Neurobiology Research Unit

Annual Report 2018

Department of Neurology, Neuroscience Centre
Copenhagen University Hospital, Rigshospitalet

www.nru.dk

Rigshospitalet

KØBENHAVNS UNIVERSITET
DET SUNDHEDSVIDENSKABELIGE
FAKULTET

Contents

Preface

It is a pleasure to present you with the 2018 annual report describing the activities of the Neurobiology Research Unit (NRU).

2018 has been a year where NRU has experienced the most exciting and promising changes. We are facing some major upgrades in our research and clinical infrastructure, to take place in 2019: We will install our new 3T Siemens Prisma MR scanner in the North Wing as soon as the keys to the building have been handed over to Rigshospitalet. The MR-scanner has been funded from different sources, most importantly from the Kirsten and Freddy Johansen Foundation. At the same time, we will install a new 3rd generation high-resolution SPECT-CT Mediso scanner, funded by Rigshospitalet, also in new facilities in the North Wing. The timely installations will allow for an overlap in the use of the scanners, so that we can appropriately test and prepare the new scanners to take over the clinical tasks and research projects. During 2018, we have continued to work with the architects and the construction team to prepare the North Wing 2 building for the move of NRU from the Rockefeller campus and from the NRU laboratories in Building 93. The expectation is that NRU will relocate to the brand-new facilities in the summer 2020. The move will not only allow us close proximity to the scanners and to the Dept. Neurology in the future, but it will also ensure that the preclinical laboratory is conveniently situated next to the other NRU facilities.

Funding-wise, 2018 has been a quite prosperous year for NRU. First, several of our post docs have each received substantial funding for their individual projects, including two of the highly competitive Marie Sklodowska-Curie Individual Fellowships from the EU (3 mio DKK in total) for Sebastian Holst and Martin Schain, a Lundbeck Foundation International Neuroscience Programme grant (2.9 mio DKK) for Hanne Demant Hansen, and a research project grant (3.9 mio DKK) from the Elsass Foundation for Melanie Ganz-Benjaminsen. Secondly, together with our close collaborators Trevor Robbins and Barbara Sahakian from Univ. Cambridge, UK, who in 2018 spend their sabbatical as NRU affiliates, we received from the Lundbeck Foundation two other International Neuroscience Programme grants (totalling 5.3 mio DKK) and, furthermore, together with Professor Adriaan Lammertsma from Dept. Nuclear Medicine and PET Research, Netherlands we received a Lundbeck Foundation Visiting Professorship grant. Last but not least, as the year was coming to a closure, we received very great news that the Lundbeck Foundation had decided also to grant 40 mio DKK for *BrainDrugs*, a 5-year thematic alliance within precision medicine in epilepsy and depression. With *BrainDrugs*, it is our ambition to set the stage for a precision medicine approach in pharmacological treatment of epilepsy and depression, for the benefit of future patients. To succeed in our mission, we have devised a strategy for implementation of research outcomes in the clinic. It is our hope that in the long run, *BrainDrugs* can serve as a model to be implemented internationally, and for other brain disorders. You can find a 2 min pitch of the *BrainDrugs* project through the NRU webpage (www.nru.dk).

The past year again generated substantial research output from the group. Three of our PhD students have after a successful defence of their theses obtained their PhD degree (page 14), and many NRU-affiliated researchers have presented their work at a large number of international congresses, conferences, and meetings. In total, NRU published 41 peer-reviewed scientific publications (page 42).

With respect to research training, we have in 2018 organized both pre- and post-graduate programmes with international speakers and well-attended programs, including an international PhD-course on pharmacokinetics. NRU senior staff members have trained more than 20 national and international PhD students and post docs, and NRU-staff members have again this year taken part in the lecturing at the Master degree program 'Neuroscience and Neuroimaging' at the University of Chinese Academy of Sciences in Beijing as part of the Sino-Danish Center for Education and Research. Furthermore, we have in 2018 hosted international research interns, including three ERASMUS interns from Austria, Scotland and Turkey, a summer intern from USA as well as a visiting PhD-student from Germany.

I would like to take this opportunity to acknowledge and thank all of the NRU staff for their dedicated work as well as to thank our host institution, Rigshospitalet, and all our highly valued national and international collaborators and the funding agencies that support our work. These have all been essential factors to ensure that 2018 was another very successful year for NRU.

I hope that you will enjoy reading this 2018 annual report and encourage interested readers to stay tuned on our website.

On behalf of the NRU management group

Gitte Moos Knudsen
Professor, Head of Department

NRU management group consisisting of Gitte Moos Knudsen and (from left to right starting in the top row) Jens D. Mikkelsen, Vibe G. Frøkjær, Olaf B. Paulson, Claus Svarer, Patrick Fisher and Lars H. Pinborg.

Our Mission & Activities

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

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

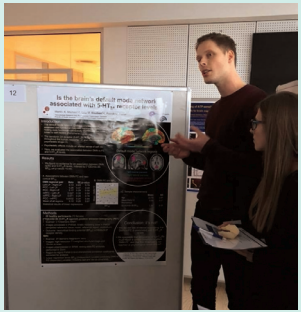
The activities within NRU fall in nine different categories:

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, universities and industry enabling immediate 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.

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



NRU research is often being presented at conferences and meetings world-wide. Here, post doc Hanne Demant Hansen (left) and PhD-student Martin Korsbak Madsen (right) are sharing their exciting results with other researchers within the field.

Facilities

NRU currently has four separate locations on Rigshospitalet, Blegdamsvej, and has access to scanning facilities at additional three sites at the hospital. As described in the preface of this annual report, some major changes are about to occur during 2019-20 (see pictures to the right).

At Juliane Maries Vej 28, in the Rockefeller building (see photo on the back of the report), 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 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 Dept. 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 the basement 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 currently uses MR-scanner facilities at the Dept. of Diagnostic Radiology, in close collaboration with the staff there.

Oct 2018

Nov 2018

Dec 2018

The North Wing 2 building which will be the new permanent premises for NRU after summer 2020 has begun to take shape. Images show construction status as of Oct, Nov and Dec 2018, respectively.

Staff in 2018

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

Chief technologist
Gerda Thomsen

Research administrators
Birgit Tang
Dorthe Givard
Peter S. Jensen

All new faces in 2018 are marked with a *

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

Post docs
Brice Ozenne, biostatistician, PhD
Johannes Björkstrand, psychologist, PhD
Liv V. Hjordt, psychologist, PhD
Louise M. Jørgensen, MD, PhD
Martin Schain, engineer, PhD *
Melanie Ganz-Benjaminsen, computer scientist, PhD
Sofi da Cunha-Bang, MD, PhD
Sebastian C. Holst, engineer, PhD

PhD students
Camilla Borgsted Larsen, MD
Cheng Teng Ip, psychologist (H. Lundbeck A/S)
Giske F. Opheim, neuroscientist
Kristin Forsberg, MD (Psychiatric Center Copenhagen)
Lene L. Donovan, Medicine with Industrial Specialization
Marie Deen Christensen, MD
Martin Korsbak Madsen, MD
Martin Nørgaard, engineer
Mette T. Foged, MD
Sagar S. Aripaka, biochemistry
Vibeke N. H. Dam, psychologist

Research assistants
Agata C. Sainz, molecular biomedicine
Agnete Dyssegaard, pharmacist
Joana Menezes, molecular genetics & biomedicine
Simone L. Bærentzen, human biologist
Victoria Nygart, MSc in public health *
Vincent Beliveau, neuroscientist, PhD

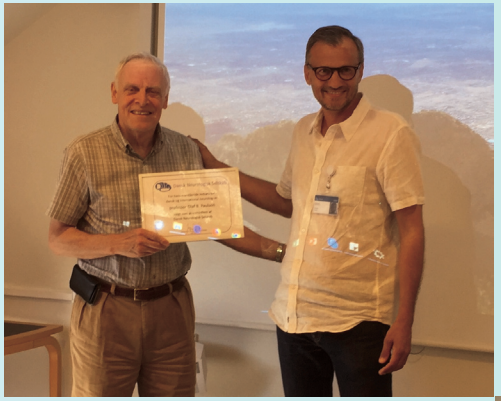
Technical research personnel
Cecilie L. Nordberg, MRI-student assistant
Cecilie F. Skovsen, MRI-student assistant
Ditte B. Christensen, MRI-student assistant
Gunild Vulpius, MRI-student assistant
Josephine Torp, HPLC student assistant
Kristin Elden Varpe, medical technologist *
Kristoffer Brendstrup-Brix, MRI-student assistant *
Lone I. Freyr, project nurse
Louise Nielsen, medical technologist
Lucas Korsgaard Andreasen, HPLC-student assistant *
Luna S. Hansen, MRI-student assistant
Minna Litman, research nurse
Sara L. Jørgensen, MRI-student assistant
Sofie Arpe, Medicine with Industrial Specialization
Svitlana Olsen, medical technologist
Søren Rønborg, MRI student assistant
Thomas Wiklund Jørgensen, IT-support *
Victor F. Hansen, IT-support

Visiting scientists
Adriaan Lammertsma, Prof, VUmc, Netherlands*
Barbara Sahakian, Prof, Univ. Cambridge, UK*
Benno John, Medical and Pharm. Biotech. (ERASMUS intern) *
Burcu Azak Pazarlar, physiology (ERASMUS intern) *
Denise Lange, biology, visiting PhD-stud *
Niki Stypidou, neuroscience (ERASMUS intern) *
Sara Bakalchuk, neuroscience *
Trevor Robbins, Prof, Univ. Cambridge, UK*

