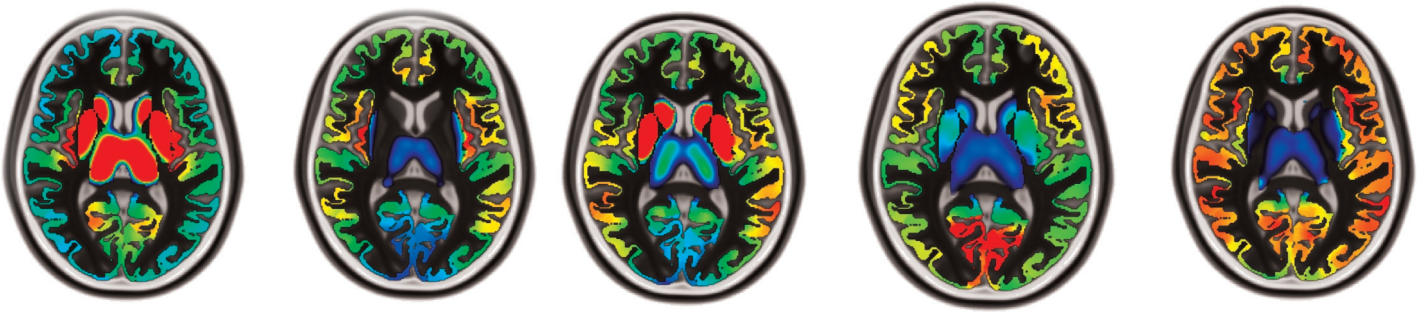
Neurobiology Research Unit

Annual Report 2017



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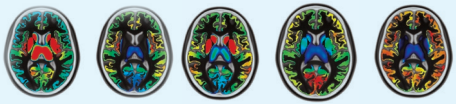

Cover image: In vivo serotonin (5-HT) atlas of the human brain. Sagittal slices showing the average density (B_{max}) maps of five 5-HT targets (5-HTT, 5-HT1A, 5-HT4, 5-HT1B, and 5-HT2A, respectively). Color scaling individually adjusted to highlight features of the distributions. Modified from [1].

REGION Rigshospitalet

KØBENHAVNS UNIVERSITET
DET SUNDHEDSVIDENSKABELIGE FAKULTET

Cimbi THE LUNDBECK FOUNDATION
Center for integrated molecular brain imaging

COGNITO
Det Strategiske Forskningsråd

Innovation Fund Denmark
NeuroPharm
Center for Experimental Medicine Neuropharmacology

Contents

Preface

Dear reader,

I am proud to present you with the 2017 annual report describing the activities of the Neurobiology Research Unit (NRU). You will here find examples of the research output obtained in 2017. These include generation of a human brain atlas of the serotonin system.

From the start of 2017, it became clear that the future establishment of the Childrens' Hospital would be at the Rockefeller campus involving that NRU moves out of its current premises. We were very pleased when we later learned that funding has been made available to build a new building in the North Wing complex to where NRU will relocate. This will not only allow us closer access to the scanners and to the Dept. of Neurology in the future, but it will also ensure that the preclinical laboratory is situated next to the other NRU facilities. The move is currently scheduled to take place in 2019 whereas the scanners are anticipated to be ready for use in the North Wing already in 2018. Moreover, a generous gift from The Kirsten and Freddy Johansen Foundation will allow us to purchase a brand new 3T MR-scanner dedicated to brain research, operated in collaboration between NRU and Dept. of Radiology.

As featured within the report, Dr. Vibe Frøkjær received the prestigious Sapere Aude grant from the Danish Research Council and this will enable her to pursue her research interest within sex hormones and mood disorders. Also, Dr. Lars Pinborg received a 5-year grant from the Lundbeck Foundation so that he can continue his work within precision medicine in epilepsy.

The past year has again been a year with substantial research output from the group. Two of our PhD students have after a successful defence of their theses obtained their PhD degree and another two have handed in their theses. NRU-affiliated researchers have presented their work at a large number of international congresses, conferences, and meetings, and in total, NRU published 44 peer-reviewed scientific publications (page 38).

With respect to research training, we have in 2017 organized both pre- and post-graduate programmes with international speakers and well-attended programs. 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 and we are currently preparing our first Summer School Course under the auspices of the University of Copenhagen.

In 2017, NRU senior staff members have trained more than 20 national and international PhD students and post docs, and we organized a pharmacokinetic PhD-course. Also, we hosted international research interns, including one ECNP research intern from Greece, one ERASMUS intern from Slovenia and one intern from Scripps College in Claremont, California.

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 2017 was another very successful year for NRU.

I hope that you will enjoy reading this 2017 annual report and encourage interested readers to stay tuned on our website (www.nru.dk).

On behalf of the NRU management group

Gitte Moos Knudsen

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 from cells and animals into healthy volunteers and patients as early as possible.

The activities within NRU fall in nine different categories:

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

We see our role at Rigshospitalet and in the Capital Region of Copenhagen as a key unit to conduct innovative diagnostic, therapeutic and preventive neuropharmacological research. This takes place in close interaction with the hospital clinics, 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.

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. We contribute with articles in popular journals, give public lectures, and participate in interviews for newspapers and TV. In 2017 we participated in two different documentaries on Danish Television about aggression (‘Vold På Hjernen’ broadcasted on DR1) and epilepsy (‘Død og pine: Lægevidenskabens Historie’ broadcasted on DR K) as well as in a BBC Two broadcast called “Trust Me I’m a Doctor”.

