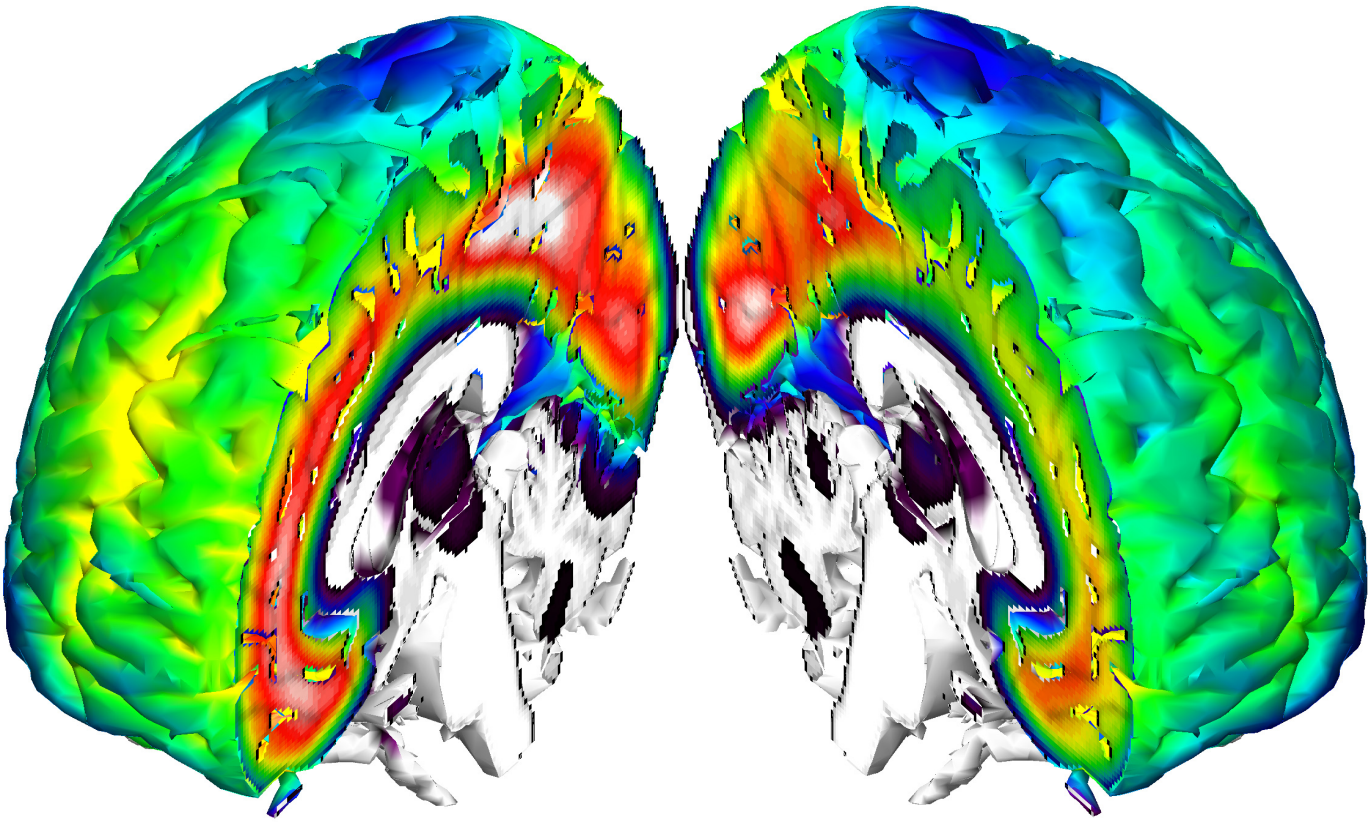
Neurobiology Research Unit

Dept. Neurology, Neuroscience Centre
Copenhagen University Hospital, Rigshospitalet

www.nru.dk

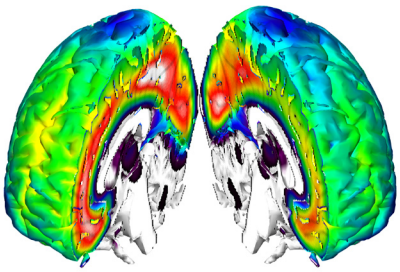
Annual Report 2015



Innovation Fund Denmark
NeuroPharm
Center for Experimental Medicine Neuropharmacology

Cimbi
Center for integrated molecular brain imaging

COGNITO
Det Strategiske Forskningsråd



Cover image showing differences in mean serotonin 2A receptor binding across neocortex in obese (left) and healthy (right) individuals. Figure from [19], Copyright © The Author 2015.

Preface

Dear reader,

I am pleased to present you with the 2015 annual report describing the activities in 2015 within 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 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 2015 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 >40 international congresses, conferences, and meetings, and in total the group has published 48 peer-reviewed scientific publications and several book chapters. The full 2015 publication list can be found on page 28.

With respect to research training, we have in 2015 organized both pre- and post-graduate programmes with international speakers and well-attended programs. In terms of pregraduate training, one of our medical students successfully defended his bachelor project and two of our non-medical students obtained their degree after a successful defence of their master theses in molecular biomedicine and biomedical engineering, respectively. Further, three psychology students have been trained in internships at NRU. In terms of postgraduate training in 2015, NRU senior staff members have supervised more than 20 national and international PhD students and post docs, and one PhD-relevant course has been given within the auspices of NRU. Furthermore, professor Olaf B. Paulson has for the fourth year in a row 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.

In 2015, a new Danish-Brazilian research collaboration within multimodality brain imaging was established between NRU and the Brain Institute (InsCer) at Pontifical Catholic University of Rio Grande do Sul (PUCRS) in Porto Alegre, Brazil. Based on a joint International Network Programme grant from the Danish Agency for Science, Technology and Innovation the new initiative involved a workshop at InsCer in April and a workshop at NRU in September, bilateral exchange of two students for a period of four weeks each, as well as proposal of and preparation for a shared symposium that was held in January 2016 at the Winter Conference on Brain Research.

The Center for Experimental Medicine Neuropharmacology (NeuroPharm), funded by the Innovation Fund was inaugurated in June 2015. NRU is the coordinating partner in the Center and we collaborate with partners from the University of Copenhagen and from university hospitals in the Capital Region of Denmark as well as partners from Massachusetts General Hospital, Imperial College London and the British-based small-medium sized enterprise Imanova Limited. You can read more about NeuroPharm on page 20.

The Center for Integrated Molecular Brain Imaging (Cimbi) came to conclusion of its funding period from the Lundbeck Foundation. The 10-year long initiative Cimbi was celebrated at an excellent 3-day symposium in September 2015, supported by and held at the Royal Danish Society for Sciences and Humanities. Cimbi will continue, but as an action confined to the radioligand development work (former Platform 1) and the name of Cimbi will still be associated with the Cimbi Database and Biobank. A description of last year's research output from Cimbi is given on page 10.

In September 2015, Professor Jens D. Mikkelsen, and senior researcher at NRU since 2008, started to work as Chief Scientific Officer at Bionomics Ltd. in Adelaide. Bionomics is one of the leaders in CNS drug discovery onion channel targets, in particular, the nicotinic alpha7 acetylcholine receptors. This work will be important for further application of the research initiated at NRU in the clinic. Professor Mikkelsen will continue his commitment at NRU on part-time through his leadership of the Danish Strategic Research Council project COGNITO, described separately on page 18.

I hope that you will enjoy reading this 2015 annual report and encourage interested readers to read more on our website which was significantly upgraded in 2015.

On behalf of the NRU management group

Gitte Moos Knudsen

Professor, Head of Department

Contents

About Neurobiology Research Unit

Mission

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 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.

Activities

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 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.

Finances

The vast majority of NRU research is funded from external sources; most notably through the establishment in 2006 of the 10-year Lundbeck Foundation *Center for Integrated Molecular Brain Imaging* (Cimbi, page 10), supported by 80 mio DKK, and *Novel treatments of cognitive dysfunction* (COGNITO, page 18), funded 2012-2017 by the Danish Council for Strategic Research with 18 mio DKK, and *Center for Experimental Medicine Neuropharmacology* (NeuroPharm, page 20) funded 2015-2020 with 15.6 mio DKK from the Innovation Fund Denmark. On page 31, all current external funding sources are acknowledged.

About Neurobiology Research Unit

Staff in 2015

NRU is chaired by Professor Gitte Moos Knudsen since 2004. In addition, the management group has in 2015 consisted of Professor Olaf B. Paulson, Chief Engineer Claus Svarer, Ass. Professor Lars H. Pinborg, and Post docs Vibe G. Frøkjær and Patrick Fisher. Professor Jens D. Mikkelsen is laboratory leader and responsible for the basic neuroscience section together with PhD Henrik B. Hansen, and Claus Svarer is responsible for the data analysis section. The Chief Technologist in the SPECT laboratory is Gerda Thomsen. The staff employed by or otherwise involved in the work at NRU in 2015 are listed below. The organizational diagram can be seen on the next page.

All new faces in 2015 are marked with a *.

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 (Psychiatric Center Copenhagen)

Administration
Birgit Tang
Dorthe Givard
Peter S. Jensen

Post Docs
Agnete Overgaard, human biologist, PhD
Anders Ettrup, human biologist, PhD
* Brice Ozenne, biostatistician, PhD (half time at Section of Biostatistics, Univ. Copenhagen)
Cornelius Donat, biologist, PhD
Hanne D. Hansen, molecular biologist, PhD
Linda Blomster, biomedical chemist, PhD (Saniona A/S)
Ling Feng, engineer, PhD
Melanie Ganz-Benjaminsen, computer scientist, PhD
* Mikael Palner, engineer, PhD

PhD Students
Brenda Mc Mahon, MD
Christian G. Jensen, psychologist
Dea S. Stenbæk, psychologist
* Henrik Steglich-Arnholm, MD (Rigshospitalet-Glostrup)
Jo Henningsen, biochemist
Liv V. H. Brüel, psychologist
Louise M. Jørgensen, MD
Marie Deen Christensen, MD (Rigshospitalet-Glostrup)
Mette T. Foged, MD
Per Jensen, MD
Sofi da Cunha-Bang, MD
Valdemar L. Andersen, pharmacist (FARMA, Univ. Copenhagen)
Vincent Beliveau, neuroscientist

Research Assistants
Agnete Dyssegaard, pharmacist
* Chantal Schlumberger, pharmacologist
* Cheng Teng Ip, psychologist
* Jens Ulrik L. Henriksen, biologist
* Lene L. Donovan, Medicine with Industrial Specialization
* Martin Nørgaard, engineer
* Thao P. Tran, medical chemist

Technical Research Personnel
Anders D. Olsen, IT-support
Gerda Thomsen, chief technologist
Glenna Skouboe, medical technologist
* 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
* Victor F. Hansen, IT-support

Visiting Scientists
Dan Peters, PhD, CEO at DanPET, Sweden
Doug Greve, PhD, Boston, US
Kishore Vakamudi, New Mexico, US
* Leif Østergaard, professor, Århus, DK
* Rasmus A. Olsen, ass. Professor, Århus, DK
Stefan Posse, professor, New Mexico, US
* Ulrich Lindberg, engineer, PhD, Glostrup, DK

Pregraduate Researchers and Students
* Annette Johansen, medicine
Anine T. W. Skibsted, medicine
Charlotte B. Mikkelsen, engineer
* Claudia G.K. Rasmussen, biochemistry
* Emil Holm, medicine
Erik Perfalk, medicine
* Franziska Wichern, human biology
Gunild Vulpius, medicine
Gustav R. Jakobsen, medicine
Janus H. Magnussen, human biology
Jonas Villadsen, molecular biomedicine
* Lars V. Knudsen, medicine
Lea Bäcker, liberal arts and sciences
Lola Torz, biology
Mathias Kølvraa, medicine
Martin K. Madsen, medicine
* Martin W. Witting, psychology
* Nanna Hansen, psychology
Nina A. Frimer, human biology
* Sabine M. Lund, psychology
* Sofie T. Pedersen, medicine
* Sophia Armand, psychology
* Terje Martens, medicine
Vibeke N. H. Dam, psychology
Zuhal Filikci, medicine

Some of the new NRU faces

Senior Researcher

Henrik Björk Hansen
Neuropharmacologist, PhD

Henrik B. Hansen holds a PhD in pharmacology and is a translational neuroscientist with 12 years of experience from the pharmaceutical industry. He has a strong track record on disease/drug-target driven research in regard to psychiatric, neurological and metabolic diseases. The overall aim of his research at NRU is to identify and in-depth characterize drugs with therapeutic potential in neurocognitive and neurodegenerative diseases. His research has emphasis on drug pharmacodynamics, drug-target validation, translational biomarkers and disease models.
His interest is generally to drive research programs with the aim to understand the underlying pharmacological mechanisms of different classes of alpha7 nicotinic acetylcholine receptor (alpha7 nAChR) enhancers for selecting the right compounds to the right treatment indications, with special emphasis on schizophrenia. The human alpha7 nAChR is different from other mammalian isoforms and is likely to consist of several functional units regulating alpha7 nAchR function in the CNS, which makes it important to specifically study the human isoform in health and disease. One current focus on his research is to investigate to what extend alpha7 nAChR function and pharmacology is influenced by co-expression of a human-specific partially duplicated alpha7 nAChR subunit.

