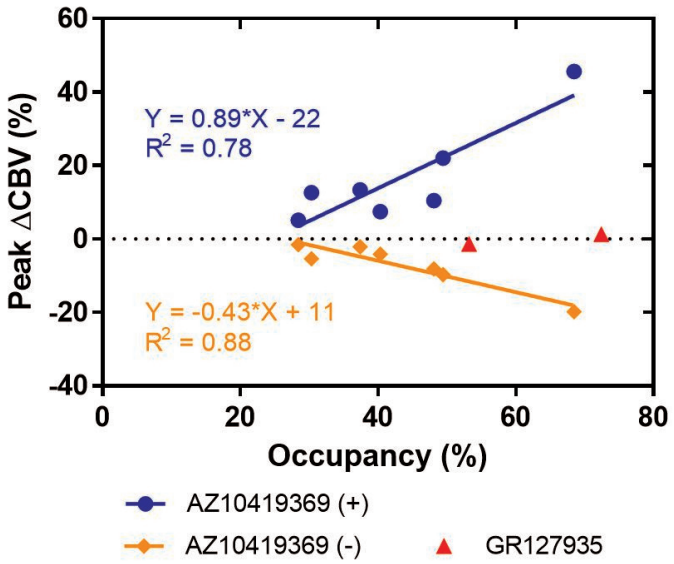


Figure 17: Linear correlations between the relative changes in 5-HT1BR occupancy and the relative peak changes in hemodynamic response (measured by changes in cerebral blood volume, CBV). The correlation with the decrease in CBV caused by the partial agonist AZ10419369 is visualized with orange diamonds, the increase in CBV with blue circles. The changes in CBV caused by the antagonist GR127935 is visualized with red triangles. Courtesy of Hanne Demant Hansen.

Project Director: Jens D. Mikkelsen

The COGNITO project is supported by the Danish Research Council (now Innovation Fund Denmark) and aims to evaluate the efficacy of new pharmacological intervention principles for impairment of neurocognitive function in patients. Apart from the NRU, 4 other Danish academic partners, 2 associated partners and 3 companies are involved in this research project. The project was initiated in 2012 and will continue until the end of 2017.

The overall goal of COGNITO is to identify and validate novel treatments for neurocognitive diseases, in particular associated with deficits in working memory, attention and decision making. It has been a challenge for many years that clinical proof-of-concept drug trials for these CNS disorders in particular have failed due to lack of efficacy. Good treatments for these patients are therefore still lacking. The alpha7 nicotinic acetylcholine receptor (alpha7 nAChR) has for many reasons been considered the most promising novel drug target for cognitive dysfunction in schizophrenia and Alzheimer's Disease (AD). However, it was reported during 2016 that an alpha7 nAChR-agonist - encenicline - did not show an effect in two randomised clinical phase-3 trials in patients with AD and schizophrenia, respectively. Even though this was a disappointment, it will be important to see the data published, and post-hoc analysis is underway to see whether there are subgroups of patients that respond. Importantly, the encenicline was developed without any target engagement data. Because the dose relationship in animal studies is an inverted U-shape, this is of particular importance and it cannot be excluded that the doses tested were not optimal. COGNITO is therefore still interested in developing tools for target engagement of this receptor, such as occupancy by PET and biomarker studies. COGNITO has also refocused the research to other modulators of the alpha7 nAChR, in particular allosteric modulators. The cross-disciplinary and international cooperation has been highly instrumental in the COGNITO project.

Genetic studies: Much of the work conducted at NRU and with partners in 2016 was aimed to study the correlation between variations in the CHRNA7 gene encoding the alpha7 nAChR subunit and disease and personality. Interestingly, the human genome contains a partly duplicated version of the CHRNA7 gene known as CHRFAM7A (**Figure 18**). This gene is interesting because it is evolutionary very recent. The duplicated alpha7 nAChR gene shows variations that are genetically linked to schizophrenia and cognitive dysfunction. In contrast to the CHRNA7 gene, the CHRFAM7A gene is unique to humans, hence not found in non-human primates and rodents. The CHRFAM7A gene encodes a truncated alpha7 nAChR subunit (dup-alpha7 subunit) lacking the extracellular ligand binding domain. When co-expressed with native alpha7 nAChR subunits, dup-alpha7 subunits are thus likely to act as dominant-negative modulators and suppress alpha7 nAChR activity in the human brain.