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 on next page), 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 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 Dept. of Diagnostic Radiology, in close collaboration with the staff there.


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Staff in 2017

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

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

Research administrators
Birgit Tang
Dorthe Givard
Peter S. Jensen

Post docs
Brice Ozenne, biostatistician, PhD
Dea S. Stenbæk, psychologist, PhD
Johannes Björkstrand, psychologist, PhD *
Ling Feng, engineer, PhD
Melanie Ganz-Benjaminsen, computer scientist, PhD
Sofi da Cunha-Bang, MD, PhD
Sebastian C. Holst, engineer, PhD

PhD students
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
Liv V. Hjordt, psychologist
Louise M. Jørgensen, MD
Marie Deen Christensen, MD
Martin Korsbak Madsen, MD
Martin Nørgaard, engineer
Mette T. Foged, MD
Per Jensen, MD
Vibeke N. H. Dam, psychologist
Vincent Beliveau, neuroscientist

Research assistants
Agata C. Sainz, molecular biomedicine
Agnete Dyssegaard, pharmacist
Annette Johansen, MD
Beatriche Henriksen, biomedicine
Ida N. Petersen, medicinal chemist, PhD

Joana Menezes, molecular genetics & biomedicine
Simone L. Bærentzen, human biologist
Shizhong Li, biologist, PhD

Technical research personnel

Cecilie L. Nordberg, MRI student assistant *
Cecilie F. Skovsen, MRI student assistant *
Ditte B. Christensen, MRI student assistant *
Luna S. Hansen, MRI student assistant *
Sara L. Jørgensen, MRI student assistant *
Gunild Vulpius, MRI student assistant
Josephine Torp, HPLC student assistant
Lone I. Freyr, project nurse
Louise Nielsen, medical technologist
Minna Litman, research nurse
Sofie Arpe, Medicine with Industrial Specialization *
Stine Andersen, HPLC student assistant
Svitlana Olsen, medical technologist
Søren Rønborg, MRI student assistant
Victor F. Hansen, IT-support

Visiting scientists

Dan Peters, PhD, CEO at DanPET, Sweden
Leif Østergaard, professor, Århus, DK
Spyridon Siafis, MD (ECNP research intern) *

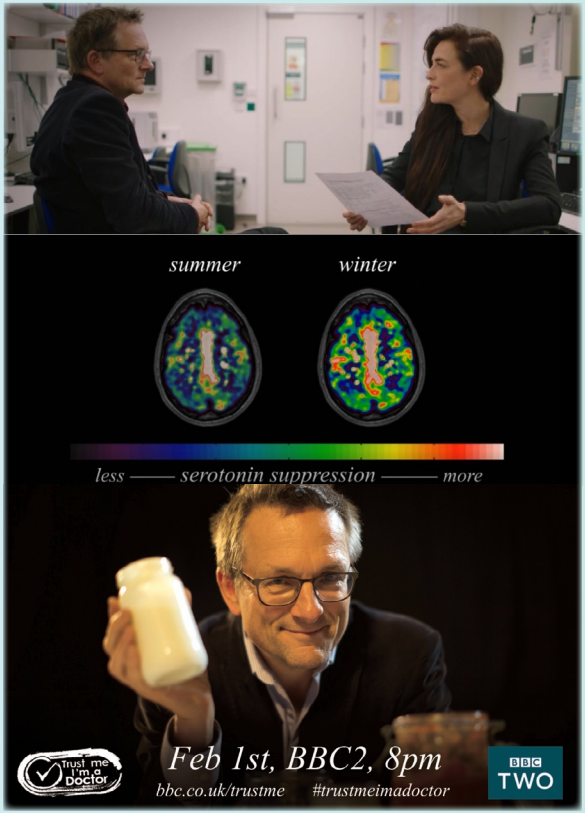
Pregraduate students

Annemette Ringsted, engineer *
Anne-Sofie T. Schneider, psychology
Anna Maria Florescu, medicine
Cecilie L.V. Jokinen, psychology *
Christa K. Thystrup, psychology
Daniel Burmester, medicine
Elizabeth B. Landman, medicine
Greta Tuckute, molecular biomedicine *
Ida Marie Brandt, molecular biomedicine *
Isabel M. Tejada, engineer *
Ivo Kosmacin, medicine (ERASMUS intern) *
Joe Lorenz, molecular biology *
Johan F. Christensen, medicine *
Johan S. Bundgaard, medicine
Kevser Sert, engineer *
Maja H. Sørensen, biochemistry
Mark U. Juul, engineer *
Mathilde M. Hansen, medicine *
Mengfei Xiong, pharmacy *
Menting Liu, biology *
Mette W. Brændgaard, medicine *
Miran Dinarzehi, pharmacy *
Nizar Hamrouni, medicine
Peter N. Hersnæs, medicine *
Sagar S. Aripaka, biochemistry *
Sara Kristiansen, psychology
Sara Marie Larsen, medicine *
Sidra Rafique, engineer *
Simone Pleinert, psychology *
Siria Medina, biology *
Siv T. Peitersen, biology
Sebastian E. Ebert, medicine
Sophia Armand, psychology *
Terje Martens, medicine
Zuhal Filikci, medicine