Visiting Professor

Leif Østergaard
MD, PhD

Since August 2015, Leif Østergaard has spent time at NRU as a visiting professor with support from a 1,5-year sabbatical stipend from the Lundbeck Foundation. He is head of Center for Functionally Integrative Neuroscience and MINDLab at Aarhus University but now works at NRU on average 1 day per week.

Leif Østergaard is interested in the ways in which the microcirculation facilitates oxygen and glucose transport in tissue, and how capillary dysfunction might be involved in disease processes such as neurodegeneration and inflammation. Olaf Paulson and Gitte Moos Knudsen conducted seminal work within capillary function and substrate extraction in the brain, and his stay will therefore allow him to interact with NRU researchers on this subject. This collaboration has so far resulted in plans to study metabolite levels in the brain using novel technologies. Leif Østergaard is also interested in the role of inflammation in late-onset depression. During his stay, Leif will benefit from interactions with NRU group members and collaborating researchers to understand how altered serotonergic neurotransmission and other disease components contribute to this complex disorder.

Post Doctoral Fellow

Brice Ozenne
Biostatistician, PhD

Brice Ozenne is new post-doc in biostatistics with a shared position between NRU and the Section of Biostatistics at University of Copenhagen. He has done his PhD in biostatistics at University Lyon 1 in France with his thesis entitled “Statistical modelling for the prognosis of stroke patients”.

Brice is interested in developing statistical models for analyzing data with complex relationships and high-dimension (e.g. medical imaging data). For this, he is working on extending Latent Variable Models (LVM) by integrating non-linear relationships between variables, and allow for spatial correlation between observations. LVM are statistical models which are able to relate measurements in a very flexible way in order to characterize immeasurable quantities. For instance, when relating psychological and Positron Emission tomography (PET) data, one has to handle several psychological outcomes (e.g. sensitivity to positive, neutral or negative signals) and PET signals, each corresponding to a different serotonin receptor. By introducing new variables also called latent variables, LVM are able to approximate the depression status of the patient and the serotonin level through the analysis of the shared information between the available measurements.

Brice will be applying these methodological developments on data collected at NRU. They may improve the understanding of the brain mechanisms involved in depression and help to derive biomarkers predicting the patient recovery regarding the treatment option. In addition to his methodological research, Brice is also providing statistical consulting on study design and statistical analysis to people from NRU.

About Neurobiology Research Unit

Awards, Grants and Honours

Recipient of the ISCBFM Lifetime Achievement Award 2015

Olaf B. Paulson
Professor, MD, DMSc

Professor Olaf B. Paulson has in 2015 received the Lifetime Achievement Award from the International Society for Cerebral Blood Flow & Metabolism (ISCBFM) for his outstanding contributions to the field of cerebral blod flow and metabolism. The award was presented at a special ceremony at the ISCBFM'15 meeting in Vancouver, Canada.

Post doc grant recipient

Mikael Palner
Engineer, PhD

In 2012, after I received my PhD degree at NRU, I moved to Stanford University to begin 3.5-years postdoctoral training. During this time, I was fortunate to learn how selective activation or inactivation of neuronal networks leads to changes in behavior and how we can use *in vivo* imaging like PET and MR to map the activation patterns on a whole-brain level. I looked at how selective activation of dopaminergic neurons in the striatum changed the binding affinity of a dopamine D_2 receptor tracer called [^{18}F]Fallypride.

These experiments paved the way for a new 2-year postdoc project at NRU, where I plan to look at two different dopaminergic projections, the striatal and prefrontal cortical. I will activate or inhibit these projections and map how this effects the dopamine and glutamate levels using [^{18}F]Fallypride PET and MR spectroscopy. Furthermore, I am also going to see how this effects different behavioral patterns and neurochemical markers. My project has received funding from the Danish Council for Independent Research and the Lundbeck Foundation, and it will start a new direction of preclinical imaging at NRU with the focus on whole-brain neuronal networks.

Post doc grant recipient

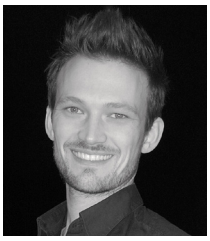
Melanie Ganz-Benjaminsen
Computer Science, PhD

From March 2008 until May 2011, I completed my PhD studies in medical image analysis at the Department of Computer Science at University of Copenhagen. After finishing my PhD, I spent two years as an external postdoc at the Martinos Center for Biomedical Imaging in Boston, USA, where I worked with the neuroimaging software FreeSurfer in a project funded by the Lundbeck and the Alfred Benzon Foundations. At the Martinos Center I got in contact with Prof. Gitte Moos Knudsen who was there in 2011-12 on 6-months sabbatical, and this contact paved the way for my return to Denmark in 2014 where I started working at NRU on a one-year postdoc project funded by the Carlsberg Foundation.

In my new postdoc project which is funded by the Lundbeck Foundation, I will explore how machine learning techniques can be applied to robustly identify variations in the human brain as determined by molecular (PET) and structural brain imaging (MR). Specifically, I will utilize a series of five unique multimodal data sets of the serotonin neurotransmitter system which have been collected at Cimbi and consist of approx. 200 high-resolution brain PET and MR scans of healthy volunteers. I will examine this high dimensional neuroimaging data by machine learning tools such as multivariate regression and utilize it to build a population-based atlas of the serotonin system that can be used as a reference and for constructing biomarkers of brain disease.

NRU PhD degrees

Christian Gaden Jensen



In November 2015, psychologist Christian Gaden Jensen defended his PhD thesis entitled "*Critical Investigations of Two Meditation-Bases Stress Reduction Programs and of Mindfulness as a Predictor of Mental Health in the Population*". Christian had been enrolled at the Faculty of Health and Medical Sciences at University of Copenhagen.

Evaluation committee:
Professor Erik Lykke Mortensen (chair), Section of Occupational and Environmental Health, Dept of Public Health, University of Copenhagen

Professor Andreas Roepstorff, Center of Functionally Integrative Neuroscience and MINDLab, Dept of Culture and Society, Aarhus University

Professor Gregory Lewis Fricchione, Associate Chief of Psychiatry, Director, Division of Psychiatry and Medicine, Benson-Henry Institute for Mind Body Medicine, Massachusetts General Hospital, Harvard University, USA

Faculty supervisor:
Professor Steen G. Hasselbalch, University of Copenhagen

Project supervisor:
Professor Peter Elsass, University of Copenhagen.

Majbrit Myrup Jensen

In March 2015, humanbiologist Majbrit Myrup Gaden Jensen defended her PhD thesis entitled "*Characterization of the alpha7 nicotinic receptor and Lynx proteins and their relation to Alzheimer's disease - a translational neurobiology study*". Majbrit had been enrolled at the Faculty of Health and Medical Sciences at University of Copenhagen.

Evaluation committee:
Ass. Professor Anders A. Jensen (Chair), Medicinal Chemistry Research, Dept of Drug Design and Pharmacology, University of Copenhagen, Denmark

Professor Poul Henning Jensen, Dept of Biomedicine, University of Aarhus, Denmark

Professor Neil S. Millar, Dept of Neuroscience, Physiology and Pharmacology, University College London, UK

Project supervisors:
Professor Jens D. Mikkelsen, Neurobiology Research Unit, Neuroscience Center, Copenhagen University Hospital, Rigshospitalet, Denmark

Ass. Professor Morten S. Thomsen, Systems Pharmacology, Dept of Drug Design and Pharmacology, University of Copenhagen, Denmark

Valdemar Lykke Andersen

In January 2015, radiochemist Valdemar Lykke Andersen defended his PhD thesis entitled "*Development of PET-tracers for the 5-HT7 receptor*". Valdemar had been enrolled at the Faculty of Health and Medical Sciences at University of Copenhagen.

Evaluation committee:
Ass. Professor Paul Robert Hansen (Chair), Dept of Drug Design and Pharmacology, University of Copenhagen, Denmark

Ass. Professor Dirk Bender, Nuclear Medicine & PET Center, Aarhus

Dr. Jan Passchier, Imanova, Centre for Imaging Sciences, Imperial College, London

Principal supervisor:
Professor Gitte Moos Knudsen, Neurobiology Research Unit and Center for Integrated Molecular Brain Imaging, Rigshospitalet

Co-supervisors:
Ass. Professor Jesper Langgaard Kristensen, Department of Drug Design and Pharmacology, University of Copenhagen

Post doc Matthias Manfred Herth, Neurobiology Research Unit and Center for Integrated Molecular Brain Imaging, Rigshospitalet

Positions of Trust

Gitte Moos Knudsen: Chairman for the steering group for research laboratories at Rigshospitalet from 1999; Scientific Advisory Board Member of the Danish Strategic Research Council from 2010 and of the Swedish Research Council and VINNOVA in 2015; Vice-president of the European College of Neuropsychopharmacology (ECNP) since 2013; Field Editor at the International Journal of Neuropsychopharmacology since 2013; Board of Directors of the Brain Prize since 2014 and of the Kristian Jebsen Foundation since 2015.

Olaf B. Paulson: Auditor for Danish Society for Neuroscience; Member of the editorial board of the Scientific World Journal; Referee for several international journals; Member of review committee for Italian Ministry for Education, University and Research (MIUR).

Jens D. Mikkelsen: Member of the Danish Medical Research Council since 2013; 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: Appointed member of The Young Academy of Denmark since 2011.

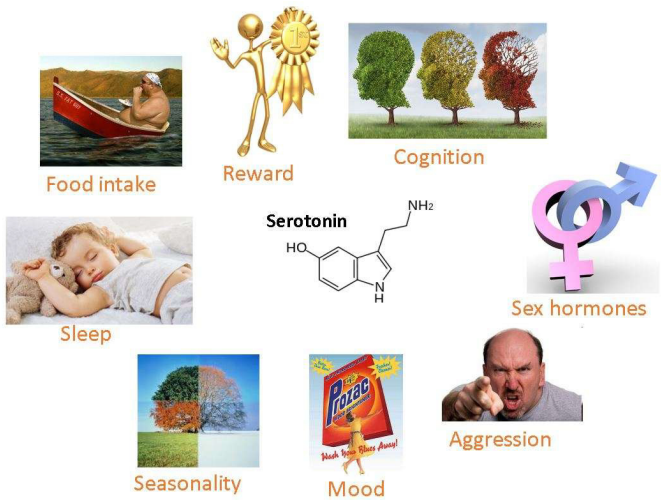
Center for Integrated Molecular Brain Imaging

www.cimbi.org

Director: Gitte Moos Knudsen

The Center for Integrated Molecular Brain Imaging (Cimbi) builds on collaborations between various research institutions in Copenhagen and was established in 2006 and extended in 2011 through two generous 5-year grants totalling 80 mio DKK from the Lundbeck Foundation. The institutions involved in Cimbi span many scientific fields and provide the strong foundation needed to carry out the diverse activities undertaken in the Center.