Pregraduate students

Alexander Kristensen, engineer *
Ali Ilhan, engineer *
Anders Elkjær Lund, medicine *
Anders Stevnhoved Olsen, engineer *
Andreas Kirknæs Færk, psychology *
Annemette Ringsted, engineer
Anne-Sofie T. Schneider, psychology
Asbjørn Poulsen, medicine *
Camilla Tvede Colding-Jørgensen, biology *
Cecilie L.V. Jokinen, psychology
Charlotte Havelund Nykjær, medicine *
Christian Kildebro, radiography *
Daniel Burmester, medicine
Dorte Bonde Zilstorff, medicine *
Elizabeth B. Landman, medicine
Emily Beaman, human biology *
Freja Jespersen, medicine *
Greta Tuckute, molecular biomedicine
Ida Marie Brandt, molecular biomedicine
Isabel Martínez Tejada, engineer
Joe Lorenz, molecular biology
Johanna Mariegaard, psychology *
Katrine Kiilerich, biochemistry *
Laya Kristina Pätzold, psychology *
Line Buchwald, public health *
Mads Heideman, psychology *
Magnus Emil Lucassen, intern *
Maja Rou Marstrand-Jørgensen, medicine *
Malte Nielsen, psychology *
Mariam Labrouzi, biomedicine *
Marianne Haugaard Hansen, linguistics *
Mathias Glorvigen, psychology *
Mengfei Xiong, pharmacy
Mengting Liu, biology
Miran Dinarzehi, pharmacy
Morten Tøstesen, radiography *
Nikolaj RaahaugeSpeth, pharmaceutical sciences *
Nizar Hamrouni, medicine
Oliver Overgaard-Hansen, psychology *
Robert Sethsen Petersen, molecular medicine *
Saba Ali, biomedicine *
Sara Kristiansen, psychology
Sara Marie Larsen, medicine
Sarah Cohen Pedersen, molecular & medical biology *
Simone Pleinert, psychology
Sebastian E. Ebert, medicine
Sofie Theilmann Kristensen, linguistics *
Sophia Armand, psychology
Søren Vinther Larsen, medicine *
Terje Martens, medicine
Thomas Kawiecki, computer science *
Victoria Fagerholt, molecular & medical biology *

Selected highlights of the year



NRU founder Olaf B. Paulson was elected as honorary member of The Danish Neurological Society (DNS) in 2018. He got his honorary diploma handed over by Jesper Erdal, who is the president of the DNS.

NRU PhD student Marie Deen Christensen won the prize of best oral presentation at NeuroGrad's Winter School 2018.

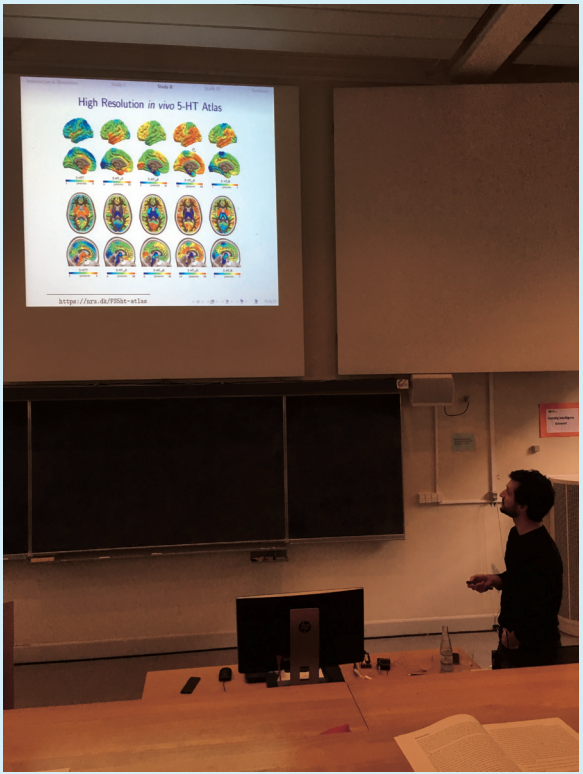
Professors Trevor Robbins and Barbara Sahakian from University of Cambridge, UK spend their sabbatical as NRU affiliates in 2018, enabling an excellent kick-off of our joint research projects funded through two separate International Neuroscience Programme grants from Lundbeck Foundation.

NRU PhD degrees

Vincent Beliveau, Neuroscience

Vincent Beliveau completed his PhD at the Neurobiology Research Unit between December 2014 and November 2017 under the supervision of Prof. Gitte Moos Knudsen, Dr. Claus Svarer, Asst. Prof. Melanie Ganz and Dr. Patrick M. Fisher. His PhD thesis titled "*Functional and Molecular Imaging of the Serotonin System in the Human Brain*" was submitted to the Graduate School of Health and Medical Sciences, University of Copenhagen on November 30th 2017, and presents some of the work he performed during his appointment at NRU.

The thesis included three papers focusing on 1) investigating the functional connectivity of the raphe nuclei in humans at rest, 2) constructing an atlas of the main 5-HT targets available in human PET imaging, and 3) developing a model to extract latent representations of neuroimaging data, while accounting for common structures across dimensions (e.g. time, subjects). Dr. Beliveau successfully defended his thesis on February 27th, 2018, with Prof. Albert Gjedde as chair, and Prof. Koen Van Leemput from Technical University of Denmark (DTU) and Ass. Prof. Rupert Lanzenberger from Medical University of Vienna, Austria as opponents.



Louise Møller Jørgensen, Medicine

Louise Møller Jørgensen completed her PhD at the Neurobiology Research Unit between October 2014 and September 2017 under the supervision of Prof. Gitte Moos Knudsen and with Prof. Jens Christian Hedemann Sørensen from Aarhus University Hospital as co-supervisor. The title of the PhD thesis is "*Pharmacological and DBS-induced changes in cerebral serotonin release*". Dr. Louise Møller Jørgensen submitted the thesis to the Graduate School of Health and Medical Sciences, University of Copenhagen on December 19th, 2017 and defended it on March 9th, 2018 with Prof. Tiit Mathiesen as chairperson, and Professors Kendall Lee from the Mayo Clinic in Rochester, USA and David Brooks from the PET Center at Aarhus University as opponents.

The thesis is based on three studies. In the first two studies in pigs, the association between microdialysis and PET measures of changes in 5-HT level is characterized upon various pharmacological interventions with the aim to raise the extracellular cerebral 5-HT level differently. We demonstrated that the PET radioligands [^{11}C]Cimbi36 and [^{11}C]AZ10419369 are sensitive to detect changes in cerebral 5-HT level. In the last study, we used this novel PET methodology to investigate the presynaptic serotonergic function in patients with Parkinson's Disease (PD) treated with Deep Brain Stimulation (DBS) and the association to mood and clinical measures of PD. We showed that DBS dynamically regulates the 5-HT system in PD patients.

Liv Vadskjær Hjordt, Psychology

Liv Vadskjær Hjordt completed her PhD at the Neurobiology Research Unit between July 2014 and August 2018 under the supervision of Prof. Gitte Moos Knudsen. Her PhD thesis entitled *"I should have been a bear. Bears are allowed to hibernate; humans are not - A Study of Cognitive and Personality Factors Involved in Seasonal Affective Disorder"* was submitted to the Graduate School of Health and Medical Sciences, University of Copenhagen on April 13th 2018.

The thesis is based on three published studies focusing on investigating seasonal changes in 1) inhibitory control and emotional face identification, 2) working memory, cognitive processing speed and motor speed 3) and self-perceived personality characteristics in individuals diagnosed with SAD compared to demographically matched healthy controls. Dr. Liv Vaskjær Hjordt successfully defended her thesis on August 24th 2018, with Prof. Martin Balslev Jørgensen as chairperson, and Prof. Kelly Rohan from University of Vermont in Burlington, USA and Adjunct Prof. Nicole Rosenberg from Århus University Hospital as opponents.

Marie Sklodowska-Curie Individual Fellowships

Martin Schain, PhD

Dr. Martin Schain took his Master's degree at Lund University, Sweden and his PhD degree from the Karolinska Institute, Stockholm, Sweden. After spending two years at Colombia University, New York City, US, he returned to Europe to join NRU.

In his MSCA postdoc fellowship, he seeks to develop a methodological framework for using simultaneous PET-MR imaging to study the interaction of drugs in the human brain. Whereas PET enables determination of whether, and the extent by which, a drug occupies a receptor, fMRI provides information about resulting hemodynamic response. By measuring and analyzing these two signals in parallel, the relationship between neurochemical interactions and neurovascular coupling can be explored.

Sebastian Holst, PhD

Dr. Sebastian Holst took a combined Master's degree in biomedical engineering from the Technical University of Denmark and the University of Copenhagen. He then moved to Switzerland to do a PhD and early postdoc in sleep research and neuroscience at the University of Zurich, before returning to Denmark and joining NRU.

In his MSCA postdoc fellowship, he uses Magnetic Resonance Imaging (MRI) to investigate a novel mechanism of sleep known as glymphatic flow. When we sleep, cerebrospinal fluid is detoured through the brain parenchyma where its flow enables the removal of metabolic waste, including the Alzheimer's associated protein, Amyloid-beta. Because evidence of the glymphatic system is so far restricted to rodents, Dr. Holst's project investigates glymphatic mechanisms solely from a human perspective. The human glymphatic system might be the key to understanding why we humans sleep and whether sleep can in fact be enhanced. In 2018 Dr. Holst published a paper describing the neurochemistry of sleep-wakefulness [14].

Preclinical Neurobiology

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

Translational Neuroimaging and Behavior

Mikael Palner
Junior Group Leader

The research focus is to gain functional and mechanistic understanding of clinical imaging results and to validate novel PET tracers. We use genetic tools to target selective brain circuits and correlate activation of these neuronal pathways to imaging outcomes and behaviour.

In order to relate PET images to brain structures, we developed a rat brain atlas and an algorithm for automated spatial normalization and kinetic modelling based on three PET tracers: [^{18}F]MHMZ (5-HT$_{2A}$), [^{18}F]Fallypride (D_2), and [^{18}F]FDG (glucose metabolism) (**Figure 1**). The work was carried out by Isabel Martinez who defended her Master's thesis in Biomedical Engineering, Mengfei Xiong who defended her Master's thesis in Pharmacy, and visiting PhD student Denise Lange from the German Aerospace Center.

Master's student Joe Lorenz defended his Master's thesis in Molecular Biology in summer 2018. He has been collecting preclinical data on psilocybin occupancy and behavioural response. The active metabolite of psilocybin, psilocin, targets several serotonin receptors and we aim to describe the biochemical mechanism of its polypharmacological actions (**Figure 2**).