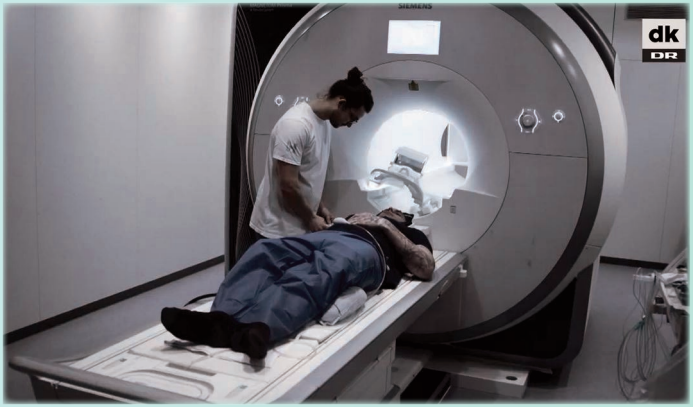
All new faces in 2017 are marked with a *.

Selected highlights of the year

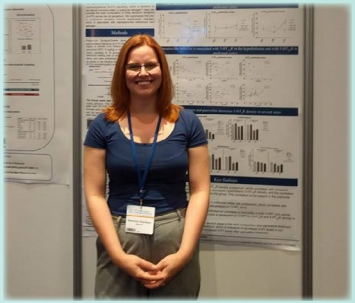
In September, 35 of the NRU staff members were gathered at a two-day retreat meeting which primarily took place on the DFDS Seaways ferry between Copenhagen and Oslo but also included a visit at the Norwegian Centre for Mental Disorders Research (NORMENT) at Oslo University Hospital. On the first day, Professor Jesper Ryberg from Roskilde University gave an interesting lecture on "Neuroscience and Criminal Justice: Ethical Issues" and afterwards we had a session about co-authorships on scientific publications. On the second day after the visit at NORMENT, a fun and extremely well-organized team building event took place at the ferry and the rest of the time was devoted to social gathering.



In February, Brenda Mc Mahon appeared on the BBC Two broadcast called "Trust Me I'm a Doctor", where she presented results from her NRU PhD research on brain serotonin in Seasonal Affective Disorder.



In May, DR1 broadcasted a documentary centered around NRU PhD research on aggression by Sofi da Cunha-Bang. By scanning the brains of very aggressive prisoners, convicted of serious personal crime, and comparing these with brain scans from non-convicted people, we have found results pointing to specific biological features that characterize the mind of aggressive people.



In June, master project student Beatriche Henriksen won the Young Investigator Best Poster Presentation competition on the first day of the 13th World Congress of Biological Psychiatry (WFSBP Congress 2017) which was held in Copenhagen.

Preclinical Neurobiology

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

Translational Neuroimaging and Behavior

Mikael Palner's team is focused on translational neuroimaging and behavioural analysis of rats. They use Designer Receptors Activated Exclusively by Designer Drugs (DREADDs) to target single neuronal pathways and assess behaviour and neuroimaging data following selective stimulation or inhibition.

In 2017 the Palner team continued with their startle and prepulse inhibition behavioural assay of hyperdopaminergic rats. They imaged these rats using Magnetic Resonance Spectroscopy (MRS) in a Bruker 9.4 Tesla microMR for in vivo detection of several brain metabolites in collaboration with Center for Translational Neuroscience at the University of Copenhagen (**Figure 1**). These data are now in the process of being published.

Last year, two MSc students from the team graduated with projects on behavioral and neuroimaging data, and Mikael Palner received funding from the Augustinus Foundation, Savværksejer Jeppe Juhl og Hustru Ovita Juhls Mindelegat and Købmand i Odense Johann og Hanne Weimann f. Seedorffs Legat.

Experimental Psychoneuroendocrinology

The serotonin (5-HT) system modulates many important brain functions and is critically involved in many neuropsychiatric disorders. In 2017 Agnete Overgaard and her experimental psychoneuroendocrinology team finished autoradiography for the 5-HT1A, 5-HT2A, and 5-HT4 receptors, and the serotonin transporter (5-HTT) in a rat model of postpartum depression, and these data are currently held up against endpoints including maternal behaviour, depressive-like behaviour, anxiety-like behaviour, corticosterone stress response, estradiol, and hippocampal neurogenesis markers. So far, our data suggest that the SSRI paroxetine increased synaptic serotonin, but concurrently compromised behavioural outcomes postpartum.