The research in Cimbi has to a major extent focused on the serotonergic neurotransmitter system. As illustrated below, the serotonin system is involved in a large variety of psychophysiological functions, including feeding, mood, aggression, and pain.



Serotonin is also a critical neurotransmitter in brain development and in the generation and regulation of emotional behaviour. Individual differences in trait effect and personality are for a large part genetically determined, and they are critical in shaping complex human behaviour, social interplay and also in overcoming challenges from the ever-changing environments. Such individual differences may also serve as important predictors of vulnerability to neuropsychiatric disorders, including depression, anxiety and memory disorders.

In the second operative period of the Center (Cimbi-II, 2011-2015) we focused on longitudinal and interventional studies in order to better address causal relationships and to substantiate the predictive value of brain imaging as biomarkers. Specifically, Cimbi-II operates with five interacting themes of relevance for the serotonergic transmitter system: Mood and Emotions, Biorhythms, Affective Cognition, Brain Development, and Decision-making. In addition, two platforms are included, one for radioligand development and validation, and another for data analysis.

The final year generated again a substantial research output from the Center. In 2015, a total of 35 peer-reviewed articles were accepted for publication. Also, one Cimbi-associated PhD thesis was successfully defended and 2 were submitted for defense.

In February 2015, our highly selective agonist PET radioligand for the serotonin 2A receptor, [11C]Cimbi-36, was officially announced as implemented as a novel imaging biomarker at Imanova, centre for imaging sciences, in London for use in clinical and preclinical PET imaging studies to investigate the serotonin system in psychiatric illness.

A large seminar was held in the Royal Society for Sciences and Letters on September 2-4, 2015 to celebrate 10 years of fruitful research (see photos above). The symposium consisted of exciting lectures from a beautiful cocktail of international speakers and Cimbi-affiliated researchers.

The branding of Cimbi is now well-established and there will at least be three lines of research that will carry on, namely 1) the nomenclature of radioligands developed within the framework 2) the Cimbi database and 3) the Cimbi biobank. The established Cimbi database/biobank are internationally recognized as unique and will continue to constitute a valuable resource for researchers within and outside of Denmark, e.g. for new hypothesis driven studies.

Mood and Emotions

by Vibe G. Frøkjær, NRU

An important endeavor in Cimbi is to advance the understanding of brain functions that drives processing of emotions and regulation of mood and stress responses in the context of risk and resilience for neuropsychiatric disorders. The serotonergic system is organized in a fashion that enables it to modulate such brain functions and also allows integration of hormonal signals, e.g., stress and sex-steroid hormone information. Serotonergic signaling is considered important for an appropriate adaption to environmental challenges across early fetal through to adult life and thus may be critical for shaping risk and resilience brain architecture of neuropsychiatric diseases and the maintenance of mental health e.g., major depressive episodes in the context of in sex-hormone milieu or environmental stress.

Through a combination of cross-sectional work, which is enabled by our unique and world-largest database of molecular brain images of key markers of serotonin signaling [29], and longitudinal experimental modeling of risk mechanisms, within Cimbi, we aim to work from epidemiology to neurobiology and ask "how does risk work". In 2015 the first set of results from natural existing clinical cohorts of subfertile women undergoing reproductive care [43], a large longitudinal placebo-controlled study on pharmacological sex-hormone manipulation in 61 healthy women as a risk model for depressive symptoms, and translational work in rodent models were published [11].

Sex hormones target serotonergic neurons and key limbic structures involved in emotion and reward processing and thus shape the adult female brain during hormonal transition periods. Therefore, changes in sex-hormone milieu may critically affect brain risk and resilience architecture, e.g. the massive hormone changes seen from pre- to postpartum transition may trigger depressive symptoms. As illustrated in Figure 1, Cimbi studies have provided direct evidence for sex-hormone manipulation to provoke subclinical depressive symptoms in about 12% of healthy women, a phenomenon that was coupled to increases in serotonin transporter binding (which lowers synaptic serotonin), and correlated with the magnitude of sex-hormone (estradiol) decline to intervention [12]. This strongly implies transiently compromised serotonin signaling in the mechanisms by which sex-steroid hormone fluctuations provoke depressive symptoms in a subgroup of sensitive individuals. In the same cohort, we have further shown that sex-hormone manipulation (a) affects processing of emotional faces in a manner dependent on depressive responses to intervention [15] and, (b) as seen in Figure 2 reduces brain responses to reward reflecting a reduced engagement in positive experiences [33]. Future studies are needed to illuminate if these findings translate to disturbed serotonin signaling and social motivation in a cohort of depressed mothers, which will be seminal in advancing the understanding of early brain development as well as mechanisms that mobilize natural maternal care capacities and promote social bonding of paramount importance to mother and infant health.

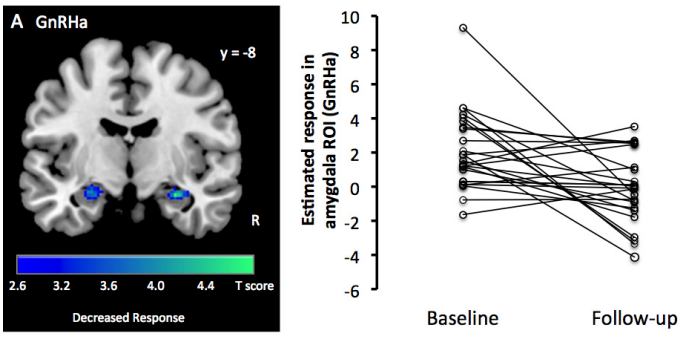


Figure 2: Sex-hormone manipulation with Gonadotrophin Releasing hormone agonist (GnRHa) reduces brain responses to reward bilaterally in amygdala relative to baseline and to placebo intervention. Here changes form baseline are shown for the GnRHa group (N=26). Figure from [33], Copyright © 2016 American College of Neuropsychopharmacology.

In conclusion, our 2015 results highlight that a certain subgroup of women appears particularly sensitive to rapid changes in sex-steroid hormone milieu, which may trigger depressive symptoms due to transiently compromised serotonin signaling and emotion processing, and disengagement in positive experiences. Identifying high-risk groups and mapping the interplay between serotonin signaling, hormone biology and other risk factors for neuropsychiatric disease and the mental health consequences is paramount to support future stratification of populations of at-risk [43] or depressed patients and thus support targeted treatment or preventive strategies in high-risk populations.

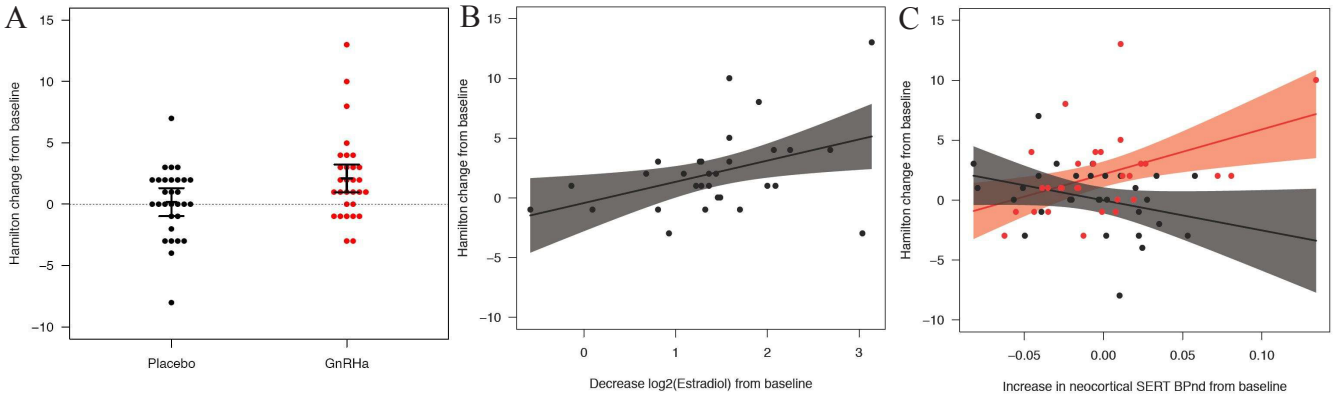


Figure 1: Sex-hormone manipulation with Gonadotrophin Releasing hormone agonist (GnRHa) triggered higher scores on depressive symptoms (17-item Hamilton Depression Rating Scale) relative to baseline and in comparison with the placebo group (panel A). The emergence of depressive symptoms was associated both with the magnitude of estradiol decrease within the GnRHa group (panel B) and with an increase from baseline in neocortical serotonin transporter binding relative to the placebo group (panel C). Figure modified from [12], Copyright © The Author 2015.

Biorhythms

by Patrick M. Fisher, NRU

A central endeavor of Cimbi has been to evaluate variability in neurobiological mechanisms as a function of environmental factors. Whether in response to a drug, exposure to light therapy or simply changes in season, these projects focus on biorhythms of the human brain. Recent analysis of data collected as part of these studies has provided novel insight into biorhythms of the human brain.

One study evaluated how the periodic emergence of depressive symptoms during winter, known as seasonal depressive disorder (SAD), was associated with concurrent fluctuations in the brain serotonin system (Mc Mahon et al., 2016). This project was in part motivated by an earlier Cimbi study showing seasonal fluctuations in serotonin transporter (5-HTT) levels in healthy individuals (Kalbitzer et al., 2010). In the current study, healthy participants and individuals with SAD completed 5-HTT neuroimaging scans with [^{11}C]DASB PET during summer and winter months, allowing us to identify seasonal changes in the brain serotonin system. Interestingly, healthy participants and SAD individuals showed similar 5-HTT levels during the summer, when depressive symptoms were absent, but SAD individuals showed relatively higher 5-HTT levels during winter, when depressive symptoms emerged (Figure 3). Notably, these changes depended upon 5-HTTLPR genotype and gender. Finally, 5-HTT levels during winter months in SAD individuals were positively related to winter depression severity. Taken together, these findings indicate that increased 5-HTT level represents a neurobiological pathway related to winter depression.

Multiple Cimbi studies provide convergent evidence that the brain serotonin system is associated with body weight and obesity ([8], Haahr et al., 2014; Haahr et al., 2012; Erritzoe et al., 2010; Erritzoe et al., 2009). Recently, and in collaboration with the Steno Diabetes Center and the Novo Nordisk Foundation Center for Basic Metabolic Research, Cimbi studied the association between obesity and the brain serotonin system further [19]. Specifically, we examined clinically obese individuals before and after Roux-in-Y gastric bypass surgery and healthy individuals allowing us to evaluate obesity-related differences in the brain serotonin system and the effect of surgery. This study replicated our previous findings including heightened serotonin 2A receptor (5-HT$_{2A}$R) levels in obese individuals (Figure 4). Additionally, pre-surgical 5-HT$_{2A}$R positively predicted weight loss after surgery and changes in both 5-HTT and 5-HT$_{2A}$R levels correlated with weight loss. These findings, through a Cimbi partnership with outside organizations, provide intriguing novel evidence that the brain serotonin system may be an informative biomarker of surgical response to obesity.

These are two examples of how Cimbi research has advanced our understanding of biorhythms of the human brain. This focus is reinforced throughout this annual report where you can find descriptions of projects related to the effects of sex hormone fluctuations and bright-light therapy.

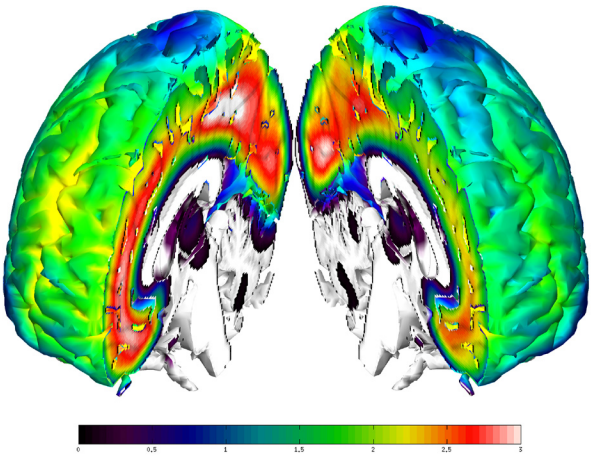


Figure 4: Elevated neocortex serotonin 2A receptor levels in obese individuals. Brain map highlights areas throughout neocortex where serotonin 2A levels are higher in obese individuals (left) compared to healthy lean individuals (right). Color bar denotes serotonin 2A levels. Figure from [19], Copyright © The Author 2015.