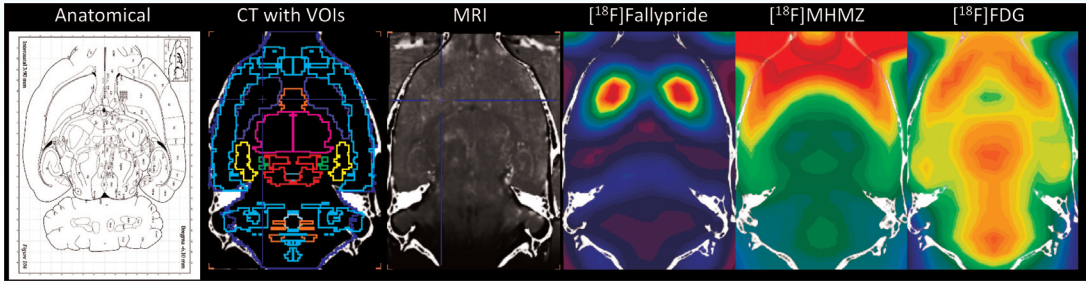


Figure 1: Rat standard brain atlas and receptor distributions in PET images of [^{18}F]fallypride, [^{18}F]MHMZ, and [^{18}F]FDG. Courtesy of Mikael Palner, NRU.

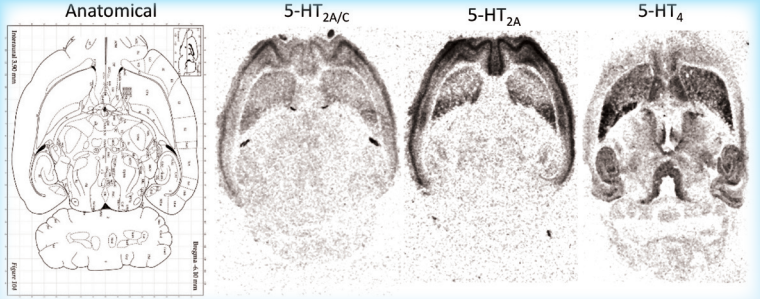


Figure 2: Figure showing anatomical atlas and serotonin receptor distributions of 5-HT$_{2A/C}$, 5-HT$_{2A}$, 5-HT$_{1A}$ and 5-HT$_4$, respectively, in the rat brain. Courtesy of Mikael Palner, NRU.

Agnete Overgaard
Junior Group Leader

Experimental Psychoneuroendocrinology

In a rat model of postpartum depression, we showed with 5-HT$_{1A}$, 5-HT$_{2A}$, and 5-HT$_4$ receptors and serotonin transporter autoradiography that the selective serotonin reuptake inhibitor paroxetine abolishes the corticosterone response to stress [28] (**Figure 3**). This finding offers new insight into the mechanism of action for SSRIs in postpartum depression.

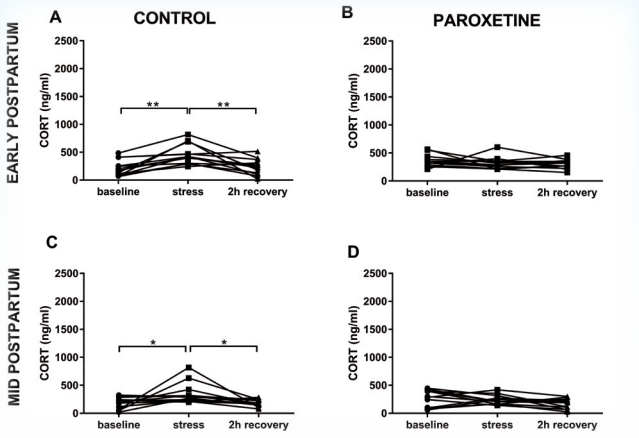


*Figure 3: Corticosterone (CORT) at baseline, immediately after stress, and after 2h recovery in early (day 2; upper panel) and mid (day 12; lower panel) postpartum, in controls (A,C) and paroxetine (PXT) treated dams (B,D). Controls elicit a stress response and full recovery early and mid-postpartum (A; main effect early: $F_{2,38}$=15.40, p<0.001; C; main effect mid: $F_{2,38}$=5.72, p<0.05). PXT groups show no stress response at either timepoint (B,D). Posthoc results are marked with * for p<0.05, and ** for p<0.01. Graphs depict individual data points, connected for individual dams. Modified figure from [28], Copyright © 2018 the authors.*

Neuropsychology

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

Dea S. Stenbæk
Junior Group Leader

As part of psychologist Liv Hjordt's PhD work (see also page 16), we investigated the impact of season on self-assessment of personality in individuals with seasonal affective disorder (SAD) and a group of matched healthy controls, using the NEO Personality Inventory [11]. We found that the groups did not differ in their personality traits during summer and that controls remained stable across the season (**Figure 4**). During winter, individuals with SAD scored higher on Neuroticism and lower on Extraversion compared to controls and to their own summer scores. Furthermore, high scores on Neuroticism in summer was associated with more severe depressive symptoms during winter in SAD individuals (**Figure 5**). Our results support that Neuroticism represents a vulnerability marker related to SAD, and that Neuroticism and Extraversion may be sensitive markers of SAD pathology during a depressive episode.

The group also took part in investigating effects of the psychedelic drug psilocybin in healthy volunteers (more about this on page 37). We have continued data collection and initiated several studies in collaboration with the Cambridge Cognition Group, UK, the Heart Centre at Rigshospitalet, and the Copenhagen Business School. Two psychology master thesis projects and one PhD project were successfully completed and we were again fortunate to accommodate several talented students from University of Copenhagen and University of Southern Denmark.

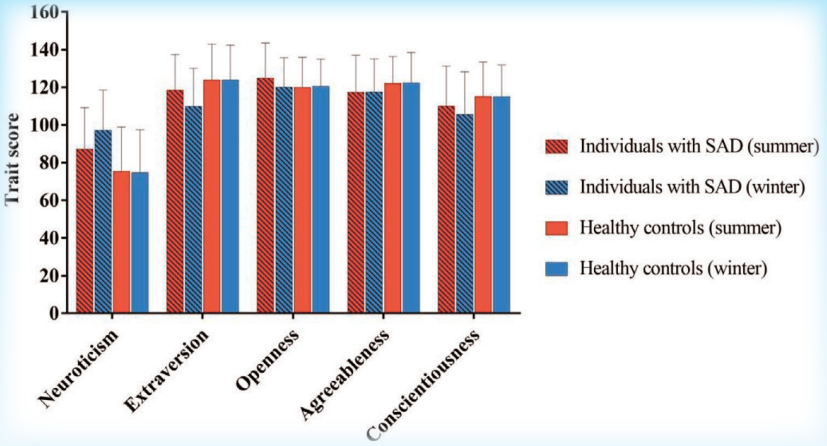


Figure 4: Mean raw scores on the five FFM traits for individuals with SAD (n=29) and healthy controls (n=30) in the summer and the winter. Error bars represent standard deviations. From [11], Copyright © 2018 Elsevier B.V.

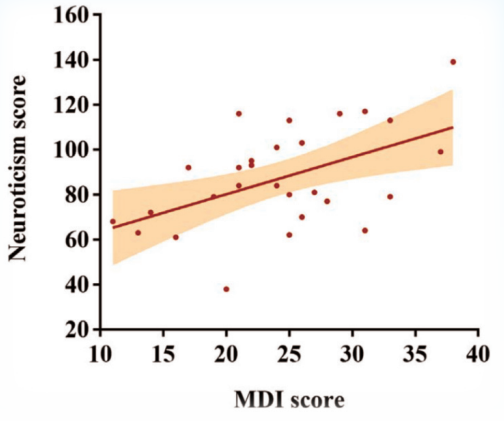


Figure 5: Association between scores on trait Neuroticism during remitted phase in summer and severity of depressive symptoms (indexed by MDI = Major Depression Inventory) during symptomatic phase in winter in individuals with SAD (n=29). In individuals with seasonal affective disorder, higher scores on Neuroticism in summer were associated with higher MDI scores in winter (p = 0.04), which was not the case for matched healthy controls (p = 0.17). From [11], Copyright © 2018 Elsevier B.V.

Data Analysis

The data analysis group continuously work on development and optimization of methods for analyzing contents of molecular and functional PET and MR scans for clinical and research purposes.

Claus Svarer
Chief engineer

A domestic pig brain MRI and PET atlas

The pig is a popular model in translational neuroscience because of its high resemblance to human brain anatomy, physiology and metabolism. To generate standardized and automated processing tools for handling quantification of pig molecular PET neuroimaging studies we created a novel automatic procedure for accurate and reproducible spatial normalization and parcellation of pig brain PET images which works for any radiotracer with reasonable blood-brain barrier penetration [38]. We used high-resolution MRI and [^{11}C]Cimbi-36 PET brain scans of sixteen pigs to develop an accurately averaged MRI template and an averaged PET template in the same space combined with a well-defined regional parcellation atlas (**Figure 6**). Also, we developed and evaluated an automatic procedure for spatial normalization of the averaged PET template to new PET images leading to automatic transfer of the atlas regional parcellation. The digital 3D MRI, PET and parcellation layers of the atlas are freely available at our NRU webpage (https://nru.dk/pigatlas).

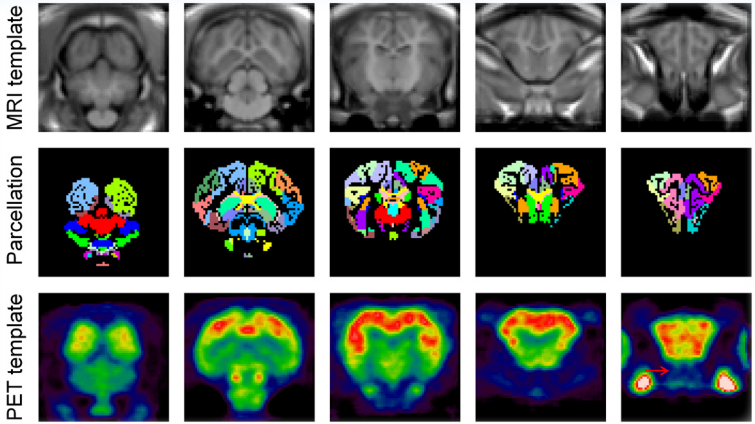


Figure 6: Overview of the atlas modalities shown as consecutive slices 13 mm apart, from back to front in the coronal plane. Top row is MRI of an individual pig in original space, the remaining rows are templates in our pig atlas space. The [^{11}C]Cimbi-36 PET data (lower row) is visualized as a template of total scan time (0-90 min). From [38], Copyright © 2018 Elsevier B.V.