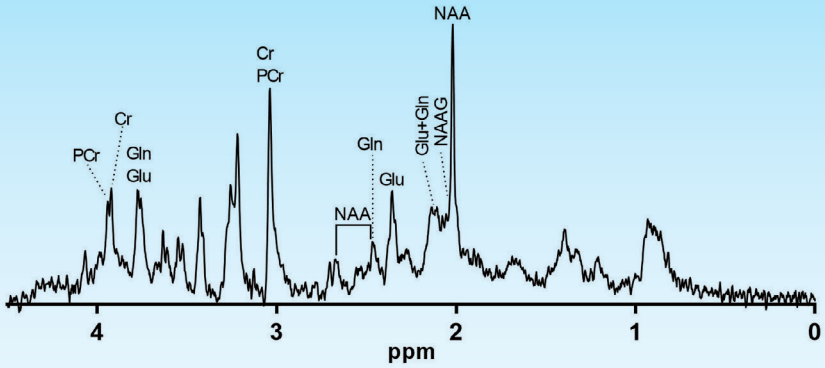
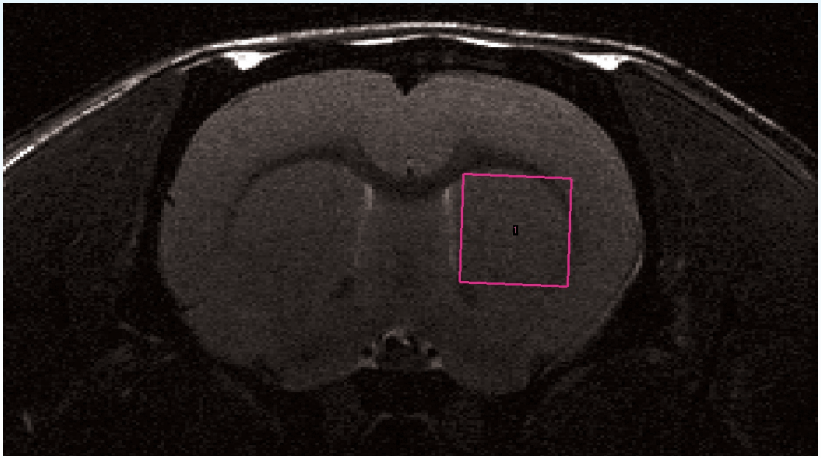


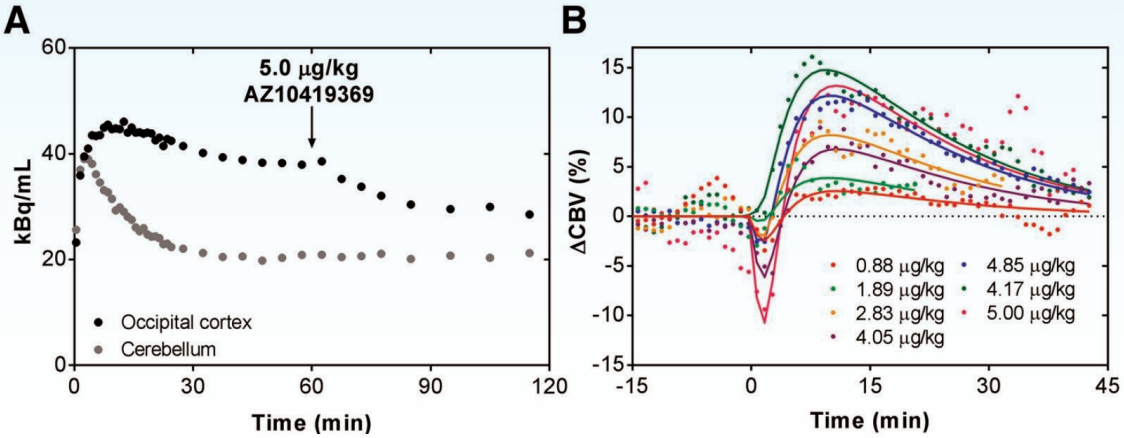
Figure 1: Representative spectrum (upper) from 18 mm³ voxel covering dorsal striatum (right) based on a STEAM Sequence (TE: 4, TR: 4000 Averages 400) on the Bruker 9.4T microMR. Courtesy of Mikael Palner, NRU.



Preclinical Neuropharmacology

Simultaneous PET-MRI (i.e. combined Positron Emission Tomography and Magnetic Resonance Imaging) has emerged as a powerful tool to investigate drug effects. In 2014, together with our collaborators at MGH, Boston, we demonstrated that functional MRI (fMRI) can reveal information about the dopaminergic level in striatum. The next question we asked was: Can we by means of simultaneous PET-MRI make a distinction between agonist versus antagonist drug action in the brain?

As part of Hanne D. Hansen's postdoc work at MGH, we studied 5-HT1B receptor occupancy and the associated hemodynamic responses in non-human primates during a range of different drug challenges [15]. We demonstrated proof-of-concept that simultaneous PET-MRI in conjunction with pharmacological interventions can critically inform about *in vivo* spatial and temporal drug actions in the central nervous system (**Figure 2**). This includes hemodynamic effects in peripheral tissue and in the brain, blood-brain barrier penetrance and target involvement, and hence the technique lends itself to a comprehensive in vivo investigation and understanding of drugs' effects in the brain.