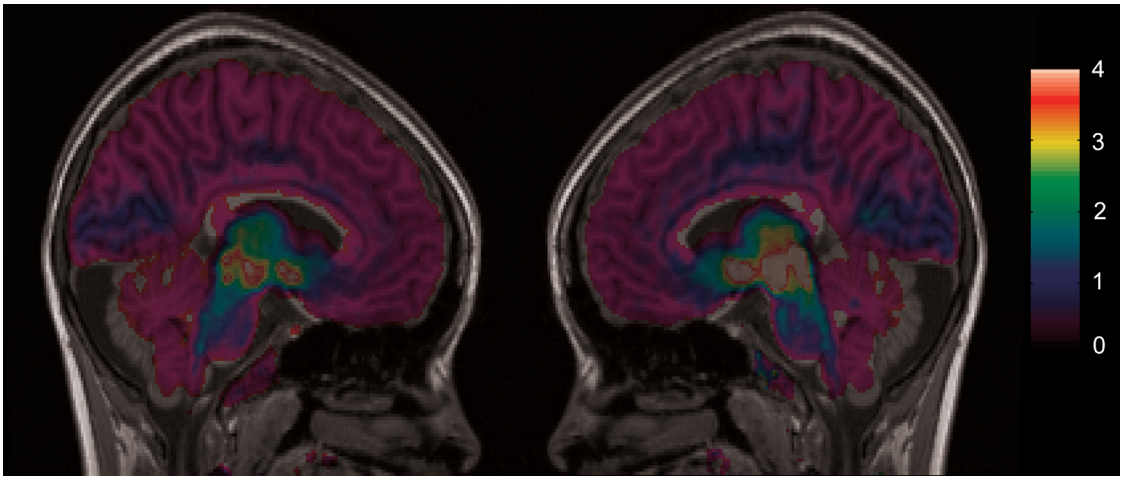


Figure 3: Summer/winter differences in serotonin transporter (5-HTT) levels in seasonal affective disorder (SAD). Brain images from an example patient with seasonal affective disorder (SAD) during summer when 5-HTT levels were low (left) and winter when 5-HTT levels were elevated and depressive symptoms present (right). Color scale denotes 5-HTT levels. Figure from (Mc Mahon et al., 2016), Copyright © The Author 2016.

Affective Cognition

by Dea S. Stenbæk, NRU

The cognitive group at NRU was established as a core facility within Cimbi with the scientific goal of contributing to an interdisciplinary understanding of neurobiological and psychological factors in human health. The cognitive group specializes in research on relationships between the brain's serotonergic system, stress-regulation and affective cognition. In 2015, the NRU cognition group continued to work on developing and validating the first Danish test of affective memory; the Verbal Affective Memory Test-24 (VAMT-24). We published a comprehensive psychometric validation of VAMT-24, where we found that the test showed satisfactory psychometric properties and that it was able to detect seasonal changes in affective verbal recall in participants with seasonal affective disorder. Transition from a non-depressed state during summer to a depressed state during winter was characterized by a significant decrease in positive word recall in participants with seasonal affective disorder compared to healthy controls [21].

In spring 2015, NRU started collaborations with Cambridge Cognition Group, UK, who developed a novel test battery, EMOTICOM, to assess affective and social cognition. During 2015, the test battery was translated into Danish and implemented in the programming system software PsychoPy at NRU. During fall 2015, the EMOTICOM tests were used for the first time in a pilot study on the effects of oxytocin on affective and social cognition in healthy participants. These pilot-data are part of a larger Danish validation study of the EMOTICOM test battery that will commence in spring 2016.

To implement a non-invasive method for investigating serotonergic involvement in mood and affective cognition, we finalized an evaluation of a novel method of acute tryptophan depletion, using a gelatin-based protein mixture. As seen in Figure 5, these results showed that intake of the gelatin-based protein mixture efficiently reduced plasma tryptophan. However, the tryptophan-supplemented gelatin-based protein mixture, used as a sham depletion, induced a large significant increase in plasma tryptophan and we therefore recommend in future studies to use a smaller dose of tryptophan supplement to the gelatin-based protein mixture [44].

Prolonged psychological stress is a risk factor for illness and constitutes an increasing public health challenge creating a need to develop public interventions specifically targeting stress. The Open and Calm project lead by PhD Christian Gaden Jensen was finalized in 2015 and showed that the standardized Open and Calm program reduced stress and improved mental health in patients who complained to their general practitioner about reduced daily functioning due to prolonged stress [22]. A larger implementation of the program in the City of Copenhagen is now in progress.

Aggressive behaviours can be evolutionary adaptive, but when uncontrolled the consequences are often fatal. Aggressive and violent behaviour is a prominent problem in society today with major consequences for public health and for the patients. The adverse social implications of increasing violence and the lack of efficient treatments necessitate a better understanding of the underlying neuropsychological and neurobiological mechanisms. Thus, as part of Liv Vadskjær Hjordt´s PhD project, the role of affective cognitive functions in aggressive behaviour was investigated during 2015 in 38 sentenced violent offenders with high levels of impulsive aggressive behaviour and 40 gender- and age matched healthy non-offenders.

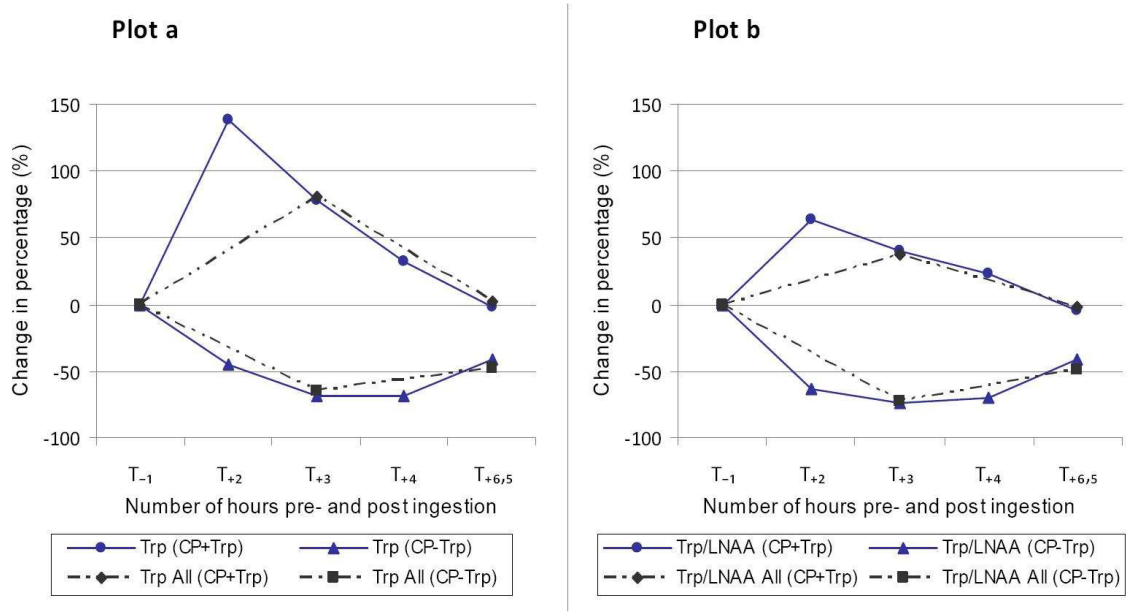


Figure 5: Percentagewise changes in (plot a) plasma tryptophan (TRP) and (plot b) Trp/LNAA as a function of time relative to ingestion of a collagen peptide mixture with (CP+TRP) and without (CP-TRP) tryptophan supplement. LNAA=Large neutral amino acids. The dotted lines represent the total sample in both conditions (CP+Trp and CP-Trp, n=29) and the non-dotted lines represent a subgroup with additional measurement points in both conditions (CP+Trp and CP-Trp, n=13). T_{-1}=1 hour pre-ingestion (baseline) and $T_{+1,+2,+3,+4,+6.5}$=1,2,3,4,6.5 hours post-ingestion. Figure from [44],

Brain maturation in children and adolescents

by Katrine Skak Madsen, DRCMR

The project capitalizes on the wealth of cross-sectional and longitudinal brain, behavioural, and biological data collected in a large group of typically-developing children and adolescents within the HUBU (*Hjernens Udvikling hos Børn og Unge*) project. Initially 94 children aged 7 to 13 years were recruited. Data has been collected with 6-month intervals for up to 11 assessments, and include more than 800 datasets. Within Cimbi, our major interests have been to define the degree of variability in the maturational trajectories of specific brain networks, and to link these to developing cognitive, emotional and neuroendocrine functions.

In 2015, PhD student Louise Baruël Johansson finalized her studies and submitted her thesis entitled "*Neuroticism and Functional Connectomics of the Resting Adolescent Brain: Insights from a Danish Child Cohort*". The personality trait neuroticism is a well-known risk factor for anxiety and mood disorders that typically emerge in childhood and adolescence, a period characterized by ongoing structural and functional maturation of the brain. Resting-state fMRI scans acquired in assessments six through eleven were used to investigate functional brain network characteristics. Firstly, cross-sectional data was used to study whether functional network characteristics associated with neuroticism observed in adults were already present in children and adolescents. As observed in Figure 6, we found that higher neuroticism scores were associated with less efficient information processing throughout the whole functional brain network, and that the higher individuals scored on neuroticism,

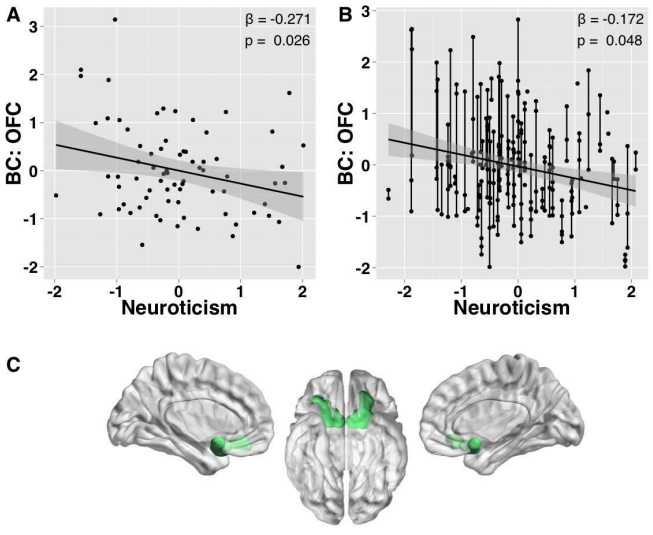


Figure 6: (A) Cross-sectional data partial regression plots showing the significant relationship between neuroticism (N) and betweenness centrality of the orbitofrontal network (BC: OFC), adjusted for age, sex, and parent education. (B) Partial regression plot of the significant relationship between neuroticism and the longitudinal betweenness centrality measures of the orbitofrontal network. The BC:OFC was adjusted for age, sex and parent education, whereas neuroticism was adjusted for within-subject mean age, sex, and parent education. Each line represents an individual subject. The 95% confidence intervals are shown in a darker shade of grey. (C) Outline of the orbitofrontal region (green). Courtesy of Louise Barüel Johansson, DRCMR.