Because the CHRFAM7A gene is only found in humans, we have limited options to study its biology. Because we have access to human tissues from neurosurgical resections, we have been able to demonstrate the expression of CHRFAM7A in the human neocortex, and will now be interested to know what cells express the duplication and what the function of this gene product is in nervous tissue. The studies are hampered by the fact that antibodies and probes against the duplication will co-react with the full-length alpha7nAChR subunit protein.

Molecular imaging: We continue to evaluate novel PET tracers for visualizing alpha7 nAChR binding *in vivo*. The ultimate goal is to exploit the clinical applicability for determining the distribution and levels of alpha7 nAChR ligand binding in health and disease. We have evaluated and compared alpha7 nAChR binding properties of radiolabelled NS14492 (agonist) and ASEM (antagonist). Our results confirm strong differences in binding capacity across mammalian species. Relatively high level of binding is found in the porcine brain, and low alpha7 nAChR ligand binding capacity in postmortem human brain sections.

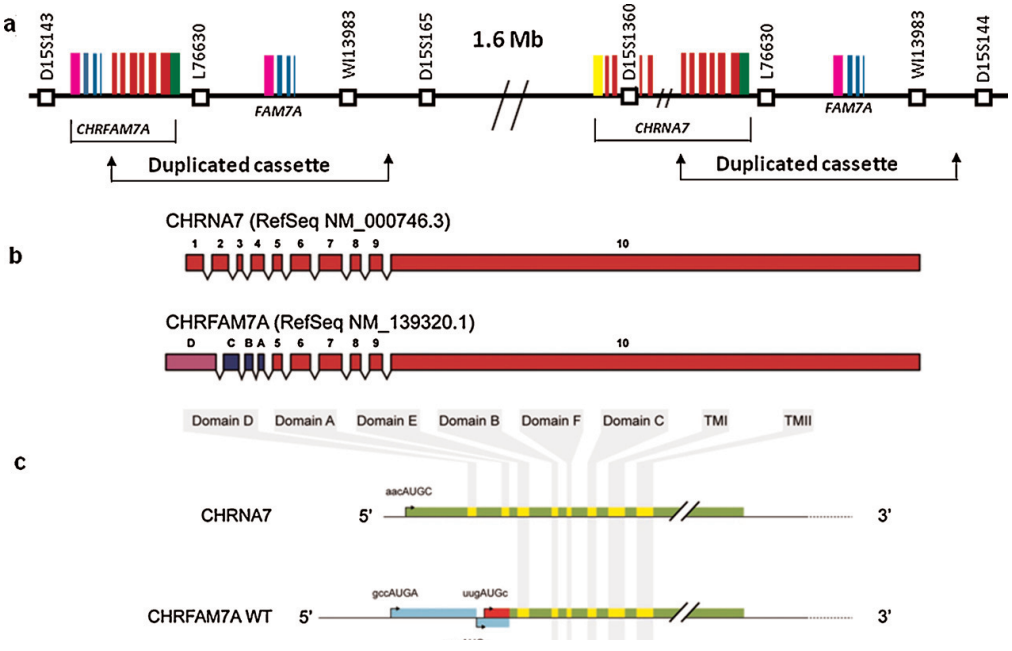


Figure 18. Structure of the CHRNA7/CHRFAM7A gene cluster on chromosome 15q13.3. (a) Map of the partial duplication of CHRNA7 on 15q13.3. Exons 5-10 of CHRNA7 were duplicated in a duplicon of 300 kb. The duplicon interrupted a partial duplication of a second gene, ULK4. CHRNA7 exons, red; ULK4 exons, blue; exon D, pink. (b) Schematic representation of the exon organization of the transcripts coding for CHRNA7, CHRFAM7A, CHRFAM7A based on the RefSeq NM_000746.3 and NM_139320.1. (c) Putative translation products from CHRNA7, CHRFAM7A, and CHRFAM7AD2 bp mRNAs. Amino acid sequence of a7 is represented in green and yellow (for the different domains). Alternative amino acids from CHRFAM7A are indicated in red and alternative amino acids from CHRFAM7AD2 bp in blue. The start codons in Kozak context are indicated, as are the stop codons. From (Araud et al., Biochemical Pharmacology, 2011), Copyright © 2011 Elsevier Ltd.