Improved cerebellum parcellation

There has been an increasing movement towards Grand Challenges in the medical imaging community in recent years. These challenges have helped to develop standards for evaluating the performance of different categories of medical imaging problems and for helping those in the periphery of the community to understand the state-of-the-art and the general direction in which the technology is moving. In 2018, we published our contribution to a Cerebellum Parcellation Challenge in a joint overview article [5], containing the performance findings from seven research teams. The NRU contribution from post doc Melanie Ganz-Benjaminsen and PhD-student Vincent Beliveau is the algorithm FS-SUIT which consists of using FreeSurfer and the SUIT algorithm in collaboration for cerebellar segmentation. While FS-SUIT improved segmentations compared to SUIT, it performed worse than other designated cerebellar lobule segmentation tools (**Figure 7**).

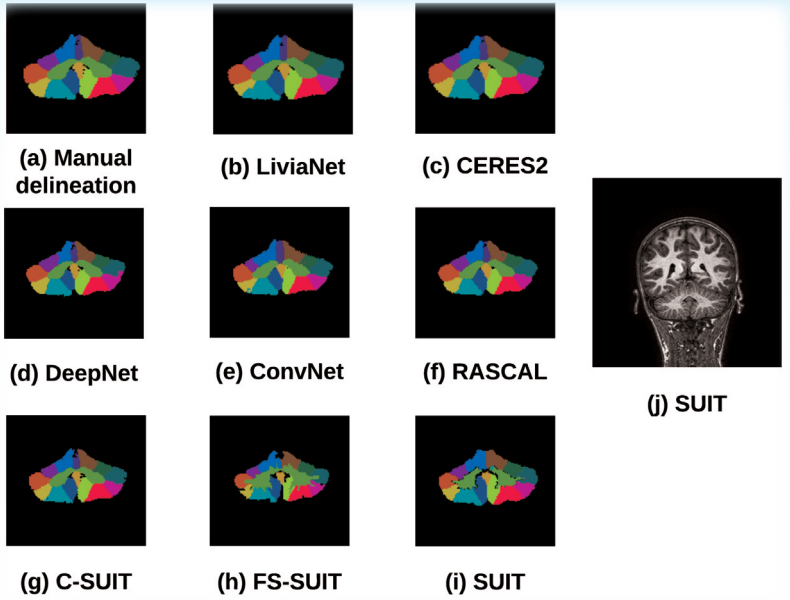


Figure 7: Test data set in the Pediatric Cohort showing (a) the manual delineation, and the results for each of the methods: (b) LiviaNET; (c) CERES2; (d) DeepNet; (e) ConvNet; (f) RASCAL; (g) C-SUIT; (h) FS-SUIT, and (i) SUIT as well as (j) the original coronal structural MR slice. Modified figure from [5], Courtesy of Melanie Ganz, NRU.

EEG data analysis

EEG provides a noninvasive method to measure electrical activity of the brain with high temporal resolution. With the increased use of EEG in clinical practices, a systematic investigation of EEG reliability becomes more important. In collaboration with H. Lundbeck, we investigated test-retest reliability of pre-intervention EEG/ERP (event-related potentials) data across a three-week period consisting of four recording intervals separated by a washout period [16]. When evaluating classical EEG spectra of resting state and vigilance-controlled, auditory steady state response, and ERP components in auditory oddball task and in hybrid flanker task, we found that θ, α and β of continuous EEG were highly reliable (Intercorrelation Coefficients ≥ 0.84, **Figure 8**), while evoked power of other tasks demonstrated lower reliability compared to the absolute power of continuous EEG. Furthermore, reliabilities of ERP measures were lower compared to those of the EEG spectra. Our results show that several EEG/ERP parameters are reliable across three-week intervals, thus enabling validated use for future investigations examining the pharmacological effects of different doses and types of drugs with effects on the brain.

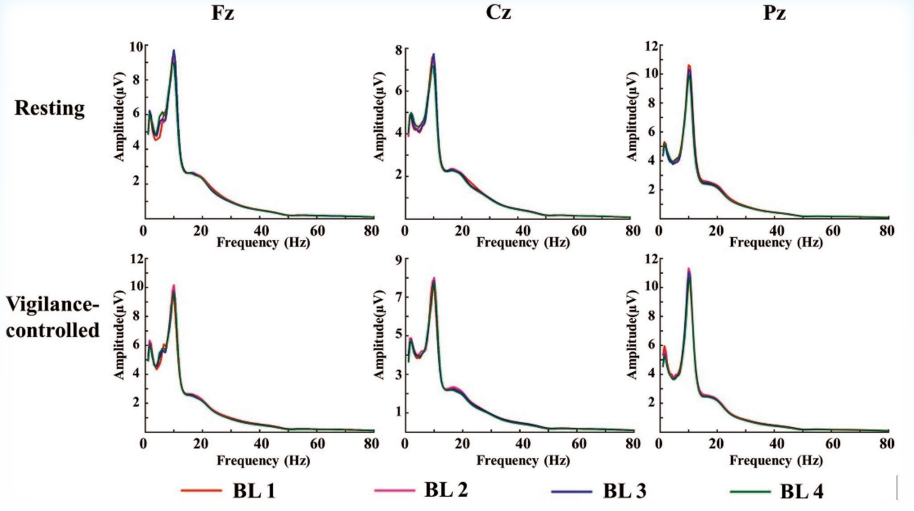


Figure 8: Spectral results for resting EEG including conditions of eye-closed and vigilance-controlled. Three midline electrodes (Fz, Cz and Pz) are shown for each condition. Four recording sessions (BL1, BL2, BL3 and BL4) are shown in different colors. From [16], Copyright © 2018 H. Lundbeck A/S.

Impact of PET preprocessing pipelines

In 2018, PhD-student Martin Nørgaard reported [P1] in a conference proceeding for the 2018 International Workshop on Pattern Recognition in Neuroimaging (PRNI) an evaluation of the impact of preprocessing choices in univariate and multivariate analyses of PET data (**Figure 9**). Thirty healthy participants were PET scanned twice using the radioligand [^{11}C]DASB with no expected changes between scans (null hypothesis). We estimated the false-positive rate (i.e. our ability to falsely reject the null hypothesis after correcting for multiple comparisons) for detecting statistical differences in serotonin transporter binding between scan 1 and scan 2, for approximately 400 different preprocessing choices using either a univariate or multivariate analysis model. The results demonstrated that univariate models are more sensitive to the selected preprocessing choice, and unless corrected for multiple comparisons, results in increased false-positive rates (=36%). Care must therefore be taken in analysis of longitudinal data to avoid attributing an effect to a treatment/condition that was due to the rescan alone.

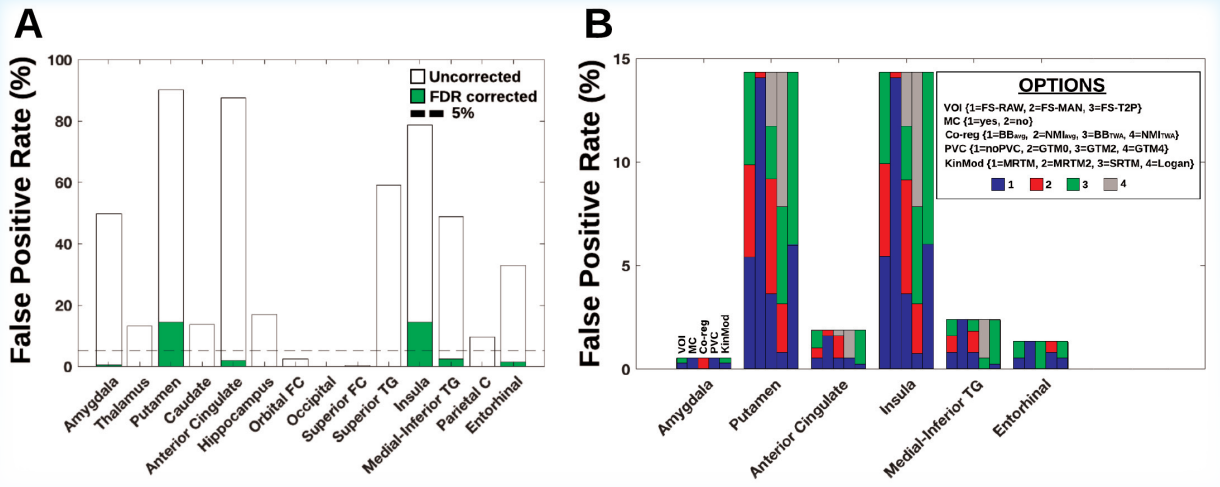


Figure 9: Number of significant results (p<0.05) in 384 pipelines (percentage) for 14 brain regions. Blank is not corrected for multiple comparisons, whereas green is corrected using FDR=0.05. (B) Five regions surviving FDR correction in (A). The five vertical bars within each region represent the distribution of choices, and have the order: 1. Volumes of interest (VOI), 2. Motion correction (MC), 3. Co-registration (Co-reg), 4. Partial volume correction (PVC), and 5. Kinetic modeling (KinMod). From [P1], Copyright © 2018 IEEE.

Functional MRI (fMRI)

At NRU, we use fMRI to assay features of brain function and connectivity that map onto 1) relevant behavioral and molecular phenotypes and 2) intervention strategies in healthy and clinical populations.

Patrick Fisher
Group Leader

Seasonal Affective Disorder

We evaluated the differences in seasonal variation in amygdala response to emotional faces between individuals with seasonal affective disorder (SAD) and healthy controls [4]. SAD individuals showed persistently decreased amygdala responses compared to healthy controls, indicating a blunted emotional response that does not emerge with depressive symptoms but may represent a trait marker of SAD (**Figure 10**).