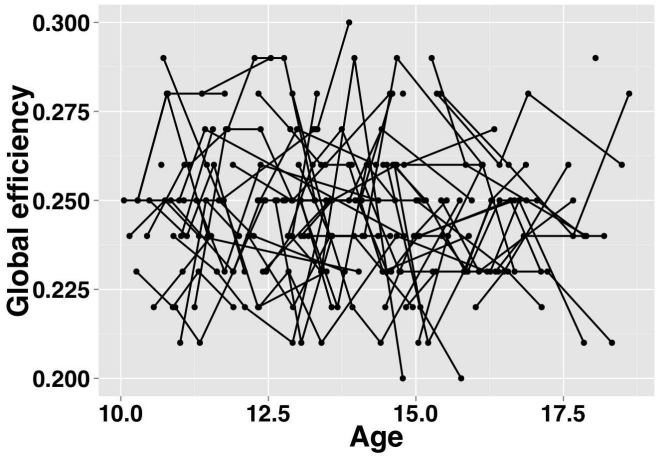


Figure 7: Longitudinal measures of global efficiency of the whole functional brain network are plotted for each of the 74 subjects against age. As can readily be seen the within subject variation in global efficiency is substantial. Intraclass correlational (ICC) analyses confirmed that the reliability with which global efficiency could be measured was poor (ICC<0.4). The same was true for most of the other functional network metrics. In contrast, reliability values for orbitofrontal network betweenness centrality was fair (ICC>0.4). Courtesy of Louise Barüel Johansson, DRCMR.

the less prominent the role of the orbitofrontal cortex (OFC) within the whole functional network. The OFC is thought to contribute to emotion-related processing and decision-making by evaluating incoming emotional and social stimuli. Secondly, longitudinal data was used to study whether the associations observed in the cross-sectional data with high neuroticism were changing during adolescence. As also observed in Figure 6, we confirmed that the OFC played a less central role in individuals with high neuroticism, and we found that this association did not change with age over the age range (10-19 years) covered by the cohort. Additionally, we observed (Figure 7) a large degree of within-subject variability for the majority of the investigated network characteristics over time. The longitudinal results stress the need to replicate findings obtained in cross-sectional studies, which are inherently "blind" to intra-individual variability. Future studies calls for a modeling strategy that accounts for the reliability of resting-state fMRI derived network properties.

Additionally, in 2015 Jonathan Holm-Skjold started his PhD studies fully funded by the Department of Psychology, University of Copenhagen, on "*Brain maturational trajectories linked to emotional and neuroendocrine functions in adolescents*". Furthermore, advanced statistical methods to model the longitudinal relationship between brain and behavioral data are developed in collaboration with lead scientist Wesley Thompson, Research Institute for Biological Psychiatry, Mental Health Centre Sct. Hans.

Neural correlates of risky decisions and reward

by Julian Macoveanu, DRCMR

Bright-light interventions are efficient in alleviating depressive symptoms. However, neurobiological mechanisms through which they may contribute to the observed antidepressant effect remain unknown. In a double-blinded study design, we performed whole-brain functional MRI at 3T in healthy participants to probe brain activity related to risk-taking during a two-choice gambling task. The participants were investigated twice, before and after a three-week bright light intervention. We also assessed the serotonin transporter-linked polymorphic region (5-HTTLPR) genotype to test whether the brain's response to bright light is modulated by inter-individual differences in serotonin transmission. Our findings show that the bright-light intervention increased the striatal response to risky decisions in a dose-dependent manner without being modulated by the 5-HTTLPR genotype. At the behavioral level, we found the bright-light intervention to cause a differential dose-dependent change in risk-taking depending on the 5-HTTLPR genotype. This is the first study probing the effects of bright-light intervention on risky decision-making providing novel insight into the observed therapeutic effects in clinical cohorts. These findings may serve as a benchmark for evaluating effects in depression disorders with or without seasonal pattern.

Platform 1: Design, Radiosynthesis, and In Vivo Evaluation of PET radioligands for Detection of 5-HT Release

by Hanne D. Hansen, NRU

Cimbi Platform 1 continues to evaluate the 5-HT_{2A} receptor PET radioligand [^{11}C]Cimbi-36 in both humans and in pigs. In pigs, a large study was undertaken to correlate the serotonin release provoked by pharmacological challenges measured with simultaneous micro dialysis and PET imaging (Jørgensen et al., 2016). As evident from Figure 8, a correlation between changes in the extracellular 5-HT level in the pig brain and the 5-HT_{2A} receptor occupancy was observed, indicating that [^{11}C]Cimbi-36 binding is sensitive to changes in endogenous serotonin (5-HT) levels, although only detectable with PET when the 5-HT release is sufficiently high.

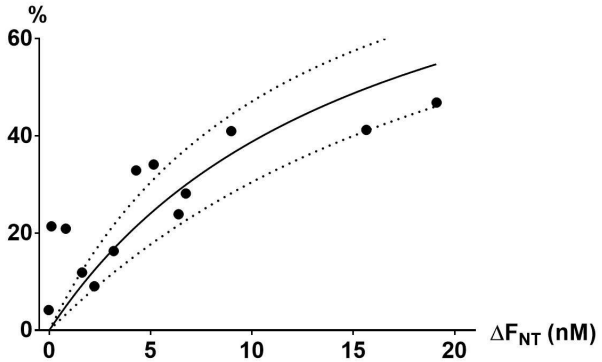


Figure 8: Change in free neurotransmitter (ΔFNT) is correlated with the change in binding of the 5-HT_{2A} receptor PET radioligand [^{11}C]Cimbi-36 (occupancy in %). Each point represents a pig experiment with simultaneous micro dialysis and PET imaging. In the experiments the binding of [^{11}C]Cimbi-36 was measured at baseline and after a pharmacological intervention that would increase the 5-HT levels in the brain. Increased 5-HT levels will compete with the radioligand for the binding to the 5-HT_{2A} receptor. Figure from (Jørgensen et al., 2016), Copyright © The Author 2016.

Large efforts have gone into evaluating the in vivo metabolism of Cimbi-36 in greater detail, with the aim of eventually finding a Cimbi-36 analogue that is more stable and with potential clinical drug effects. Also, because Cimbi-36 has three potential 11C-labeling positions, it is important to know which labelling position is more favourable radiochemically and in terms of most optimal signal-to-noise ratio of the radioligand in the brain. In 2015, we published a study where we identified the phase I and phase II metabolites of Cimbi-36 in pigs as well as in humans [31]. This truly interdisciplinary study combines data from medicinal chemistry, analytical chemistry, radiochemistry, preclinical and clinical imaging data.

Since 2010, we have also been developing and evaluating PET radioligands for the 5-HT_7 receptor. This receptor is interesting because 5-HT has a very high affinity for this target, which means that there is an increased chance of detecting changes in 5-HT in the brain. We have evaluated a total of nine different 5-HT_7 receptor PET radioligands, and the results of [^{11}C]E55888, [^{11}C]Cimbi-772 and [^{11}C]Cimbi-775 were published in 2015 [14,16]. Unfortunately, the results of these three ligands were negative because we could not identify specific binding to the 5-HT_7 receptor in the pig brain.

Platform 2: Data Analysis

by Claus Svarer, NRU
& Lars Kai Hansen, DTU

In 2015, PhD student Vincent Beliveau from the NRU group has continued the creation of a high-resolution atlas of the binding potential of the serotonin transporter and four different serotonin receptors (5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A} and 5-HT_4) based on PET data from our one-of-a-kind Cimbi Database [29] and the FreeSurfer PET pipeline (surfer.nmr.mgh.harvard.edu) previously developed and published by our close collaborators from the FreeSurfer lab at the Martinos Center for Biomedical Imaging, MGH, Boston, USA. The atlas is soon to be published and it can potentially be queried by pattern recognition and machine learning tools and hence accelerate the deciphering of the serotonin system and its involvement in human disease.

In another study performed by Vincent Beliveau we aimed at identifying which brain regions fluctuate synchronously with the raphe nuclei when the brain is not engaged in an active task, i.e. when being in resting-state. Using a multimodal approach combining PET and MR data we were able to delineate the raphe nuclei as a target region (Figure 10) and identify key brain regions involved with these nuclei (Figure 11). The dorsal and median raphe nuclei are the center of serotonin production within the brain and therefore these regions potentially constitute specific targets for pharmacological challenges.

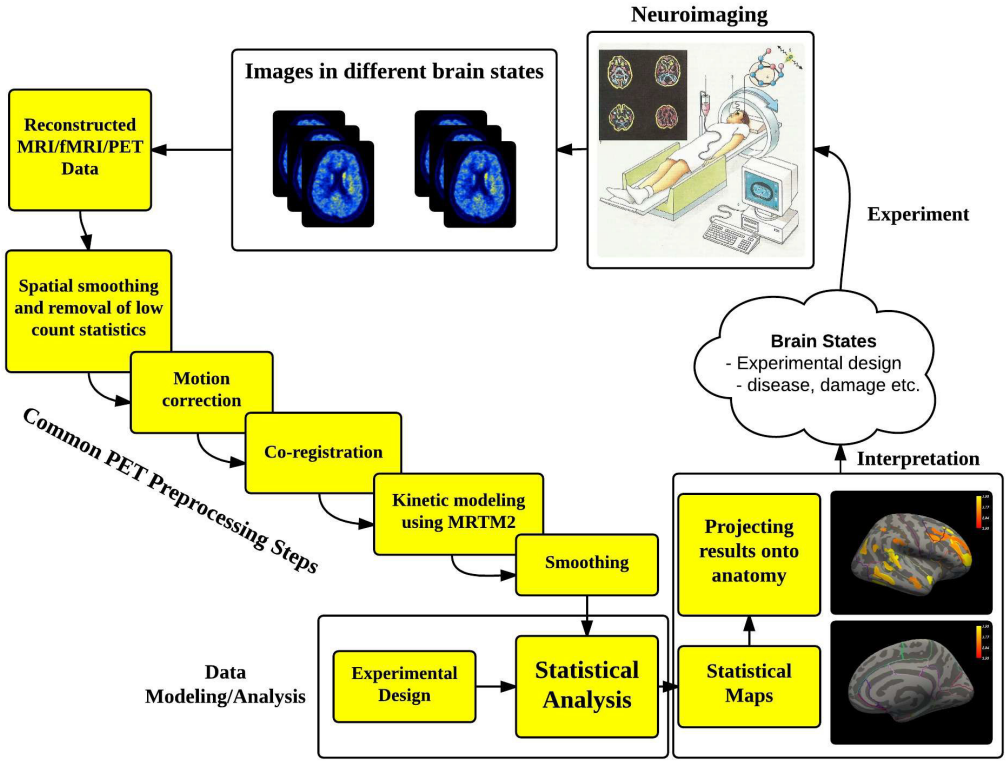


Figure 9: Flowchart depicting a common pipeline in neuroimaging (PET), showing the causal relationship between data acquisition, preprocessing, data analysis, interpretation and finally development of new hypotheses. Courtesy of Martin Nørgaard.

In a project run by Martin Nørgaard the performance of the FreeSurfer PET pipeline was compared to the existing PVElab pipeline (developed previously at NRU) when used for estimation of parametric PET images. This was carried out mainly with the purpose of evaluating preprocessing pitfalls towards a feasible usage in future neuroimaging studies (Figure 9). The project identified both advantages and disadvantages with respect to the FreeSurfer pipeline, and more specifically the project directly pointed out the pipeline variation, by directly comparing the pipeline performance within the same neuroimaging experiment. In conclusion, PET analysis using the FreeSurfer PET pipeline was able to reproduce the results estimated by gold standard procedures such as PVElab.