Cimbi

Center Director: Gitte Moos Knudsen

The overall aim of The Center for Integrated Molecular Brain Imaging (Cimbi) has been to uncover basic questions regarding interindividual differences in behaviour and personality in healthy people with a particular emphasis on phenotypical variations that are likely to be causally related to variations in the serotonergic transmitter system.

Neuroimaging studies, including molecular, structural and functional MRI studies have been used to uncover the neural substrates of interindividual variability with a particular emphasis on the serotonergic transmitter system. At the same time, genetic variation substantially adds to interindividual variability. The latter work is continued by NRU group leader PhD Patrick Fisher.

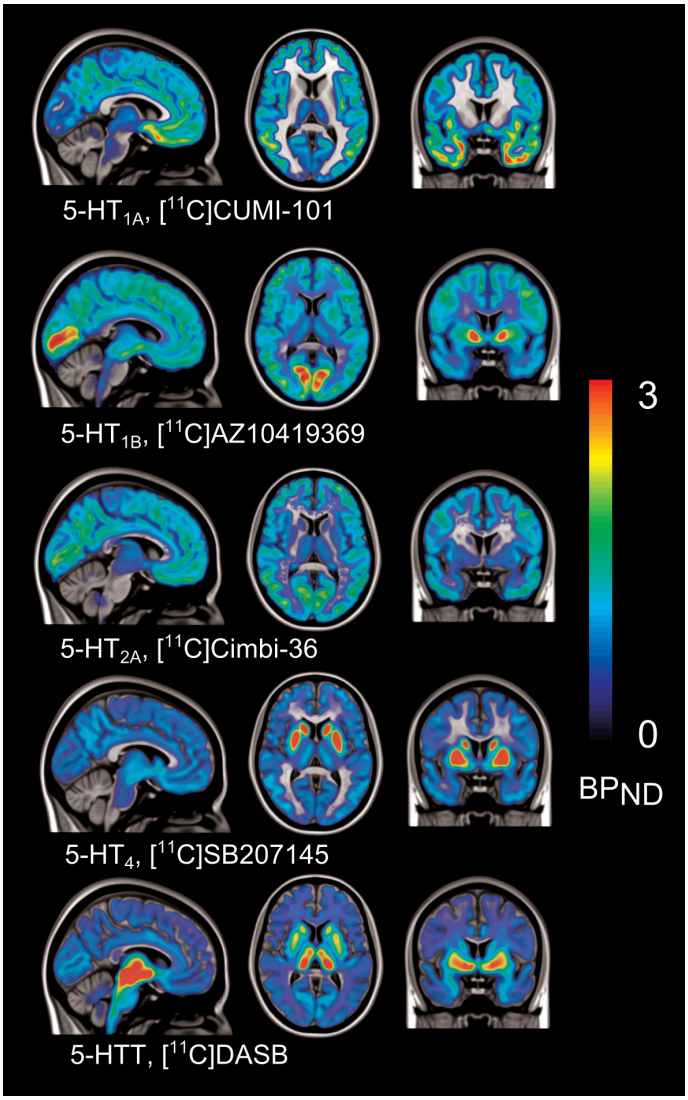


Figure 19. Coregistered structural MRI and PET brain images of (from top row and down) the 5-HT1A, 5-HT1B, 5-HT2A, and 5-HT4 receptors and the 5-HT transporter (5-HTT). Each image represents an average of five scans. The color bar shows the non-displaceable binding potentials (BP_{ND}). From [24], Copyright © 2015 The Authors.

Cimbi is about to come to conclusion of its funding period from the Lundbeck Foundation. The branding of Cimbi is now strong and well-established and after the funding period has been concluded, three lines of research will be continued, the biobank, the database, and the radioligand development. A seminal paper summarizing the Cimbi database inventory and describing the content of the biobank was published in 2016 [24]. The paper also describes how access to the data can be granted, following a simple application procedure. In 2016, 13 applications were reviewed and approved by Cimbi scientists.