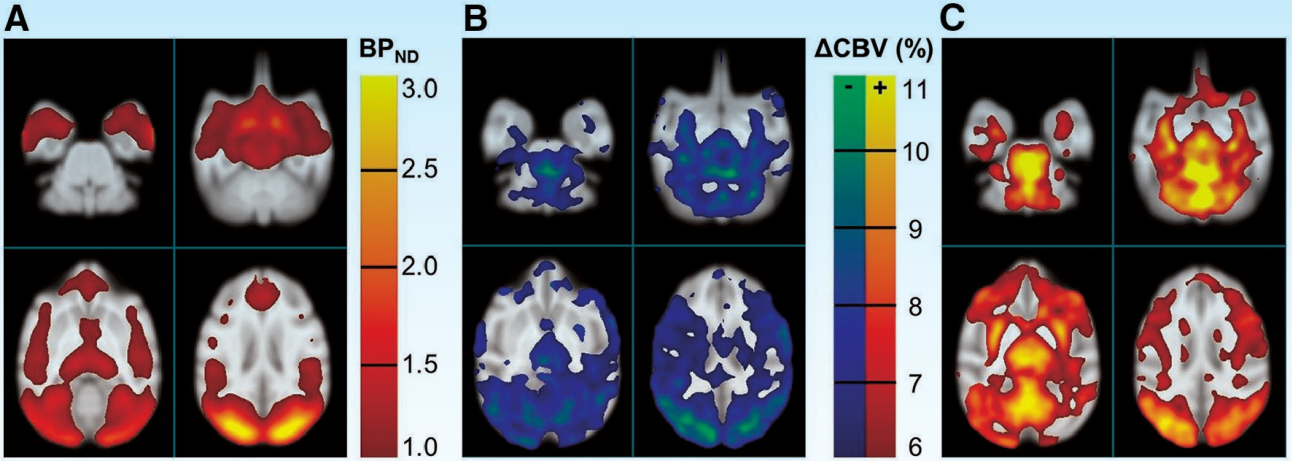


Figure 2: (Figure to the left) Dose-response relationship following AZ10419369 administration: (A) Representative time-activity curve of [^{11}C]AZ10419369 with the partial 5-HT1BR agonist AZ10419369 (5.0g/kg) intravenously administrated 60 min after injection of the radioligand. (B) Percentage change in cerebral blood volume in the occipital cortex after intravenous injection of varying doses of AZ10419369. (Figure above) Spatial distribution of PET and MR signals: (A) Binding potential map of [^{11}C]AZ10419369 (averaged across 7 scans) and (B) negative and (C) positive CBV changes. Images are averages across six experiments with AZ10419369 doses ranging between 0.88 and 5.0g/kg. PET data were smoothed with a 3.5mm Gaussian filter. The p value for thresholding of CBV change was p < 0.001. From [15], Copyright © 2017 the authors.

Data Analysis

Optimization of ways to look at molecular neuroimaging data for research and clinical use is the major topic in the data analysis group. This includes more classical signal processing methods used for quantification of SPECT and PET scans, e.g. estimation of the binding potentials, as well as modern multivariate data analysis techniques for optimization of imaging pipelines.

Creating a high-resolution serotonin atlas

In 2017 we published [1] a high-resolution multi-dimensional in vivo atlas (**Figure 3**) of four of the human brain's 5-HT receptors (5-HT1A, 5-HT1B, 5-HT2A, and 5-HT4) as well as of the 5-HT transporter. The atlas was created from molecular (PET) and structural (MRI) neuroimaging data from 210 healthy individuals from the Cimbi Database. By comparing the regional PET binding measures to postmortem human brain autoradiography outcomes, the atlas was calibrated to represent protein densities (pmol/ml). We also assessed the regional association between protein concentration and mRNA expression in the human brain by comparing the 5-HT density across the atlas to data from the Allen Human Brain atlas and identified receptor- and transporter specific associations which inform about the regional relation between the two measures. Together, these data provide unparalleled insight into the serotonin system of the human brain. The atlas is freely available at www.nru.dk.

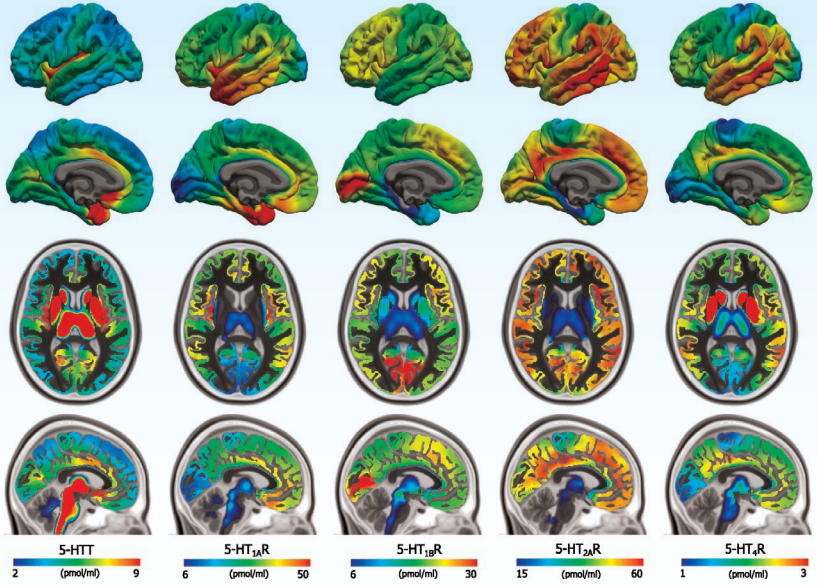


Figure 3: Average density (B_{max}) maps for five 5-HT targets on the (upper panel) common FreeSurfer surface and in the (lower panel) common MNI152 space. From [1], Copyright © 2017 the authors.