The DTU group lead by Lars Kai Hansen has in 2015 continued their work on precision imaging of brain activity, which indeed has been one of the main research lines of Cimbi Platform II. While imaging modalities such as MRI and PET have contributed significantly to our understanding of the spatial organization of information processing in the human brain, temporal phenomena are severely undersampled with these techniques. With electro-encephalography (EEG) based brain imaging the situation is reversed: temporal resolution is excellent, though spatial information is both undersampled and confounded by the complex propagation path of electro-static fields through the highly variable conductivity geometry of the human head. Mathematically, EEG brain imaging is an inverse problem:

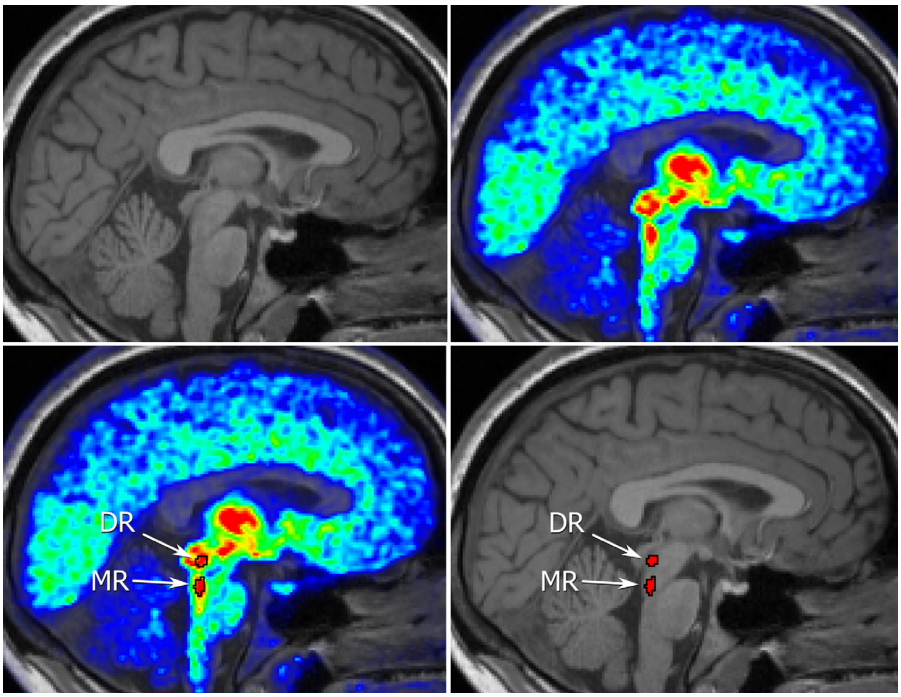


Figure 10: (A) Structural MRI image, where the dorsal and median raphe (DR and MR) nuclei are not identifiable. (B) [^{11}C]DASB PET image superimposed on the corresponding structural image, highlighting the 5-HTT system. The raphe nuclei are visible within brainstem as regions of higher binding. (C) Delineation of the DR and MR nuclei based on [^{11}C]DASB PET. (D) DR and MR identified from the [^{11}C]DASB PET image transferred as seeds onto the structural image.Figure from [3], Copyright © 2015 Elsevier Inc.

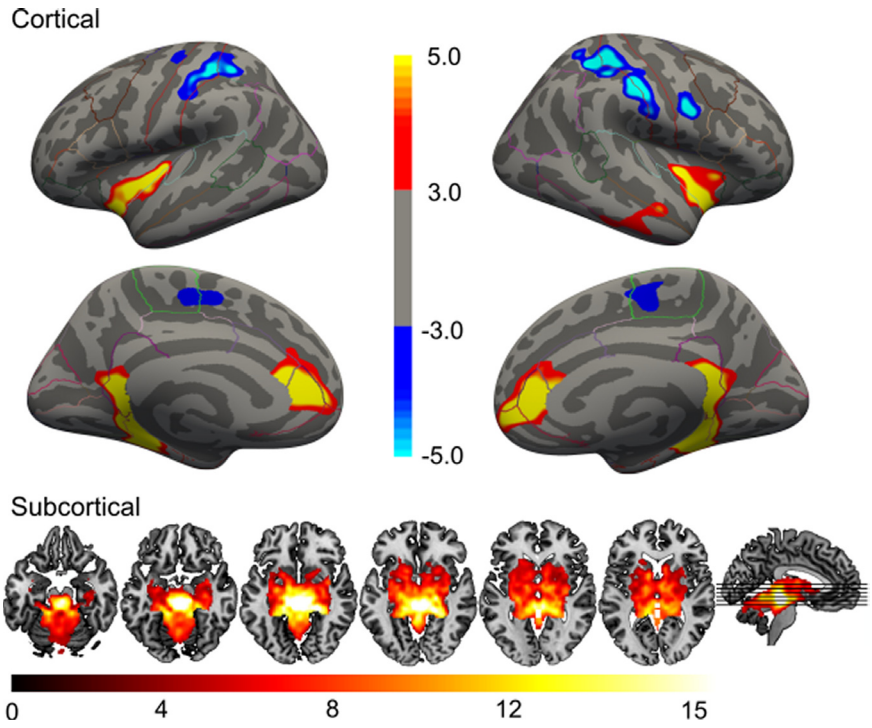


Figure 11: Group-level FCmap for the DR seed, inflated cortical surface and in volume. The map displays clusters of statistically significant FC, corrected for multiple comparisons. Color scales reflect − $\log_{10}$(p) values. Negative p-values (blue) are used to denote regions exhibiting negative FC. The six axial slices correspond to Z = −20, −15, −10, −5, 0 and 5 (left to right). Right is right in axial images. Figure from [3], Copyright © 2015 Elsevier Inc.

Based on measured electrostatic fields at the scalp we aim to make inferences about the 3D spatial distribution of the dipolar sources. While it is easy to formulate the mission; the inverse problem faces two major challenges: Due to spatial undersampling - typically we have access to a rather small number of scalp measures and we aim to make inference about thousands of brain sources - the problem is formally very ill-posed. Furthermore, the forward propagation path is complex and only partially known.

The main progress in 2015 is a new data driven approach to EEG forward model inference. Using public data, the DTU group has established a database of 1600 forward models covering a range of head shapes and conductivity profiles. With the database we have created a low-dimensional representation that can be used to constrain the huge search space for forward models; for the first time allowing inference of both head geometry and conductivity from EEG data. We have tested the approach in simulation and in publicly available benchmark data to demonstrate the viability. As larger databases become available world-wide we will be able to build more accurate “priors” that will enable routine use of individual forward models without access to extensive anatomical data, thus removing one of the significant barriers to EEG precision imaging.

COGNITO

www.cognitoproject.com

Director: Jens D. Mikkelsen

The COGNITO project lead by Professor Jens D. Mikkelsen is supported by the Danish Research Council and aimed to evaluate the efficacy of new pharmacological intervention principles for impaired neurocognitive function. Apart from 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 trials have not been successful due to lack of efficacy. Sufficient therapeutic treatments for these patients are therefore still lacking. The alpha7 nicotinic acetylcholine receptor (alpha7 nAChR) is considered one of the most promising novel drug target for cognitive dysfunction in schizophrenia and Alzheimer's disease. Several alpha7 nAChR-selective enhancers including agonists and positive allosteric modulators have been developed by the pharmaceutical industry. These compounds have shown cognition enhancing effects in numerous preclinical animal models. Importantly, a number of proof-of-concept clinical trials have recently confirmed pro-cognitive efficacy of the alpha-7 nAChR partial agonists EVP6124 (encenicline) in patients with schizophrenia, and is anticipated to represent a novel pharmacological treatment paradigm in schizophrenia in the years to come.

It is our aim to provide further insight into the underlying mechanisms of different classes of alpha7 nAChR modulators for targeting the right compounds to the right treatment indications. As a research unit within Rigshospitalet we have opportunities to study the function of genes and receptors in the human brain. Hence, to provide optimal translational value of our research, we utilize human tissues and cell systems.

Research highlights from 2015

Much of the work at NRU and together with partners in 2015 was aimed to study the correlation between variations in the CHRNA7 gene encoding the alpha7 nAChR subunit and disease and personalities. We have found a correlation between variations in the promotor region of the CHRNA7 gene and schizophrenia. The CHRNA7 gene variations lead to lower CHRNA7 gene expression in cell lines, thus suggesting that impaired alpha7 nAChR function contributes to the pathology in these psychiatric diseases.

Humans carry a unique alpha7 nAChR gene variant

Because upregulation of alpha7 nAChR function represents an attractive therapeutic goal, it is important to elucidate the cellular mechanisms that regulate the activity of the receptor. Interestingly, the alpha7 nAChR gene also exists as partially duplicated variant, and this truncated gene is termed CHRFAM7A. Most strikingly, the CHRFAM7A gene is human-specific, hence not found in non-human primates and rodents. As a consequence, the expression and function of the CHRFAM7A gene can only be studied in humans. The observations raise the intriguing possibility that there exist uniquely human mechanisms to regulate the function and activity of alpha7 nAChRs. The CHRFAM7A gene encodes a truncated alpha7 nAChR subunit (dup-alpha7) lacking major parts of the extracellular ligand binding domain. The expression of CHRFAM7A co-localizes with native alpha7 nAChRs in the brain and, 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. In addition, a variant of CHRFAM7A carrying a two base-pair deletion has been identified, conferring a gene polymorphism with further truncation of dup-alpha7 resulting in a further dominant-negative influence on alpha7 nAChR activity.

Because CHRFAM7A is only present in humans it may also represent an evolutionary important gene involved in cognition. In agreement with this notion, carrying at least one copy of this deletion polymorphism in the CHRFAM7A gene is significantly associated with schizophrenia, impaired sensory processing and reduced episodic memory. In combination with the CHRFAM7A gene being present with different copy numbers in the population, this could point to the intriguing possibility that differential expression of CHRFAM7A variants may translate into variability in alpha7 nAChR activity in the brain and also confer differential responsiveness to alpha7 nAChR modulator treatment, but this has so far not been investigated. We have demonstrated the expression of CHRFAM7A in the human brain and are interested to study if CHRFAM7A genotypes is linked to lowered cognitive abilities in normal human subjects and differential alpha7 nAChR ligand binding.

Human alpha7 nAChRs exist as heteromeric receptors

Our research has shown the human alpha7 nAChR can also exist in an additional heteromeric configuration by including a beta2 subunit. Similar to dup-alpha7, alpha7-beta2 nAChR combinations has profound consequences for the pharmacology of alpha7 nAChR enhancers. Our research therefore highlights that the human alpha7 nAChR is different from the rodent isoform, is likely to consist of several functional units regulating alpha7 nAChR function in the human CNS, and may suggest different functional activity of various alpha7 nAChR isoforms in the human brain in both health and disease. Evidently, this has important implications with regard to the understanding of alpha7 nAChR drug pharmacodynamics in the human brain, as the expression, composition and functional activity of different alpha7 nAChR isoforms may vary in different patient populations.

Development of alpha7 nAChR ligands for PET imaging

Access to a suitable alpha7 nAChR PET ligand would be an important tool for demonstrating blood-brain barrier permeability and target engagement in vivo, which will be needed for progressing novel alpha7 nAChR drug candidates in clinical trials. Our ultimate goal is also to exploit their clinical applicability for determining the distribution and levels of alpha7 nAChR ligand binding in health and disease. We have evaluated 11C-NS14492 with the intention to use it clinically. Studies with 3H-NS14492 have indicated that the ligand shows significant species differences with relative low binding capacity in the human brain. We have therefore paused further development of 11C-NS14492 for human use. In addition, we have evaluated alpha7 nAChR binding properties of 18F-ASEM and 125I-ASEM. Our results confirm strong differences across mammalian species with relatively low alpha7 nAChR ligand binding capacity in the human brain, which therefore constitutes a challenge

in development of alpha7 nAChR PET ligands with sufficient target affinity, selectivity and pharmacokinetic properties to be employed in human settings.

The COGNITO partners

The COGNITO project has clear applications, and we collaborate with pharmaceutical companies to identify and characterize compounds that modulate alpha7 nAChR function in an appropriate fashion. The cross-disciplinary cooperation has been highly instrumental in the COGNITO project, culminating in 2015 with a large annual meeting, where also associated partners and pharmaceutical companies participated (see photo below). Several new collaborations with international research groups have been initiated, including the Johns Hopkins School of Medicine, USA (Dr. Andrew Horti), Institute of Radiopharmaceutical Cancer Research, Leipzig, Germany (Professor Peter Brust), and The Ohio State University, Columbus, Ohio (Professor John Bruno).

Photo of the participants at the latest COGNITO annual meeting. The meeting took place in January 2015 at Schæffergården in Gentofte.