Cimbi Biobank

Manager: Agnete Dyssegaard

The database-associated Cimbi biobank currently contains blood and in some instances saliva samples from more than 500 healthy volunteers and around 300 patients with e.g., major depression, dementia, substance abuse, obesity, and impulsive aggression.

Cimbi Database

Manager: Peter Steen Jensen

The database is of particular relevance for neurobiological research questions related to the serotonergic transmitter system with its normative data on the serotonergic subtype receptors 5-HT1A, 5-HT1B, 5-HT2A, and 5-HT4 and the 5-HT transporter (5-HTT), but can easily serve other purposes (**Figure 19**). The Cimbi database was formally established in 2008 with the purpose to store the wealth of Cimbi-acquired data in a highly structured and standardized manner in accordance with the regulations issued by the Danish Data Protection Agency as well as to provide a quality-controlled resource for future hypothesis-generating and hypothesis-driven studies. The Cimbi database currently comprises more than 1.250 PET and structural and functional MRI scans and it holds a multitude of additional data, such as genetic and biochemical data, and scores from self-reported questionnaires and neuropsychological paper/computer tests. Data continue to be added to the Cimbi database and biobank.

Cimbi Radioligands

Manager: Hanne Demant Hansen

We continue to develop novel radioligands in a subset of the Cimbi consortium, led by scientists from **medicinal chemistry**, the Faculty of Health and Medical Sciences (associate professors Jesper L. Kristensen and Matthias Herth), **radiochemistry**, PET- and Cyclotron Unit, Rigshospitalet (Drs. Nic Gillings, Jacob Madsen, and Szabolcs Lehel) and **neurobiology**, NRU, Rigshospitalet (professor Gitte Moos Knudsen and PhD Hanne Demant Hansen). Funding for these activities comes from different sources, and with an increasing involvement of pharmaceutical industry. Novel radioligands developed within the framework continue to follow the Cimbi nomenclature. Some of the work is described on page 12.

Strategic Collaborations

PET and Cyclotron Unit, RH

We highly appreciate our long-lasting and outstanding collaboration with Professor Liselotte Højgaard and her dedicated staff (see photo below) at the PET and Cyclotron Unit at Department of Clinical Physiology, Nuclear Medicine & PET. The collaboration covers both research and developmental activities and provides NRU with both excellent expertise and infrastructure for radiochemistry, as well as PET- and MR-PET scanner facilities. We highly appreciate this crucial collaboration and look forward to continuing the joint research activities in 2017 and beyond.

The Blegdamsvej staff at the Department of Clinical Physiology, Nuclear Medicine & PET, Rigshospitalet.

Martinos Center, MGH, US

The Athinoula A. Martinos Center for Biomedical Imaging under the Directorship of Professor Bruce R. Rosen, MD, PhD, and the Center has been pioneering brain imaging with MRI. The Center is located on the MGH research campus in the Charlestown Navy Yard with a satellite facility on the MIT campus in Boston, US. In 2011, director Bruce Rosen was awarded the Kirsten and Freddy Jørgensen Prize at Rigshospitalet, and a fruitful collaboration was established between the two sites. The collaboration was further strengthened at later retreat meetings, the first one in Boston in 2012 and the second one in Copenhagen in 2014, leading to the successful achievement of first a joint 2-year NIH grant (2014-16, lead by Dr. Doug Greve from the Laboratory for Computational Neuroimaging at Martinos) and later the NRU-anchored 6-year grant from the Innovation Fund Denmark for the NeuroPharm project (2015-20). Since 2011, bilateral exchange of scientists has also taken place as part of the collaboration in order to conduct joint scientific work within:

- PET-MR brain imaging under pharmacological challenges
- Improvement of technical performance of PET-MR, including attenuation correction and motion correction
- Testing novel PET radioligands
- Quantification of PET imaging data using FreeSurfer

MGH/HST Athinoula A. Martinos Center for Biomedical Imaging

MASSACHUSETTS GENERAL HOSPITAL HST Harvard-MIT Health Sciences & Technology

Psychiatric Centre Copenhagen

NRU has a close collaboration with Psychiatric Centre Copenhagen, in particular with professor Martin Balslev Jørgensen who is directly involved in one of the four work packages in NeuroPharm, with professor Lars Vedel Kessing and senior researcher Kamilla Miskowiak and her Neurocognition and Emotion in Affective Disorders (NEAD) group who are doing research in depression and bipolar disorder, as well as with professors Anders Fink Jensen and Birte Glenthøj. We highly appreciate this collaboration and look forward to strengthen even more the joint research activities in the future.