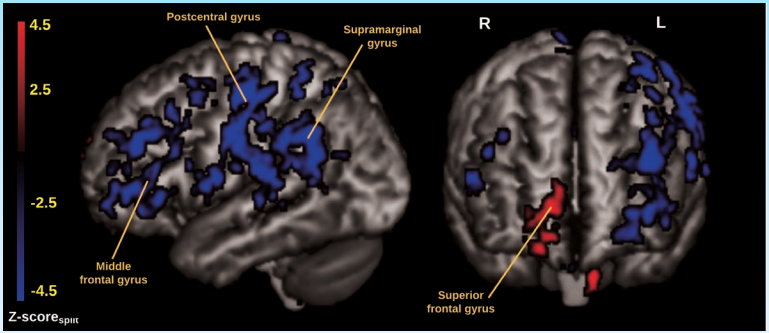


Figure 4: Cortical rendering of the 5-HTT brain network predicted by the PLS analysis. The image is thresholded at $|Z\text{-score}_{split}| > 2.8$ ($P \leq 0.005$) and with cluster extent threshold > 640 voxels. Red areas represent an increased 5-HTT response for resilient female S' carriers compared to female S' carriers with SAD. Blue areas represent an increased 5-HTT response in female S' carriers with SAD compared to resilient female S' carriers. The data is visualized using mricron (https://www.nitrc.org/projects/mricron). From [31], Copyright © 2017 the authors.

Identifying serotonergic brain networks in SAD

In 2017 we also published a study [31] aiming at identifying a brain network of the serotonin transporter that accounts for the adaption to the environmental stressor of winter in females with the short 5-HTTLPR genotype, a specific subgroup previously reported to be at increased risk for developing Seasonal Affective Disorder (SAD). By means of a data-driven Partial Least Squares (PLS) approach we identified a specific network (**Figure 4**) which were optimized (**Figure 5**) using PCA regularization to remove noise variability. The findings provide insight into the neurobiological components through which the anatomical distribution of serotonergic discrepancies between individuals genetically predisposed to SAD, but with different phenotypic presentations during the environmental stressor of winter, may constitute a potential biomarker for both resilience and SAD.

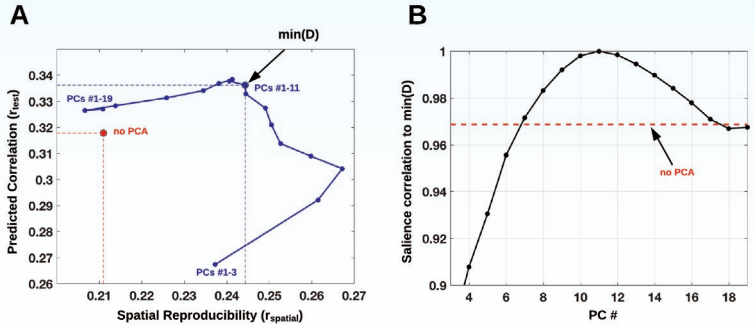


Figure 5: (A) PLS analysis performed on an adaptive optimized PCA subspace with mean predicted contrast-correlation of the significant LV plotted against the mean spatial reproducibility (blue). This PCA subspace was varied from 1 to k PCs with k = 19 (total number of scans in a split-half), and its performance was defined as the distance D from $r_{spatial} = 1$ and $r_{test} = 1$. A subspace of PCs 1-6 minimized D, which is displayed as a blue dot with a black circle. As a reference we also plot the mean ($r_{spatial}$, r_{test}) point, directly estimated from matrix X (red circle). (B) Correlation of brain pattern (salience) to min(D, k = 11) across different choices of k (PC #). The red dotted line indicates the correlation without PC-subspace optimization. From [31], Copyright © 2017 the authors.

Evaluating novel SPECT biomarker of TSPO

As part of the EU-funded INMiND project we have previously demonstrated the feasibility of the SPECT tracer [^{123}I]CLINDE in revealing the 18-kDa translocator protein (TSPO) upregulation in neurological patients. As a continuation of the evaluation of [^{123}I]CLINDE as a biomarker of TSPO, we have recently in healthy subjects demonstrated a test-retest reproducibility of [^{123}I]CLINDE comparable to or better than that reported for commonly used PET TSPO tracers [9]. Due to binding of [^{123}I]CLINDE to blood cells, the study suggests prompt blood sample centrifugation to avoid erroneous estimation of tracer concentration in plasma.

Investigating cerebellar heterogeneity

The reference tissue model is a very commonly used method for quantification of PET radiotracer binding. This model necessitates a proper reference region devoid of binding targets and cerebellum is the most commonly used for G-protein coupled receptors. However, the cerebellum is a heterogenous brain region and should hence be divided into sub-regions. In a recent publication [13], we investigated regional differences in uptake within the grey matter of the cerebellar hemispheres (CH) and the cerebellar vermis (CV) for five 5-HT targeting PET radioligands (**Figure 6**). We demonstrated radioligand-specific regional differences in cerebellar uptake between CV and CH for four of the radioligands. These differences may be ascribed to differences in concentration of the receptor or transporter in question in CV versus CH or it could reflect off-target binding of the radioligands or differences in the non-displaceable binding in the two regions. Our data highlight the importance of validating each radioligand carefully for defining the optimal reference region.