Aggression

We probed associations between the brain response to social aggression in violent offenders and healthy controls and serotonin brain chemistry [6]. Across violent offenders and healthy individuals, we observed that amygdala reactivity to social provocations correlates positively with brain serotonin 1B receptor binding (**Figure 11**). This finding provides novel evidence further supporting serotonin as a central molecular pathway in shaping individual differences in core threat processing circuits.

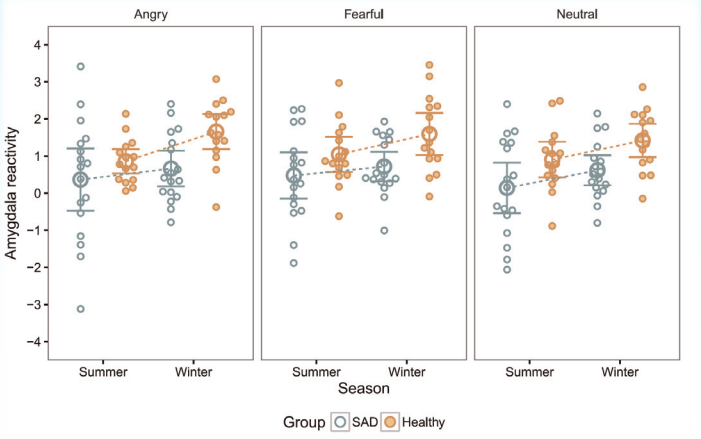


Figure 10: Seasonal changes in amygdala activation to angry, fearful and neutral faces for individuals with seasonsal affective disorder (SAD) and healthy controls (Healthy). Outlined points represent the mean left and right amygdala activation estimates for each participant. Dashed lines represent change in mean group activation. From [4], Copyright © 2018 Elsevier B.V.

Neuroticism and serotonin challenge

Neuroticism is a core personality trait link to risk for depression. Using a cross-over study design where participants received placebo or two types of serotonin intervention, we found that prefrontal cortex responses to emotional faces is associated with neuroticism [15] (**Figure 12**). Interestingly, the nature of this association depended on the serotonin intervention, reinforcing the intimate relation between serotonin, emotion processing and neuroticism.

NeuroPharm

2018 was a year of intensive data collection for NeuroPharm (more information on page 36). Completed aspects of NP1-3 have acquired task-related and rs-fMRI in healthy and depressed individuals that will serve as a foundation for numerous manuscripts planned for 2019. We look forward to these developments and additional developing research projects.

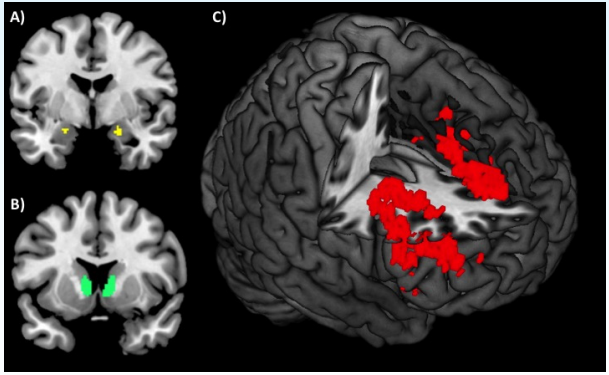


Figure 11: Brain reactivity to provocations within the regions of interest. Amygdala clusters are shown in yellow at y=2 (A), striatal clusters are shown in green at y=10 (B), and prefrontal clusters are shown in red (C). Mean signal values from the clusters shown in this figure were extracted and used for comparison with PET data in the latent variable model. From [6], Copyright © 2018 Elsevier Inc.

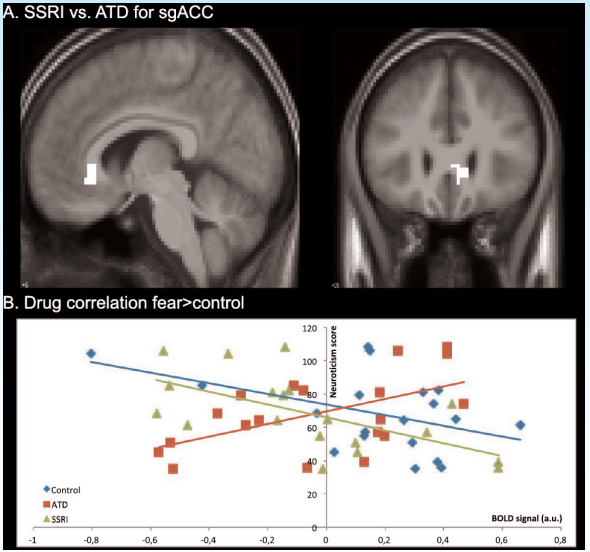


Figure 12: (A) Brain map showing changes in the subgenual cortex (sgACC) activation for fearful face expressions during SSRI (left) and ATD (right) challenges. The white areas indicate changes in BOLD signal (thresholded at p<0.001; uncorrected). (B) Correlation between the individual neuroticism scores and the BOLD response in the sgACC for SSRI, control and ATD challenges. From [15], Copyright © 2018 the authors.

Clinical Psychiatry

Vibe G. Frøkjær
Group Leader

We use imaging to map brain architecture in risk and resilience to mental disorders to provide a rationale for targeted prevention and treatment. We hold an expertise in molecular brain imaging of key features of the serotonin signaling system [18,19] which is profoundly involved in mood disorders, schizophrenia, neurodegenerative disorders and their treatments. In particular, we are interested in serotonin brain biology as a driver of healthy adaptation to e.g. seasons [21], stressors, genetic make-up, personality [11,15], sex-steroid hormone milieu and healthy navigation in social relations.

Aggressive behavior is an enormous societal challenge. We pursue an interest in the neural mechanisms involved in aggression which may inform tactics for development of anti-aggressive treatments. In a seminal study of violent offender inmates, we have shown (**Figure 13**) that men with high serotonin 1B (5-HT_{1B}) receptor binding respond to provocations with heightened amygdala reactivity [6].

Adaptation to season is critical for mental health and Scandinavian populations provide a unique naturalistic model to study season related brain architecture. Individuals who respond to winter with depressive symptoms show profound changes in brain networks responsible for healthy cognitive processing of emotions [4], something that they may be to compensate for only in the summer,

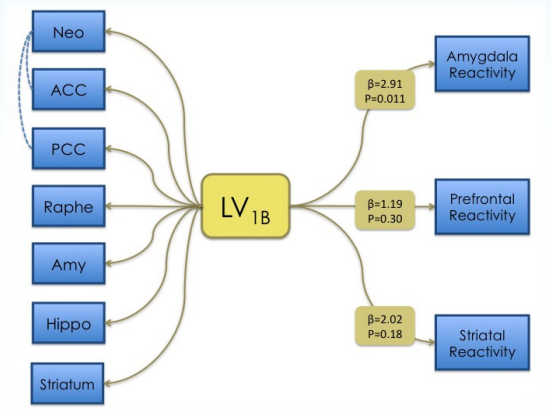


Figure 13: Latent variable model of 5-HT_{1B} receptor binding on amygdala and striatal reactivity to provocations. The yellow oval box represents the latent variable (LV_{1B}), while blue boxes represent measured variables including regional 5-HT_{1B} receptor binding and reactivity to provocations within the amygdala, prefrontal cortex and striatum. Blue hatched lines between neocortex (Neo) and anterior cingulate cortex (ACC) and posterior cingulate cortex (PCC), respectively, denote additional shared correlations. From [6], Copyright © 2018 Elsevier Inc.

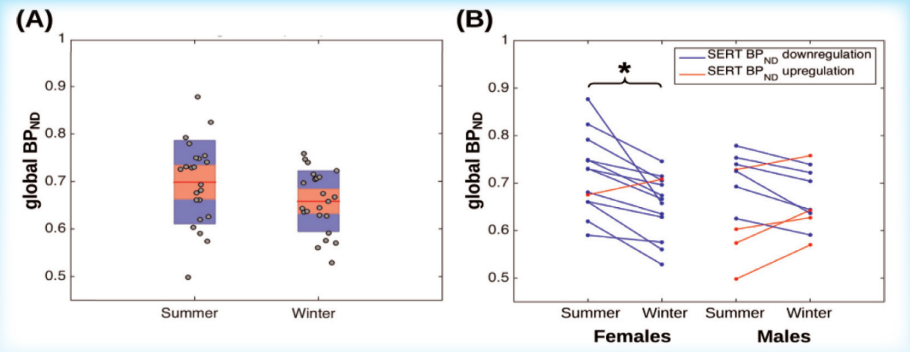


Figure 14: Serotonin transporter (SERT) binding across seasons for (A) all participants and (B) for males and females separately. Data are from individuals who are resilient to seasonal affective disorder. Together, all participants show (A) a significant (P_{season} = 0.003) down-regulation of global SERT BP_{ND} in the winter. The sex-by-season interaction effect, $P_{sex\ by\ season}$ = 0.03, was driven by the female participants showing (B) a larger down-regulation in BP_{ND} from summer to winter. Individual summer to winter adjustments are indicated by the colour bars (red = up-regulation, blue = down-regulation). From [21], Copyright © 2018 Elsevier B.V. and ECNP.

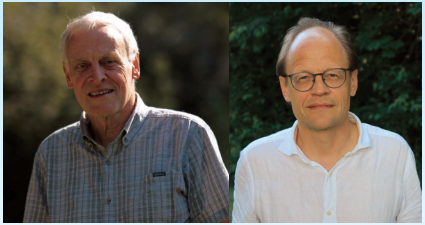
possibly via serotonergic flexibility. Indeed, we have provided direct evidence (**Figure 14**) that flexibility in the serotonin signaling system across summer to winter season characterizes women who stay mentally healthy in the winter [21]. We propose that the capacity to adapt serotonin transporter levels may balance serotonergic tone in the winter, or in other environmental stress conditions, and protect mental health.

This highlights serotonin- and cognitive markers as tools to predict or monitor effect of prevention and treatments of depressive episodes, including non-pharmacological strategies, such as electroconvulsive therapy (ECT) [23,24].