INMiND Consortium

NRU is part of the INMiND (**I**maging of **N**euroinfla**m**mation **I**n **N**eurodegenerative **D**isease) consortium consisting of 22 mostly European academic partners and 6 SMEs, i.e. small and medium enterprises. Since 2012 the INMiND consortium has been supported by the EU 7th Framework. The purpose of INMiND is to identify mechanisms linking neuroinflammation and neurodegeneration and to make this knowledge useful in a clinical context for the benefit of neurological and psychiatric patients. NRU is involved in several work packages from the cellular level to TSPO imaging using [^{123}I]Clinde-SPECT in neurological patients, and from training activities to dissemination of knowledge.

INMiND corsortium participants at the fourth INMiND annual meeting which was held in February in Salzburg.

DanPET AB

DanPET AB (www.danpet.eu) is a Swedish company with focus on biomarkers and preclinical programs within the areas of nicotine and monoamine reuptake. It is founded and directed by Dan Peters who is associated researcher to NRU. The collaboration between NRU and DanPET AB primarily focuses on investigation of new potential alpha7 PET-ligands as well as the supply and research-implementation of new ligands of relevance within the nicotinic field, e.g. the alpha6 nicotine area.

Teaching and Training

Pre- and postgraduate training

NRU is a major teaching and training site for pre- and postgraduate students. In terms of postgraduate training, NRU senior staff members have supervised more than 20 national and international PhD students and post docs. For the fifth time, we have contributed to the Sino-Danish Center for Education and Research by lecturing at the Master degree program 'Neuroscience and Neuroimaging' at the University of Chinese Academy of Sciences in Beijing, and in March we hosted our yearly one-week PhD course "*Basic Kinetic Modelling in Molecular Imaging*". Also, in August we organized and hosted for the second time a 3-day PhD course on the popular Neuroimage analysis package, FreeSurfer.

Participants at the 2016 FreeSurfer PhD course in Copenhagen.

Brain Prize Master Class on Translational Neuroscience

In April, Gitte Moos Knudsen was in the programme committee for the 2016 Brain Prize Master Class that was held in Copenhagen. The Master Class is a high-level small audience meeting where twenty talented European junior neuroscientists have the opportunity to present and discuss their work with a Brain Prize winner and selected senior scientists.

Participants at the 2016 Brain Prize Master Class.

The Master degree programme "Neuroscience and Neuroimaging" in Beijing

The Sino-Danish Center for Education and Research (SDC) is a joint project on education and research between the eight Danish universities, the Danish Ministry of Science, Innovation and Higher Education, the University of the Chinese Academy of Sciences and the Chinese Academy of Sciences. The overall aim of SDC is to promote and strengthen collaboration between Danish and Chinese learning environments and increase mobility of students and researchers between Denmark and China.

In 2012 SDC established in Beijing an international Master of Science (two-year) programme in Neuroscience and Neuroimaging. This is offered to up to 30 students every year, and ideally half should be admitted via the University of the Chinese Academy of Sciences and half via Danish (Aarhus) universities. A semester runs over 13 full weeks, and NRU staff has since the start been responsible for two to four weeks of teaching with 12 one hour sessions per week. Since 2012 the teaching has predominantly been lectures, however, in 2014 the first semester was reorganized and the teaching made more interactive with compressed lectures and time for the student to present important aspects of the curriculum.

Until 2016, Professor Olaf B. Paulson had the main responsibility for planning of the education and the written exam. The topics of the NRU teaching have primarily covered molecular neurobiology of neuroimaging, cerebral blood flow, glucose metabolism, and translational neuropharmacology. In 2016, Professor Olaf B. Paulson was also in China to teach. Further in 2016, Olaf B. Paulson started supervising a student with her SDC master thesis, a supervision in collaboration with Chinese colleagues.