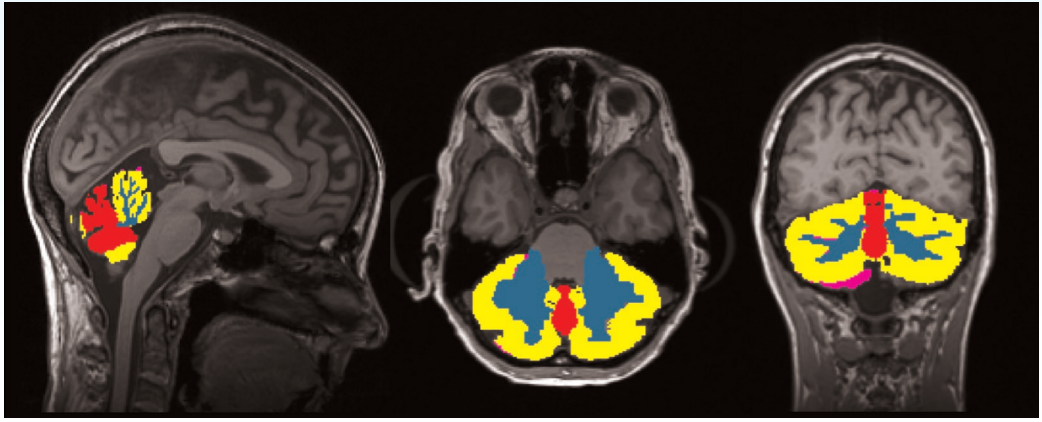


Figure 6: Using a combination of FreeSurfer and SUIT, the cerebellum is automatically segmented from a T1-weighted MRI scan and labelled as cerebellar gray matter (yellow), cerebellar white matter (blue) and cerebellar vermis (red). Labeling differences between the two software packages are highlighted in pink. From cover of JCBFM [13], Copyright © 2017 the authors.

Crowdsourcing-supported MR-image annotations

With the recent trend towards big data analysis, neuroimaging datasets have grown substantially in the past years. While larger datasets potentially offer important insights for medical research, one major bottleneck is the requirement for resources of medical experts needed to validate automatic processing results. To address this issue, the goal of another of our 2017 papers [14] was to assess whether anonymous non-experts from an online community can perform quality control of MR-based cortical surface delineations derived by an automatic FreeSurfer algorithm. So-called knowledge workers from an online crowdsourcing platform were asked to annotate errors in automatic cortical surface delineations on 100 central, coronal slices of MR images (**Figure 7**). When using expert annotations as reference, the crowd on average achieved a sensitivity of 82% and a precision of 42%, demonstrating that the detection of errors in automatic cortical surface delineations generated by anonymous untrained workers is feasible.

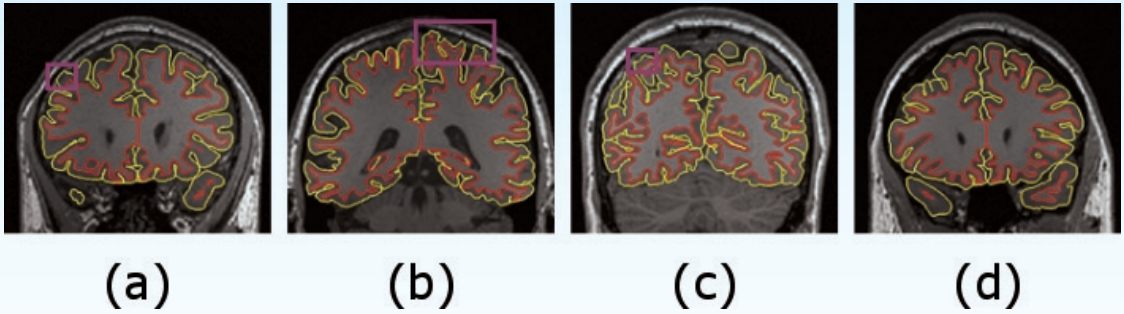


Figure 7: Examples of errors - (a) easy, (b) medium, (c) hard to detect and (d) no error - in cortical segmentations performed by FreeSurfer (red = white matter surface delineation, yellow = pial surface delineation). The errors are surrounded by purple bounding boxes. From [13], Copyright © 2017 the authors.

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.

Aggression Project

In 2017 we published [36] the first description of distributed brain responses to the point-subtraction aggression paradigm (PSAP) implemented in an fMRI environment. Also, we published a paper [3] detailing fMRI brain responses to aggressive provocation during the PSAP in incarcerated violent offenders and healthy controls. Violent offenders increased activation and showed diminished circuit function in behaviorally relevant regions (**Figure 8**), suggesting that the disruption of core neural pathways guiding social interaction may underlie pathologically aggressive behavior to perceived provocation.