The dynamic interplay between brain biology and sex-steroid hormone systems represents a potent driver of risk and resilience, which we aim to understand better in order to illuminate targetable risk and disease mechanisms. We have previously shown how changes in sex-hormone levels may trigger depressive symptoms in some women; this involves changes in serotonergic signaling, functional brain connectivity, and emotion and reward processing. In rat studies we have now also shown that targeting the serotonin system with SSRI medication cannot stand alone in supporting stress-regulation and reversing depressive-like behaviors in the early postpartum [28], which may inform augmentation strategies beyond SSRIs in clinical reproductive mental health care. In ongoing studies, Sapere Aude recipient Vibe Frøkjær and her group pursue opportunities to protect mother and infant mental health across pregnancy and the postpartum.

Clinical Neurology

Epilepsy



Olaf B. Paulson & Lars H. Pinborg
Group Leaders

Patients with medically intractable epilepsy and 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. Lars H. Pinborg is head of the Danish Epilepsy Surgery program.

We analysed data on all Danish patients operated 2009-14 with 1-2 years of follow-up [12] and found that the outcomes of the Danish epilepsy surgery programme align with international standards found in recent meta-analyses. Although serious complications to epilepsy surgery are rare, Danish drug-resistant patients with focal-onset epilepsy wait far beyond international recommendations before being referred for epilepsy surgery evaluation. Our publication has led to targeted information to Danish medical professionals [31], the Danish Epilepsy Association, media and the Danish Health Authority.

We investigated visual field defects occurring after temporal lobe resection for epilepsy together with professor Miram Kolko [35] and found that visual field defects still is a frequent adverse event after epilepsy surgery; in 20% of patients it may impact their permission to drive a car. In another study we concluded that selective amygdalohippocampectomy in patients with temporal lobe epilepsy without MRI signs of dual pathology results in sustained seizure freedom and better memory function compared with patients operated with non-selective temporal lobe resection [10].

Together with professor Sándor Beniczky from the Epilepsy Hospital Filadelfia and Aarhus University, we tested the feasibility and accuracy of EEG source imaging for detection of the epileptogenic zone in epilepsy surgery candidates [3,33]. We demonstrated a localization accuracy at the sublobar level of EEG source imaging using both automated and semi-automated approaches that compares well with neuroimaging methods like MRI and FDG-PET.

Resected brain tissue from epilepsy surgery patients represents a unique option to test novel treatment strategies for epilepsy directly in target tissue. Together with professor Merab Kokaia at Lund University and associate professor David Woldbye at Univ. Copenhagen, we developed a method (**Figure 15**) for keeping acute human brain slices viable up to 48 hours [39].

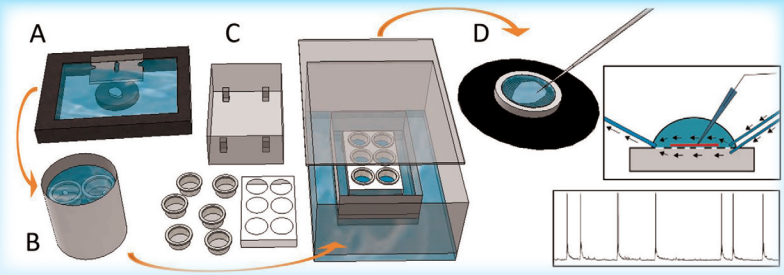


Figure 15: Overview of Experimental setup. (A) The tissue is resected en bloc and sliced on a vibratome. (B) The slices rest for 15 min submerged in continuously bubbled (95% O_2/5% CO_2) aCSF and (C) are then moved to the incubation chamber for 3-48 hours of incubation with a constant flow of bubbled aCSF in the small chamber and humidified air crated by bubbling the aCSF in the outer box which is sealed with a lid. After incubation the slices are transferred to the dual-flow recording chamber (D) where electrophysiological whole-cell patchclamp recordings are made. From [15], Copyright © 2018 the authors.

Migraine

In close collaboration with the Human Migraine Research Unit, led by professor Messoud Ashina at the Danish Headache Center, we have conducted a series of research projects that aim to elucidate the effect of the serotonin system in migraine. The outcome of these studies is described on page 37 (NP3 section).

Consciousness in the Neurocritical Patient (CONNECT-ME)

We wish to establish a cutting-edge tertiary care clinical service for unresponsive patients in the intensive care unit and lay the foundation for a fruitful multidisciplinary research environment for the study of consciousness in acute brain injury. Of note, CONNECT-ME will not only enhance our understanding of consciousness disorders in acute brain injury but it will also raise awareness for these patients who, for obvious reasons, have lacked a voice so far. For this purpose, under the leadership of associate professor Daniel Kondziella, a protocol for a longitudinal prospective study and a tertiary clinical care service has been elaborated [34]. As part of the bedside evaluation of the neurocritical patient, we investigated the pupillary light reflex in stroke patients. Cortical infarcts of the prefrontal eye field or insula did not impair the pupillary light reflex in humans [29]. We found, however, subtle changes when the pupils dilate back to baseline, probably due to autonomic dysfunction.

The SPECT Laboratory

Clinical work

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

One of the standard diagnostic investigations available by the SPECT-laboratory is clinical DAT-SPECT scans, i.e. striatal dopamine transporter imaging with the SPECT ligand [^{123}I]FP-CIT. It is a robust technique for early detection of dopaminergic deficits and is helpful when considering differential diagnoses in patients with movements disorder and/or dementias. The diagnostic report comes with a reference to a healthy age-matched population and is evaluated and commented by a neurologist specialized in reading the DAT-SPECT scan data.

We also measure regional cerebral blood flow with the SPECT ligand [^{99m}Tc]HMPAO. The examination is mostly used as technique for localizing the epileptic focus in patients with drug-resistant epilepsy that are candidates for epilepsy surgery (33). We are the only laboratory in Denmark to conduct ictal-interictal SPECT imaging with co-registration to MRI (SISCOM). This requires personnel specifically trained to inject as soon as the epileptic activity commences.

Currently offered as a research tool and in special patient cases, we also conduct imaging of neuroinflammation in terms of the Translocator Protein which is an 18 kDa protein mainly found on the outer mitochondrial membrane. The protein is upregulated when glial cells are activated and we use the radioligand [^{123}I]CLINDE (reported in earlier annual reports) for SPECT-imaging.

Research projects

The SPECT-laboratory is also engaged in several of ongoing research projects at NRU. We have completed the final [^{123}I]CLINDE-SPECT investigation in a study on the role of neuroinflamation in patients with brain concussion and started a new project regarding neuroinflamation and multiple sclerosis.

We also continue the data acquisition in a study trial that investigates if glucagon-like peptide-1 (GLP-1) receptor agonist stimulation reduces alcohol intake in people with alcohol dependence; the study protocol is a randomised, double-blinded, placebo-controlled clinical trial [1]. The project is led by professor Anders Fink Jensen from the Psychiatric Centre Copenhagen

and the first subproject investigates if the cerebral dopamine transporter is altered in healthy individuals by an acute infusion of a GLP-1 receptor agonist (Byetta® or exenatide). In the main project, people with alcohol dependence are scanned twice, before and after 26 weeks of intervention with GLP-1R agonist or place. Data acquisition is still ongoing.

New molecular imaging system

As mentioned in the Preface, the SPECT scanner facility will soon re-open in new location, at the ground floor close to the main entrance of the North Wing of Rigshospitalet. A brand new AnyScan SPECT-CT scanner was in December 2018 purchased from Mediso; it will be the first of its kind to be installed outside the factory site in Hungary and has unprecedented spatial resolution and high sensitivity.

SPECT-Lab technician Svitlana Olsen helping out PhD-student Camilla Borgsted Larsen in her research project on perinatal depression which involves handling and analysing many different types of biological samples.

Radioligand Development

Hanne D. Hansen
Junior Group Leader

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

We compared two different versions of one of the 5-HT_{2A} receptor agonist radioligand, namely [^{11}C]Cimbi-36 and [^{11}C]Cimbi-36_5, where the only difference is the labelling position [18]. We found that [^{11}C]Cimbi-36_5 gives rise to (small) polar metabolites that cross the blood-brain barrier which leads to an unfavourable signal-to-background ratio (**Figure 16**).Thus, we continue to use [^{11}C]Cimbi-36 for a preclinical and clinical neuroimaging studies of the 5-HT_{2A} receptor.

We have previously shown in pigs that [^{11}C]Cimbi-36 binding is sensitive to acute changes in brain 5-HT levels. In a follow-up study we investigated if this was also the case for the 5-HT_{1B} receptor partial agonist [^{11}C]AZ10419369. By elegantly combining microdialysis, pharmacological interventions and PET in a pig study, we found (**Figure 17**) a correlation between changes in 5-HT as measured with microdialysis and the changes in [^{11}C]AZ10419369 binding [19]. This confirms that [^{11}C]AZ10419369 is sensitive to changes in 5-HT levels in the pig brain.

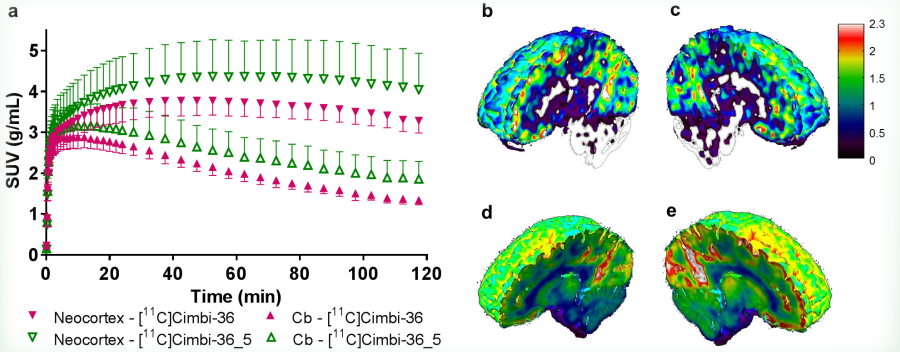
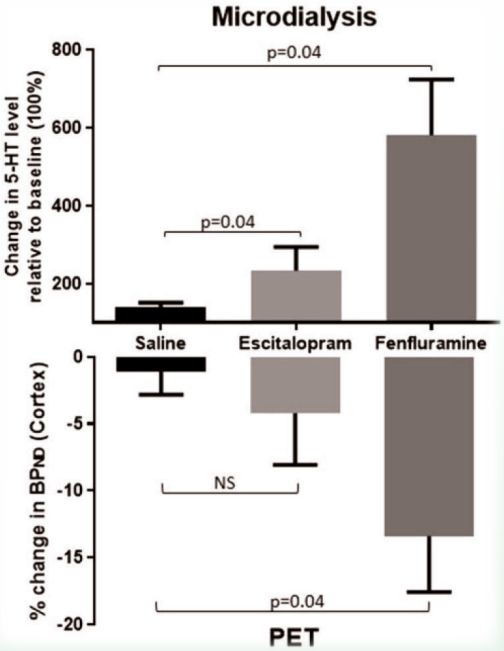


Figure 16: (a) Standard uptake values (SUV) in neocortex and cerebellum (Cb) for [^{11}C]Cimbi-36 and [^{11}C]Cimbi-36_5 (points represent mean ± SD, n=6). (b-e) Maps of BP_{ND} (b and c) and corresponding SUV images (d and e) in one subject scanned with [^{11}C]Cimbi-36 (b, d) and [^{11}C]Cimbi-36_5 (c, e). From [18], Copyright © 2018 the authors.