Photo from professor Olaf B. Paulson's teaching session with the SDC students in China.

Highlights from 2016

NRU 20-year anniversary

In September, the 20-year anniversary of NRU was celebrated with a symposium with interesting talks from former and present NRU employees, including Peter Lund Madsen (see photo to the right). After the symposium the celebration continued with a dinner in the restaurant of the Sailing Club Sundet.

40-year anniversary

In December, professor Olaf B. Paulson was able to celebrate his impressive 40-year anniversary as a consultant at Rigshospitalet. Many of Olaf's former and present colleagues and collaborators participated in the reception that was held at the Department of Neurology.

NRU Christmas Party

In December, NRU staff celebrated the end of another successful scientific year with a legandary thematic Christmas party. In line with some of our ongoing research activites, this year the Christman party had "Psychedelics" as it's theme.

Younger Researcher of the Year

PhD student Sofi da Cunha-Bang was in May honoured as the Younger Researcher of the Year (Årets Yngre Forsker 2016) by the Collaboration of Young Researchers at Rigshospitalet. Sofi won the title based on her oral presentation on her PhD project "*High serotonin 1B receptor binding is associated with high trait anger and heightened amygdala and striatal reactiviy to provacations*".

Publications 2016

NRU has in 2016 published a total of 5 PhD dissertations, 7 Master's theses or research year reports, 11 book chapters, and 47 scientific peer-reviewed papers.

PhD dissertations

- Brenda Mc Mahon. Seasonal changes in cerebral serotonin transporter binding in individuals with or resilient to Seasonal Affective Disorder. University of Copenhagen, Faculty of Health and Medical Sciences. Defended Apr 01, 2016
- Dea Siggaard Stenbæk. Sex steroid hormone manipulations and serotonergic neurotransmission in relation to verbal affective memory recall, simple reaction time, and mental distress. University of Copenhagen, Faculty of Health and Medical Sciences. Defended Jan 14, 2016
- Henrik Emig-Nørbak. Frontal Dopamine D2/3 Receptors and Brain Structure in Antipsychotic-Naïve Schizophrenia Patients Before and After Their First Antipsychotic Treatment. University of Copenhagen, Faculty of Health and Medical Sciences. Defended Aug 24, 2016
- Jo Beldring Henningsen. The roles of RFRP in the central control of reproduction: photoperiodic and sex-specific differences. University of Strasbourg, Faculty of Life Sciences. Defended May 18, 2016
- Sofi da Cunha-Bang. Multimodal Neuroimaging of Aggression in Violent Offenders. University of Copenhagen, Faculty of Health and Medical Sciences. Defended Jul 08, 2016

Master's theses and research year reports

The following list of NRU-affiliated students successfully defended their theses or research year reports in 2016:

- Annette Johansen, "*Small Polar Radiometabolites Cross the Blood-Brain Barrier and Increase the Non-displaceable Signal: A PET Study with [11C]Cimbi-36 Labeled in Two Different Positions*", Master's thesis and research year report, Faculty of Health and Medical Sciences, UCPH
- Björg Vigfúsdóttir, "*Multivariate Estimation of Regional Seasonal Variations in SERT-levels in Seasonal Affective Disorder*", Master's thesis in Biomedical Engineering, DTU and UCPH
- Claudia Guldager Kring Rasmussen, "*Pharmacological characterization of nicotinic receptors in differentiated PC12 cells*", Master's thesis in Biochemistry, Faculty of Science, UCPH
- Emil Holm, "Efficacy of the Danish Epilepsy Surgery Programme", Master's thesis and research year report, Faculty of Health and Medical Sciences, UCPH
- Lars Vestergaard Knudsen, "*Cerebral aktivering ved komplekse håndbevægelser - Et nyt fMRI Paradigme*", Research year report, Faculty of Health and Medical Sciences, UCPH
- Matthias Kølvraa, "*Do human annotations on MRI data pay off? A statistical comparison of two manually annotated and two automatically computed surfaces*", Master's thesis and research year report, Faculty of Health and Medical Sciences, UCPH
- Rana Al-tayar and Sana Ahmed, "*Evaluating preprocessing pitfalls in parametric PET/MR Neuroimaging*", Master's thesis in Biomedical Engineering, DTU and UCPH
- Sofie Trolle Pedersen, "*The association between endogenous steroid hormone levels, brain SERT binding, sensory gating and prepulse inhibition in healthy women*", Master's thesis and research year report, Faculty of Health and Medical Sciences, UCPH