Center for Experimental Medicine Neuropharmacology

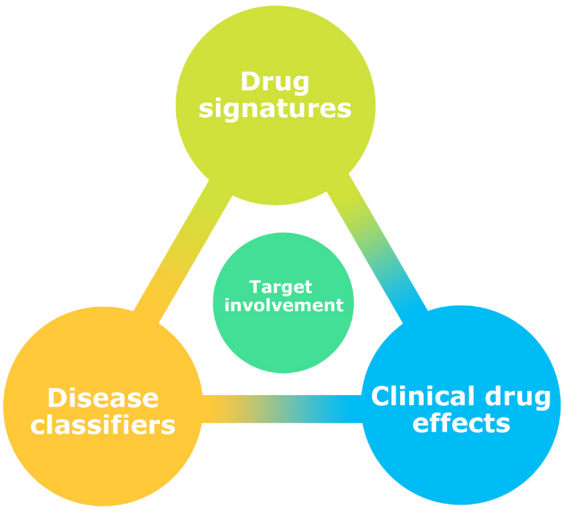
www.neuropharm.eu

Director: Gitte Moos Knudsen

The Center for Experimental Medicine Neuropharmacology (NeuroPharm) is a new research center under Rigshospitalet and University of Copenhagen (UCPH) funded by a 6-year (2015-2020) grant of 15.6 mio DKK from the Innovation Fund Denmark. NRU is the coordinating partner in the Center. 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. Additionally, Imperial College London and the two large pharmaceutical drug companies Pfizer Inc. in USA and Takeda in Japan are involved as affiliated partners.

In order for Denmark to remain an active global partner within clinical research it is mandatory to improve conditions for early clinical trials and experimental treatment. This will ensure industry-financed proof of concept studies. The long term goal of NeuroPharm is to become an international center for human experimental medicine models in brain disorders which can serve industrial partners globally as a next-generation platform for drug discovery. An important part of the 6-year project plan is to have NeuroPharm engaged in novel activities and to establish formal collaboration contracts with industrial partners. This task is going to be the responsibility of the Center Director, by the assistance of the NeuroPharm Steering Group.

The diagram below summarizes the overall framework of NeuroPharm, in the context of drug assessments where the main goal is to identify *target involvement*. Based on data outcome from the various methods available within the Center, e.g., brain imaging techniques we will gain novel insight into the specific patterns characteristic for individual brain-targeting drugs (*Drug signatures*). The same endophenotype data can also critically aid to stratify patients and categorize disease subtypes (*Disease classifiers*) which will enhance prediction of treatment efficacy (*Clinical drug effects*). Conversely, individuals' clinical outcome after drug intervention can itself be part of the drug signature and can help inform the disease classification.



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. By means of PET and MR brain scanning we will 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 will employ these brain imaging tools in patients with, e.g., depression and migraine. We will make use of existing data and biological samples to be analysed in the context of a multivariate data analysis framework. Generation of predictive statistical models will allow for a more informed use of data acquired within the Center and will provide a foundation for better study designs.

An official inauguration of NeuroPharm took place June 10th, 2015, with a 1-day kick-off meeting held at NRU. At this meeting, first Center Director Gitte Moos Knudsen and Center Manager Peter Steen Jensen presented the overall framework of the center and then several other key members of the center presented the more detailed research plans for the individual projects which were subsequently openly discussed among all participants, including members of the Steering Group.

The imminent 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 may inform 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 such stratification of MDD patients would, importantly, allow for individualised 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 the 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 will be carried out in a close collaboration between NRU and Psychiatric Center Copenhagen and it will include a newly established PET-based marker of the brain serotonin system (5-HT_4 receptor binding determined by ^{11}C-SB207145 PET), various MRI techniques, and EEG. We will enrol 100 MDD patients and examine how these markers relate to the outcome of a standard antidepressant treatment. Patients will be carefully evaluated by a trained psychiatrist before inclusion, including cognitive assessments, physical examination and patient history, e.g. self-reported stressful life events. The patients will be treated with standard antidepressive 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 ^{11}C-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 of the patients that are identified as either remitters or non-responders. Prior to intervention and repeated in week 12 all patients will undergo neuropsychological testing to assess affective and non-affective cognition. Further, biological samples will be collected at various time points and enable genotyping and determination of cortisol awakening response, inflammatory markers and epigenetic variations across the study period. The project is currently in the process of obtaining approvals from the ethics committee and the Danish Medicines Agency.

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., pimavanserin, a 5- HT_{2A}R inverse agonist) 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 pimavanserin 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 currently in the process of obtaining approvals from the ethics committee and other relevant Danish authorities.

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, stimulation with a partial 5-HT_{1B} receptor (5-HT_{1B}R) agonist has different effects: We have preliminary data showing that µg-doses of a 5-HT_{1B}R agonist given to non-human primates results not only in significant brain 5-HT_{1B}R occupancy but also in the emergence of an MR-detectable biphasic neurovascular response. Such differences demonstrate the potential to further develop and evaluate neuroimaging methods that allow simultaneous determination of the neurovascular responses (in terms of fMRI), the electrophysiological events (EEG), and target occupancy (PET) in the context of a small and transient pharmacological challenge paradigm. In this work package, we wish to translate this methodology to humans in order to assess its potential to present a completely novel and safe way of evaluating regional cerebral drug effects in the early stages of drug development.

We will use NHPs available at our collaborating partner at the Martinos Center in USA to investigate the hemodynamic effects and 5-HT_{1B}R occupancy by comparing the effects of microdoses and clinically relevant doses of 5-HT_{1B}R agonists with different BBB penetration properties. This allows us to determine if the vascular response differs depending on their BBB permeability properties and elucidate which part of the hemodynamic response is mediated through vascular 5-HT_{1B}R and whether it is related to the clinical symptoms in an acute migraine attack. The paradigm will subsequently be tested in healthy volunteers at Rigshospitalet who undergo two PET-MR examinations in randomized orders with scans being performed with >1-week interval. The project has received approval from the Ethical Committee and the protocol has been submitted to the Danish Medicines Agency.

In our investigations of cerebral spatial and temporal response to triptans following experimental induction of migraine, we are well underway with the data collection. In this project, all patients will undergo three PET scans with ^{11}C-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 of this last project is now finalized and the data processing is ongoing.

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 will be 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 challenge is that the number of predictors may be much larger than the number of subjects, but this may be solved by modern statistical tools such as random forests and regularized regression. A validated prediction model may serve as an important step in translating the knowledge gathered from WP1-WP3 into directly clinically applicable tools.

Clinical Neurology

Olaf B. Paulson

Lars H. Pinborg

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, and annually approximately 100 patients are evaluated here and at the Epilepsy Hospital Filadelfia in Dianalund.

In 2015, PhD student Mette Thrane Foged completed analysis of neuropsychology tests and seizure outcome after epilepsy surgery performed with two different techniques in patients with pathologically verified hippocampal sclerosis. We expect to be able to publish the interesting results in 2016.

The construction of a prospective database for patients enrolled in the Danish Epilepsy Surgery program, which is an initiative supported by the Danish Council for Independent Research, was continued in 2015. The database covers many aspects of importance for patients with epilepsy from sociodemographic data, seizure semiology, intra- and extra-cranial EEG, MEG, MRI including fMRI, molecular imaging, and psychological and psychiatric data. More than 25 members of the Danish Epilepsy Surgery team, including close collaborators at the Epilepsy Hospital Filadelfia in Dianalund, Hvidovre Hospital, and Rigshospitalet-Glostrup have contributed to the content of the database. The database will be hosted at Rigshospitalet and in order to support future research and exchange of data between countries, the actual design of the database is coordinated with close collaborators in Nordic and European countries.

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.

PhD student Mette Thrane Foged has in 2015 in collaboration with Associate Professor Sándor Benickzy from the Epilepsy Hospital Filadelfia started to record and analyse 256 channels EEG in epilepsy surgery candidates. The patient's individual MR scanning together with the exact location of the electrodes (from 11 different cameras) is used to perform a source localization. These results will be compared to the golden standard (the outcome of surgery), and the aim is to estimate the added value of this new method in epilepsy surgery evaluation.

NRU has together with Professor Carsten Thomsen from the Department of Radiology at Rigshospitalet and professor Henrik Larsson and postdoc Ulrich Lindberg from the Functional Imaging Unit at Rigshospitalet-Glostrup set up an MR protocol to scan epilepsy patients before and after their stay in the video-monitoring unit. The aim is to see what many seizures in a short time frame actually do to the brain with regard to resting state networks, diffusion imaging and the blood brain barrier.

Imaging of neuroinflammation

Molecular imaging of neuroinflammatory changes in the brains of patients with neurological, neurosurgical and psychiatric disorders are methods of great potential for research and clinical application. As part of our involvement in the INMiND consortium (described on page 25) we have previously developed a SPECT method for imaging the 18-kDa translocator protein (TSPO) using the tracer [^{123}I]CLINDE (Feng et al., 2014). 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 collaboration with INMiND partners and partners at Rigshospitalet and Bispebjerg Hospital we have initiated several

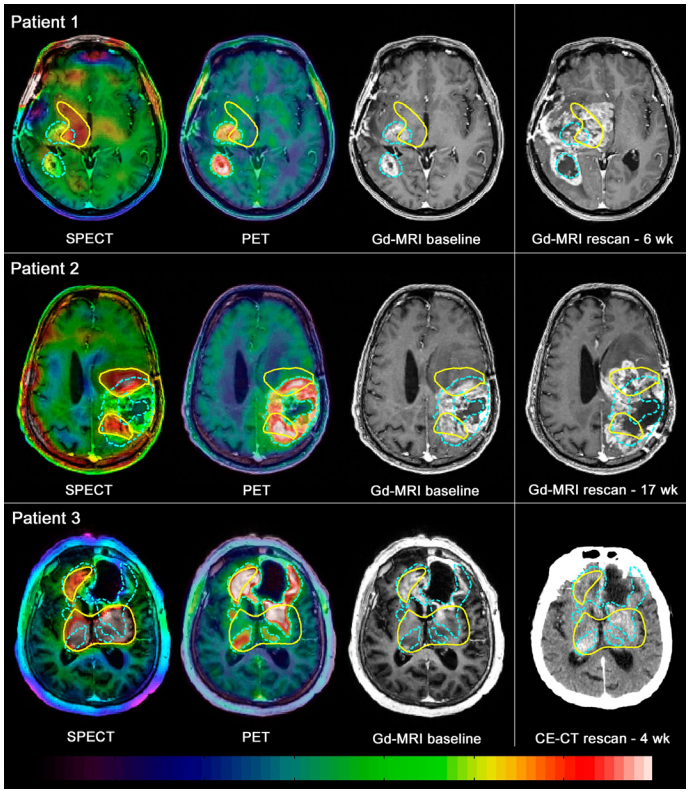


Figure 12: Corresponding (A) [^{123}I]CLINDE-SPECT (demonstrating activated microglia and probably also glioblastoma cells), (B) [^{18}F]FET-PET (demonstrating amino acid uptake) and (C) structural imaging with contrast enhancement in three patients with advanced glioblastoma multiforme (GBM). Figure from [25], Copyright © 2015 American Academy of Neurology.

clinical studies using [^{123}I]CLINDE-SPECT, and in 2015 preliminary findings were reported in three separate publications.

Firstly, we published (front cover of Neurology) a case study of a 35-years old man diagnosed with anti-NMDA receptor encephalitis in which we used [^{123}I]CLINDE-SPECT to demonstrate that imaging of TSPO is useful for diagnosis and monitoring of the effect of immunotherapy [24].

Secondly, we have in a case study of three patients with advanced glioblastoma multiforme (GBM) used [^{123}I]CLINDE-SPECT together with [18F]FET-PET and structural imaging to demonstrate (Figure 12) that TSPO imaging is a sensitive and specific marker of GBM and that regional binding predicts areas of active tumor cell proliferation in GBM at rescan 4-17 weeks after the baseline scans [25]. Based on these preliminary results suggesting that TSPO is upregulated on cells on the frontline of the tumor, favorable implications can be foreseen for planning surgery and radiotherapy and monitoring the effect of oncologic therapy.