Figure 17: Changes in brain interstitial 5-HT levels as measured by microdialysis in the mPFC (upper panel) and BP_{ND} as measured by PET in the pig brain neocortex (lower panel) following a within-scan challenge of saline (n=10), escitalopram (n=5), or fenfluramine (n=5). From [19], Copyright © 2018 the authors.



Peter Steen Jensen
Database Manager

Agnete Dyssegaard
Biobank Manager

Cimbi Database and Biobank

At NRU we have for more than a decade systematically investigated the 5-HT neurotransmitter system in humans by acquiring high-resolution brain imaging data (PET, MRI, rsMRI, and fMRI) from several hundreds of carefully screened and well-characterized healthy individuals and patients with various neuropsychiatric disorders. We have imaged the system to the extent that this is possible today, i.e. the serotonin transporter and the 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A}, and 5-HT_{4} receptors. Thereby, we have been able to build a large cohort database (the **Cimbi Database**) that contains a wide range of imaging associated data including demographic, neuropsychological, biochemical, genetic and imaging data. The **Cimbi biobank** is the associated collection of biological specimens from the cohort, including saliva, blood, and in some instances, urine and hair samples, which allow for additional biochemical and genetic analyses.

The Cimbi database and biobank represent a unique and valuable research instrument serving the purpose of storing the wealth of acquired data in a highly structured and safe manner as well as providing a quality-controlled resource for future hypothesis-generating and hypothesis-driven studies. From an international perspective, the comprehensive nature and the sample sizes are exceptional. In 2018 a total of 13 official requests for data were approved.

Innovation Fund Denmark

NeuroPharm

Center for Experimental
Medicine Neuropharmacology

Center for Experimental Medicine Neuropharmacology (NeuroPharm, www.neuropharm.eu) is funded by the Innovation Fund Denmark and resides at NRU. National partners include the pharmaceutical company H. Lundbeck A/S and four academic partners: one from University of Copenhagen and three from university hospitals in the Capital Region of Denmark. International partners include Massachusetts General Hospital/Harvard and Invicro London. Additionally, Imperial College London and the two large pharmaceutical drug companies Pfizer Inc. in USA and Takeda in Japan are involved as affiliated partners.

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

Vibe G. Frøkjær
NP1 WP leader

NP1: Treatment outcome in Major Depressive Disorder

Our goal is to identify neurobiological and other predictors of response to pharmacological treatment of depression. We study basic mechanisms of action of pharmacological treatment of Major depressive disorder (MDD) which in the long term can provide a basis for tailored treatment choices for MDD patients, based on predictors such as quantitative measures of brain function, rather than - as is the case today - rely exclusively on clinical assessment and a tedious trial and error strategy.

We enroll a total of 100 MDD patients and examine how different markers (neuropsychology, MRI, PET, EEG) relate to the outcome of a standard antidepressant treatment, i.e., escitalopram, adjusted contingent on effects and side effects. Patients are followed across a period of 12 weeks from treatment start. Neuroimaging is repeated at week 8 in a subgroup of 40 patients with variable antidepressant response. The patient enrolment was completed in January 2019.

Patrick Fisher
NP2 WP leader

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

The goal of NP2 is to apply an experimental medicine strategy coupled with human functional neuroimaging to elucidate the effects of 5-HT_{2A} receptor (5-HT_{2A}R) modulation on brain function and mood in healthy individuals. We are comparing psilocybin (5-HT_{2A}R agonist) and ketanserin (5-HT_{2A}R antagonist) effects on brain function to identify neural mechanisms mediating the clinical effects of psilocybin and more broadly to establish this comparative strategy as a pathway for delineating pharmacological effects on the brain in humans.

We have finalized data collection for the first subproject and at the ECNP meeting in October in Barcelona, we presented the first *in vivo* measure of 5-HT_{2A}R occupancy in humans with [^{11}C]Cimbi-36 PET following psilocybin. In the next subproject, we measure if there are lasting changes in cerebral 5-HT_{2A}R in psychedelic naïve people after ingestion of a single dose of psilocybin. The last subproject was initiated in fall 2018; here, we directly contrast psilocybin and ketanserin effects on brain function, connectivity and blood flow.

Hanne D. Hansen
NP3 WP leader

NP3: Novel neuroimaging methods for an experimental medicine approach

The most prescribed anti-migraine drugs, the triptans, act as partial agonists on the 5-HT_{1B} receptor (5-HT_{1B}R) and it has long been speculated that serotonergic dysfunction is causally involved in the emergence of migraine attacks. In close collaboration with the Human Migraine Research Unit, led by professor Messoud Ashina at the Danish Headache Center, we have conducted a series of research projects that aim to elucidate the effect of the serotonin system in migraine. We investigate for the first time cerebral 5-HT_{1B}R binding with PET in migraine patients and find that patients have lower 5-HT_{1B}R binding in pain modulating regions, reflecting decreased receptor density [9]. This is either a primary constitutive trait of the migraine brain or secondary to repeated exposure to migraine attacks. We also provide indirect support for the dorsal raphe 5-HT_{1B} receptors being temporarily downregulated during the migraine attack, presumably in response to higher cerebral serotonin levels in the ictal phase. Further, in contrast with the current belief that migraine is associated with low brain 5-HT levels, we here report that patients with episodic and chronic migraine without aura have cerebral 5-HT_4 receptor binding (**Figure 18**), suggesting that migraine patients have higher brain 5-HT levels [8]. Again, this may represent a trait of the migraine brain or it could be a consequence of migraine attacks.

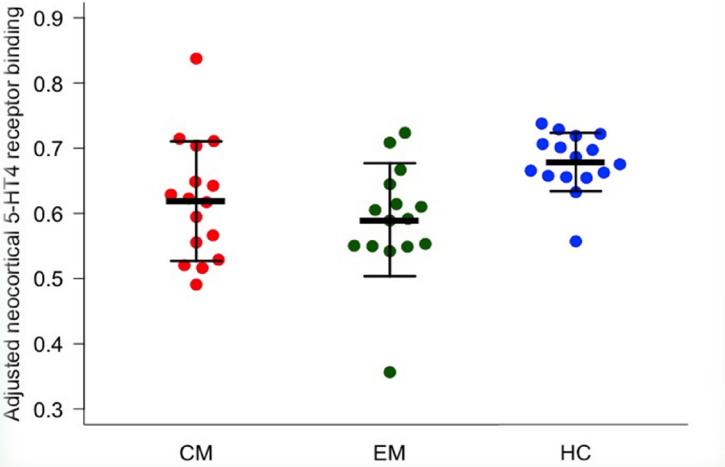
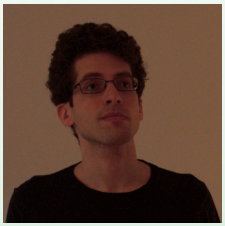


Figure 18: Chronic (CM) and episodic (EM) migraine patients have lower neocortical 5-HT$_4$ receptor binding than controls (HC) after adjusting for co-variates (5-HTTLPR status, age, and sex). Black bars indicate mean±SD. Modified figure from [8], Courtesy of Hanne Demant Hansen, NRU.

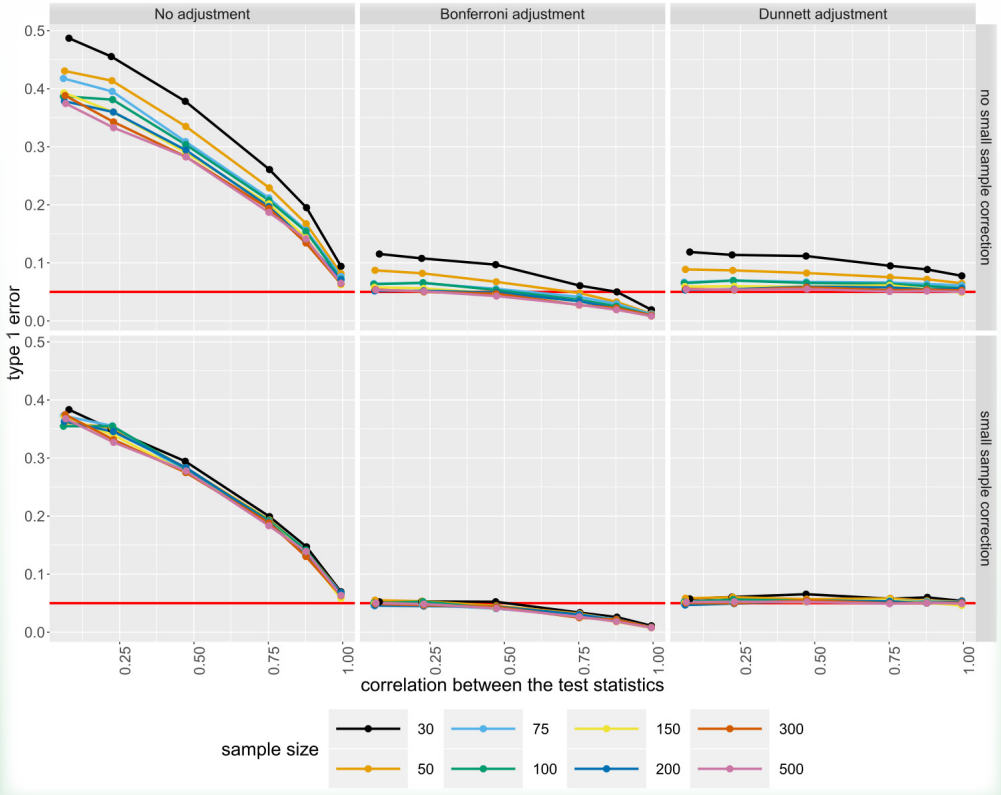


Brice Ozenne
NP4 WP leader

NP4: Bioinformatics, statistical and predictive models

NP4 aims at addressing the need for flexible statistical methods to analyse the data produced by the other work packages (NP1-3). We are particularly interested in Latent Variable Models (LVMs), a multivariate technique using latent variables, to model the relationship between indirect measurements of quantities of interest, e.g. of the brain serotonin level and the depression status of the patient. We have continued our work on efficient adjustments for multiple comparisons in LVMs and in the presence of small samples (**Figure 19**). These developments have been integrated into the R package '*lavaSearch2*' and the corresponding documentation can be found in the vignette of the package (https://cran.r-project.org/web/packages/lavaSearch2/). NP4 has also provided direct statistical support for NP1-3.