Book chapters

- Fisher PM, Knudsen GM. Molecular Neuroimaging Genetics. In: Bigos, K.L., Hariri, A.R., Weinberger, D.R. (Eds.) Neuroimaging Genetics – Principles and Practices (2016). Oxford University Press, New York (USA), ISBN: 9780199920211
- Sørensen PS, Paulson OB, Gjerris F (eds). Nervesystemets sygdomme. Neurologi for fysioterapeuter, ergoterapeuter og neurologisk personale. 4. udgave. København: Gads Forlag, 2016:1-552
    - Paulson OB. Kognitive funktioner, sprog og tale. In: Sørensen PS, Paulson OB, Gjerris F (eds). Nervesystemets sygdomme. Neurologi for fysioterapeuter, ergoterapeuter og neurologisk personale. 4. udgave. København: Gads Forlag, 2016:39-45
    - Paulson OB. Det motoriske system. In: Sørensen PS, Paulson OB, Gjerris F (eds). Nervesystemets sygdomme. Neurologi for fysioterapeuter, ergoterapeuter og neurologisk personale. 4. udgave. København: Gads Forlag, 2016:77-119
    - Paulson OB. Bevidstløshed. In: Sørensen PS, Paulson OB, Gjerris F (eds). Nervesystemets sygdomme. Neurologi for fysioterapeuter, ergoterapeuter og neurologisk personale. 4. udgave. København: Gads Forlag, 2016:249-257
    - Paulson OB. Demens og andre neuropsykologiske dysfunktioner. In: Sørensen PS, Paulson OB, Gjerris F (eds). Nervesystemets sygdomme. Neurologi for fysioterapeuter, ergoterapeuter og neurologisk personale. 4. udgave. København: Gads Forlag, 2016:271-282
    - Paulson OB. Cerebrovaskulære sygdomme. In: Sørensen PS, Paulson OB, Gjerris F (eds). Nervesystemets sygdomme. Neurologi for fysioterapeuter, ergoterapeuter og neurologisk personale. 4. udgave. København: Gads Forlag, 2016:329-355
    - Paulson OB. Neurodegenerative og motoriske neuronsygdomme. In: Sørensen PS, Paulson OB, Gjerris F (eds). Nervesystemets sygdomme. Neurologi for fysioterapeuter, ergoterapeuter og neurologisk personale. 4. udgave. København: Gads Forlag, 2016:375-379
    - Paulson OB. Infektioner I nervesystemet. In: Sørensen PS, Paulson OB, Gjerris F (eds). Nervesystemets sygdomme. Neurologi for fysioterapeuter, ergoterapeuter og neurologisk personale. 4. udgave. København: Gads Forlag, 2016:439-451

- Paulson OB. Demensgivende sygdomme. In: Sørensen PS, Paulson OB, Gjerris F (eds). Nervesystemets sygdomme. Neurologi for fysioterapeuter, ergoterapeuter og neurologisk personale. 4. udgave. København: Gads Forlag, 2016:453-459
- Paulson OB. Neurologiske komplikationer til metaboliske og endokrine sygdomme. In: Sørensen PS, Paulson OB, Gjerris F (eds). Nervesystemets sygdomme. Neurologi for fysioterapeuter, ergoterapeuter og neurologisk personale. 4. udgave. København: Gads Forlag, 2016:527-531
- Paulson OB. Intoksikationer og ernæringsdeficit. In: Sørensen PS, Paulson OB, Gjerris F (eds). Nervesystemets sygdomme. Neurologi for fysioterapeuter, ergoterapeuter og neurologisk personale. 4. udgave. København: Gads Forlag, 2016:533-537

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