Thirdly, we have in a case study of a 67-years old male subject who has suffered from a middle cerebral artery stroke used [^{123}I]CLINDE-SPECT together with structural MRI and fMRI to demonstrate corresponding cellular and functional changes in the brain during the highly dynamic recovery phase after the acute brain damage [26]. As evident in Figure 13, the [^{123}I]CLINDE-SPECT scans show that microglia (and probably also to some extent astroglia) are active around the lesion early after stroke, but over the next weeks also increasingly active in areas remote to the lesion including areas important for motor function in the contra-lesional hemisphere. In concordance with these findings, at the cellular level the fMRI scans show that areas active during fist closure of the paretic hand change with time. In this case, imaging of TSPO using [^{123}I]CLINDE-SPECT implied that microglia is actively involved in stroke recovery not only in relation to the infarcted area but also in remote areas probably reflecting functional reorganization and neuronal plasticity.

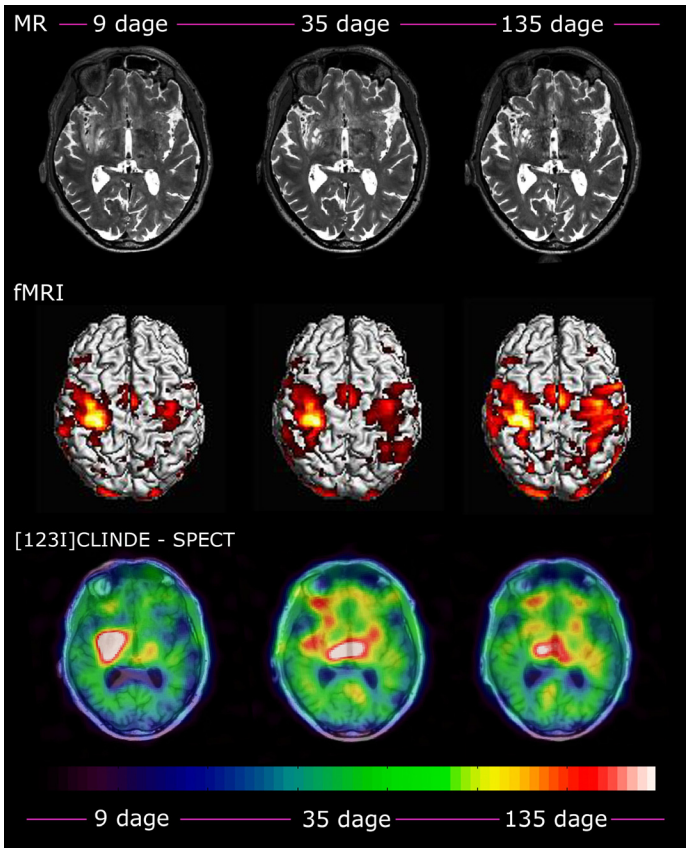


Figure 13: T2 weighted MRI (upper panel), functional MRI from fist closure motor paradigm (middle panel) and [^{123}I]CLINDE-SPECT (lower panel) images from an apoplexia cerebri patient scanned 9 (left), 35 (middle) and 135 (right) days after stroke. On the T2 weighted MRI the initial damage is seen as a hyper intensity in the right thalamus and insula cortex. The functional MRI shows ipsilesional motor activation and increasing contralesional motor activation from 9 to 135 days, when the patient is instructed to perform fist closures. The [^{123}I]CLINDE-SPECT images overlaid with T1 weighted MRI images show a lesional and perilesional increase in tracer binding at 9 days. At 35 days, the [^{123}I]CLINDE binding has decreased lesionally and perilesionally but increased in the ipsilesional and contralesional thalamus. After 135 days, the [^{123}I]CLINDE binding has decreased again, in concordance with the clinical recovery. Figure from [26], Copyright © The Author 2015.

The SPECT Laboratory

Gerda Thomsen

Clinical work in the SPECT-lab

Patients with neurological disorders are referred to the SPECT-lab for diagnostic SPECT-scanning, mostly from the Department of Neurology, Rigshospitalet, but also from Dianalund, Hillerød and other hospitals in Denmark. In 2015, the SPECT-lab conducted more than 200 diagnostic scans.

One type of the clinical SPECT scans conducted at the SPECT-lab is DaTSCAN which is striatal dopamine transporter (DAT) imaging with the ligand [^{123}I]FP-CIT. This technique is used in evaluation of adult patients with suspected parkinsonian syndromes since it may help differentiate essential tremor from idiopathic Parkinson's disease, multiple system atrophy and progressive supranuclear palsy. Furthermore, the technique can help differentiate Lewy body dementia from 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. Finally, a trained clinician evaluates the scan visually, guided by the outcome of the semi-quantitative analysis. In 2015, the SPECT-lab performed a total of 135 DaTSCAN investigations.

Another type of clinical SPECT scans performed by the SPECT-lab is blood flow imaging with the ligand [^{99m}Tc]HMPAO. This technique is unique since after injection of [^{99m}Tc]HMPAO the lipophilic compound crosses the intact blood-brain barrier, distribute in proportion to cerebral blood flow with a peak brain activity within 2 min after injection. 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 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 2015, the SPECT-lab performed a total of 20 SISCOM-analyses.

Research in the SPECT-lab

In 2015, the SPECT-lab has been engaged in different research projects and directly involved in several new peer-reviewed publications. Two very recent publications [Albert et al., 2016; Buchert et al., 2016] are based on data from the ENC-DAT database of [^{123}I]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. The main purpose of the ENC-DAT database is for comparison of the outcome in patients with Parkinson's disease to assist the clinicians' evaluation quantitatively.

SPECT-lab is also 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, e.g., stroke patients during recovery (Figure 13), multiple sclerosis patients, and patients with anti-NMDA receptor encephalitis.

Goodbye to Glenna Skouboe

In March 2015 it was time to say goodbye to medical technologist Glenna Skouboe who retired after impressive 42 years of employment at Rigshospitalet, 37 of these at the Department of Neurology (see photo below). Glenna has been a dedicated, skilled and conscientious employee in the SPECT-lab for many many years, and she has in particular been highly specialized in performing accurate [^{99m}Tc]HMPAO injections in medically refractory epileptic patients for the SISCOM-analyses that are conducted in the SPECT-lab as part of these patients' presurgical epilepsy surgery work-up. In 2013, Glenna received the Queen's medal(Dronningens Fortjenstmedalje) for her 40 years anniversary at Rigshospitalet.

Photo from Glenna Skouboe's farewell reception that was held on March 25th, 2015.

Strategic Collaborations

PET and Cyclotron Unit, RH

For several years, NRU has had an 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 2016 and beyond.

The staff at the Department of Clinical Physiology, Nuclear Medicine & PET with whom NRU has an excellent collaboration.

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.

Martinos Center, MGH, US

The Athinoula A. Martinos Center for Biomedical Imaging was launched in 2000 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

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 has earlier been working at NRU as an associated researcher in an EU-program called CCJobs (Creating Competitive Jobs, http://ccjobs.se/en). The main purpose of Dan Peters' project was to mature the alpha7 PET-ligand 11C-NS14492 so it can be used in the clinic in the future but the project also generated the biomarker 3H-NS14492 as a poster and publication that also became a product, with customers all over the world, commercialized together with Novandi Chemistry AB in Stockholm.

Future collaboration between NRU and DanPET AB will include investigation of two new potential [^{18}F] alpha7 PET-ligands (NS14552 and NS14562) 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 pregraduate training, the following list of NRU-affiliated students successfully defended their theses or research year reports in 2015:

- Gustav R. Jakobsen, "*Cerebral serotonin 4 receptor binding is negatively coupled to the cortisol awakening response*", Bachelor thesis and research year report, Faculty of Health and Medical Sciences, University of Copenhagen
- Jonas Villadsen, "*In vivo* evaluation of agonist radiotracers for brain PET imaging of the 5-HT_{2A} receptor", Master's thesis in Molecular Biomedicine, Faculty of Science, University of Copenhagen
- Martin Nørgaard, "*Multivariate Estimation of Regional Seasonal Variations in SERT-levels in Seasonal Affective Disorder*", Master's thesis in Biomedical Engineering, Technical University of Denmark and University of Copenhagen

In terms of postgraduate training, NRU senior staff members have supervised more than 20 national and international PhD students and post docs. For the fourth 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*".

Participants and Faculty at the PhD course "*Basic Kinetic Modelling in Molecular Imaging*" - on the winded road to understand motion of molecules.

ECNP

ECNP is an independent, non-governmental, scientific association dedicated to the science and treatment of disorders of the brain. The ECNP is today the most active non-institutional supporter of applied neuroscience research and education in Europe.

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 have since the start been responsible for two and a half 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.

Since the start, Professor Olaf B. Paulson has 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 2015, Professor Olaf B. Paulson was also in China to teach.

Other highlights in 2015

DHL relay in Fælledparken

The yearly DHL relay in Fælledparken was held in August. The relay is a good athletic activity and a fantastic social event. Like previous years, NRU participated with four incredibly fast running teams.

NRU retreat meeting

In September, NRU staff were gathered at a two-day retreat meeting in Jutland. First, we visited Center for Functionally Integrative Neuroscience and MINDLab at Aarhus University where we first got a nice introduction to some of their ongoing research and then had guided tours around their facilities. Afterwards we went to a fun and well-organized team building event at Sletten in Ry. Finally, we went to Svejbæk Færgegård where the rest of the program was devoted to social gathering and staying overnight.

Establishing new Danish-Brazilian (NRU-PUCRS) collaboration

In April, seven NRU researchers went to a joint workshop at the Brain Institute (InsCer) at Pontifical Catholic University of Rio Grande do Sul (PUCRS) in Porto Alegre, Brazil, to initiate a new Danish-Brazilian research collaboration within multimodality brain imaging. The new initiative was based on a joint International Network Programme grant from the Danish Agency for Science, Technology and Innovation. In September, the PUCRS visited NRU for another joint workshop.

NRU Christmas Space Party

In December, NRU staff celebrated the end of another successful scientific year with a legandary Christmas party which had "Space" as it's theme.

Publications 2015

As is evident from the lists in this section, NRU has in 2015 published a total of 4 PhD dissertations, 7 book chapters, and 48 scientific peer-reviewed papers (including 5 papers that were published online in 2015 but eventually get a formal publication date in 2016).

NRU collaborators in Cimbi published 4 papers without NRU affiliation, and these external Cimbi publications are listed separately below but with a continued number from the NRU list in order to ease the general referencing in this report.

NRU PhD dissertations

- Christian Gaden Jensen. Critical Investigations of Two Meditation-Bases Stress Reduction Programs and of Mindfulness as a Predictor of Mental Health in the Population. University of Copenhagen, Faculty of Health and Medical Sciences. Defended Nov 23, 2015
- Majbrit Myrup Jensen. Characterization of the alpha7 nicotinic receptor and Lynx proteins and their relation to Alzheimer's disease – a translational neurobiology study. University of Copenhagen, Faculty of Health and Medical Sciences. Defended Mar 26, 2015
- Sanne Wulff. The connection between dopamine D_2 activity, reward disturbances and psychopathology in antipsychotic-naïve first-episode patients with schizophrenia. University of Copenhagen, Faculty of Health and Medical Sciences. Defended Feb 16, 2015
- Valdemar Lykke Andersen. Development of probes for in vivo molecular brain imaging of serotonin markers. University of Copenhagen, Faculty of Health and Medical Sciences. Defended Jan 16, 2015

NRU Book chapters

- Paulson OB, Sørensen PS. Intoksikationer og ernæringsdeficit. In: Paulson OB, Gjerris F, Sørensen PS (eds). Klinisk neurologi og neurokirurgi (2015). Copenhagen: FADL, (6 ed., pp. 668-688)
- Paulson OB, Gjerris F. Neurologisk undersøgelse. In: Paulson OB, Gjerris F, Sørensen PS (eds). Klinisk neurologi og neurokirurgi (2015). Copenhagen: FADL, (6 ed., pp. 14-18)
- Paulson OB, Sørensen PS. Det sensoriske system. In: Paulson OB, Gjerris F, Sørensen PS (eds). Klinisk neurologi og neurokirurgi (2015). Copenhagen: FADL, (6 ed., pp. 52-64)
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