Figure 19: Results of simulation study investigating the type 1 error for different sample sizes when performing 9 tests in a LVM. The proposed Dunnett adjustment with the small sample correction (lower row, third panel) is able to maintain a type 1 error below 5% regardless of the sample size or the correlation between the test statistics. Courtesy of Brice Ozenne, NRU & University of Copenhagen.



Strategic Collaborations

PET and Cyclotron Unit, RH

We highly appreciate our long-lasting and outstanding collaboration with Professor Liselotte Højgaard and her dedicated staff at the PET and Cyclotron Unit at Dept. of Clinical Physiology, Nuclear Medicine & PET.

The collaboration covers 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 2018 and beyond.

Staff at the Dept. of Clinical Physiology, Nuclear Medicine & PET, Rigshospitalet-Blegdamsvej.

Dept. of Radiology, RH

The Dept. of Radiology has been instrumental in providing the 3T MR-scanner facilities for NRU available after regular working hours; over the last six years this has provided us with key access to the research facility and we highly appreciate the collaboration with Dr. Vibeke Andrée Larsen, Chief Radiographer Bo Haugaard Jørgensen and project radiographers Christian Hammer Nielsen and Poul-Henrik Mejer Frandsen.

Mental Health Services in the Capital Region of Denmark

NRU has close collaborations with Mental Health Services in the Capital Region of Denmark, in particular with professor Martin Balslev Jørgensen who is directly involved in NP1 of NeuroPharm, with professor Lars Vedel Kessing, and professor Kamilla Miskowiak and her Neurocognition and Emotion in Affective Disorders (NEAD) group, as well as with professors Anders Fink Jensen and Birte Glenthøj. We highly appreciate these collaborations and look forward to continued joint research activities in the future. For NP1, we have also engaged in a close collaboration with CVD, a unique new central referral site for 'treatment packages', e.g. for patients with depression or OCD who can be treated in outpatient settings. This infrastructure and collaboration critically facilitate that these large patient populations can enter frontline clinical research projects and, ideally, will enable a fast translation of research results to optimize clinical mental health care.

Martinos Center, MGH, US

Since 2011, we have had an extremely fruitful collaboration with the Athinoula A. Martinos Center for Biomedical Imaging in Boston, US, who has been pioneering brain imaging with MRI. The director of the Center is Professor Bruce R. Rosen, MD, PhD, who was the first recipient of the Kirsten and Freddy Jørgensen Prize at Rigshospitalet. The collaboration has so far included retreat meetings, the successful achievement of a joint 2-year NIH grant (2014-16, led by Dr. Doug Greve from the Laboratory for Computational Neuroimaging at Martinos), the NRU-anchored NeuroPharm Center grant (2015-22) from the Innovation Fund Denmark, and funding from Lundbeck Foundation for an international postdoc position for Hanne Demant Hansen, as well as bilateral exchange of scientists with the aim of conducting joint scientific work within:

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

Publications 2018

NRU has in 2018 published a total of 3 PhD dissertations, 13 Master's or Bachelor theses, and 41 scientific peer-reviewed papers.

PhD dissertations

- Liv Vadskjær Hjordt. "I should have been a bear. Bears are allowed to hibernate; humans are not" - A Study of Cognitive and Personality Factors Involved in Seasonal Affective Disorder. University of Copenhagen, Faculty of Health and Medical Sciences. Defended Aug 24, 2018
- Louise Møller Jørgensen. Pharmacological and DBS-induced changes in cerebral serotonin release. University of Copenhagen, Faculty of Health and Medical Sciences. Defended Mar 9, 2018
- Vincent Beliveau. Functional and Molecular Imaging of the Serotonin System in the Human Brain. University of Copenhagen, Faculty of Health and Medical Sciences. Defended Feb 27, 2018

Theses and reports

The following list of NRU-affiliated students have successfully defended their theses or research year reports during 2018:

- Alexander Borch Kristensen, "Does a brain parcellation based on 5-HT markers improve the detection of changes or differences in the 5-HT system?", Bachelor thesis in Biomedical Engineering, DTU & University of Copenhagen
- Anders Stevnhoved Olsen, "Removal of Ultra-Fast MR-gradient and Ballistocardiogram Artifacts in High-Density EEG Data to Detect Sleep", Bachelor thesis in Biomedical Engineering, DTU & University of Copenhagen
- Asbjørn Poulsen, "Serotonin 4 Receptor binding is associated with increased striatal response to monetary reward", Master's thesis in Medicine, Faculty of Health and Medical Sciences, University of Copenhagen
- Christian Kildebro & Morten Tøstesen, "Manuel annotering af FCD på MR - Vurdering af nøjagtighed ved præ-kirurgisk epilepsi udredning", Bachelor thesis in Radiography, University College Copenhagen
- Daniel Burmester, "No Association Between Affective States and 5-HT2AR Binding Potential in Healthy Individuals", Master's thesis in Medicine, Faculty of Health and Medical Sciences, University of Copenhagen
- Isabel Martínez Tejada, "*Automatic spatial normalization to standard space and quantification of preclinical PET images*", Master's thesis in Biomedical Engineering, DTU & University of Copenhagen

- Joseph Lorenz, “Effects of chronic, low dose psilocybin administration in the Long Evans rat”, Master’s thesis in Molecular Biology, Faculty of Science, University of Copenhagen
- Mengfei Xiong, “From rat to pig brain imaging - How easy can PET measurements be translated from one species to the other?”, Master’s thesis in Pharmacy, Faculty of Health and Medical Sciences, University of Copenhagen
- Sagar Sanjay Aripaka, “The effect of α7 nicotine acetylcholine receptor modulators on LPS-induced inflammation in human primary microglia and BV2 (non abbreviated) cells”, Master’s thesis in Biomedical-Engineering, Martin-Luther University, Halle-Wittenberg and Hochschule Anhalt (FH), Köthen, Germany
- Sara Marie Larsen, "Genetic variants in the glymphatic-associated water channel AQP4modulates slow waves in human non-rapid eye movement sleep", Master's thesis in Medicine, Faculty of Health and Medical Sciences, University of Copenhagen
- Sofie Arpe, “*α7 nAChR Autoantibodies in Schizophrenia*”, Master’s thesis in Medicine with Industrial Specialization, Biomedicine, School of Medicine and Health, University of Aalborg
- Thomas Kawiecki, "Analysis of network connectivity in subjects with Seasonal Affective Disorder using graph theory", Bachelor thesis in Computer Science, Faculty of Science, University of Copenhagen
- Victoria Fagerholt, “Detection of Synaptic vesicle protein 2A in the mammalian brain determined by radioligand binding and immunoblotting”, Master’s thesis in Medical- and Molecular Biology, Department of Science, Systems and Models, Roskilde University

Book chapters

- Herth MM, Knudsen GM. PET Imaging of the 5-HT2A Receptor System: A Tool to Study the Receptor’s In Vivo Brain Function. In: Guiard BP, Di Giovanni G. (Eds.). 5HT2A Receptors in the Central Nervous System. The Receptors, Vol. 32. Springer International Publishing, New York (USA). ISBN: 9783319704722

Peer-reviewed conference proceedings

P1. Nørgaard M, Douglas N. Greve, Svarer C, Stephen C. Strother, Knudsen GM, Ganz M. The Impact of Preprocessing Pipeline Choice in Univariate and Multivariate Analyses of PET Data. Pattern Recognition in Neuroimaging (PRNI), Singapore, 2018, pp. 1-4. DOI: 10.1109/PRNI.2018.8423962.

Papers in peer-reviewed journals

1. Antonsen KK#, Klausen MK#, Brunchmann AS, le Dous N, Jensen ME, Miskowiak KW, Fisher PM, Thomsen GK, Rindom H, Fahmy TP, Vollstaedt-Klein S, Benveniste H, Volkow ND, Becker U, Ekstrøm C, Knudsen GM, Vilsbøll T, Fink-Jensen A. Does glucagon-like peptide-1 (GLP-1) receptor agonist stimulation reduce alcohol intake in patients with alcohol dependence: study protocol of a randomised, double-blinded, placebo-controlled clinical trial. BMJ Open. 2018 Jul 16;8(7):e019562

2. Bailey DL, Pichler BJ, Gückel B, Antoch G, Barthel H, Bhujwalla ZM, Biskup S, Biswal S, Bitzer M, Boellaard R, Braren RF, Brendle C, Brindle K, Chiti A, la Fougère C, Gillies R, Goh V, Goyen M, Hacker M, Heukamp L, Knudsen GM, Krackhardt AM, Law I, Morris JC, Nikolaou K, Nuyts J, Ordonez AA, Pantel K, Quick HH, Riklund K, Sabri O, Sattler B, Troost EGC, Zaiss M, Zender L, Beyer T. Combined PET/MRI: Global Warming-Summary Report of the 6th International Workshop on PET/MRI, March 27-29, 2017, Tübingen, Germany. Mol Imaging Biol. 2018 Feb;20(1):4-20
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