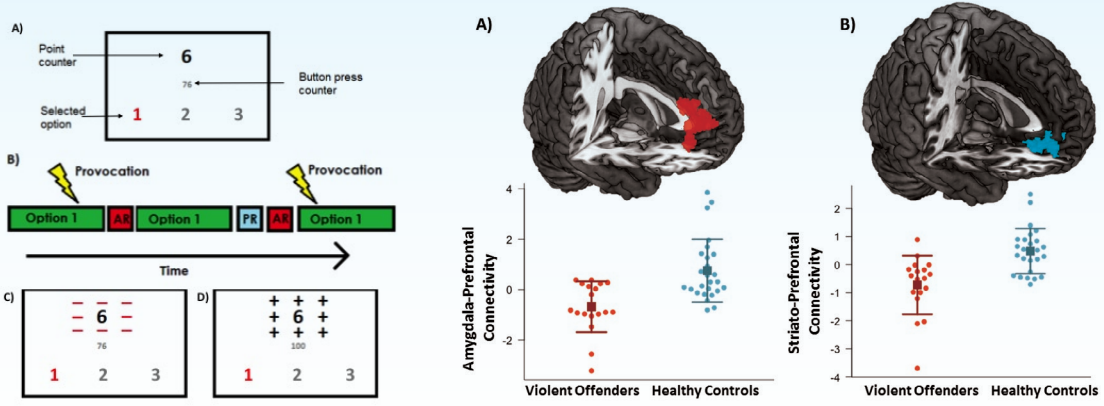


Figure 8: (Left panel) Visual display of the point subtraction aggression paradigm (PSAP) adapted to the fMRI environment. (Right panel) Functional communication between brain regions when experiencing a provocation differs between healthy and violent-aggressive individuals. From [3], Copyright © 2017 the authors.

Resting-state fMRI (rs-fMRI)

Patrick Fisher led a study [10] showing that the emergence of depressive symptoms following pharmacologically induced sex hormone fluctuations in otherwise healthy women may emerge as a function of changes in behaviorally relevant rs-fMRI brain networks (**Figure 14**).

The NRU is collaborating with Rigshospitalet neurologist Daniel Kondziella to develop an fMRI framework to inform clinicians of preserved brain function in patients with traumatic brain injury and diminished consciousness. This exciting clinical project is on-going and in 2017 we published [26] our first observations linking rs-fMRI and patient prognosis (**Figure 9**).

NeuroPharm

In the NeuroPharm project (see page 32), we are collecting task-related and rs-fMRI in healthy individuals and depressed individuals to evaluate whether brain activation informs antidepressant treatment responsiveness (NP1) as well as collecting fMRI datasets in conjunction with projects evaluating psilocybin effects on brain serotonin 2A receptor levels (NP2) and to establish a correspondence between pharmacologically induced changes in fMRI and PET (NP3). Moreover, in an add-on project about sleep we are collecting fast-fMRI sequences to probe sleep-related neural dynamics reflecting glymphatic flow.

We are excited for the continued development of fMRI as a research strategy at NRU and its application across diverse research projects.

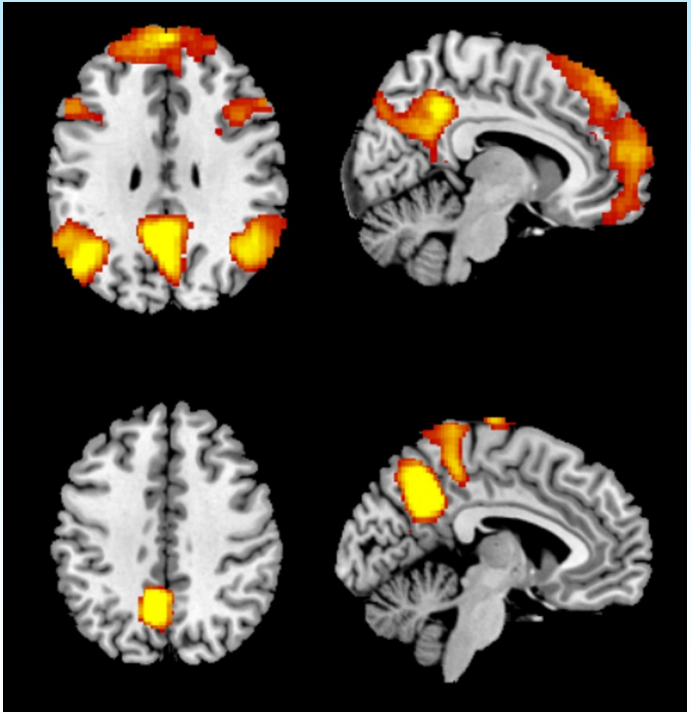


Figure 9: Resting state functional MR images showing normal (top) and abnormal (bottom) default-mode network in individuals with impaired consciousness. From [26], Copyright © 2017 Springer Science+Business Media New York.

Neuropsychology

The psychology group at NRU was established as a core facility to advance an interdisciplinary scientific approach to the understanding of risk and resilience factors in human health. We specialize in psychological effects and correlates of pharmacologically induced neuroendocrine changes and serotonergic neurotransmission.

In 2017 we continued to validate and improve our affective- and social-cognitive test-battery. This included data collection for a Danish psychometric validation of the EMOTICOM test battery, developed at Cambridge Cognition Group. Selected tests from the EMOTICOM were used in a study investigating the effects of intranasal administration of oxytocin on affective and social processing, which are currently being analysed and prepared for publication. Selected tests are also currently applied to study affective- and social-cognitive characteristics of responders versus non-responders to antidepressant treatment with SSRI.

Parallel to the validation of EMOTICOM, the association of serotonergic neurotransmission via the 5-HT4 receptor (5-HT4R) with personality (**Figure 10**) and cognition (**Figure 11**) were also investigated [39,38]. In addition, we studied changes in cold cognition (**Figure 12**) in patients with Seasonal Affective Disorder across the seasons [19]. Two studies were successfully initiated: (a) the first controlled Danish study investigating psychological effects of the hallucinogenic drug psilocybin in healthy volunteers (more information on page 30), and (b) a study of cognitive and emotional complications after cardiac arrest rescue in collaboration with the Heart Centre at Rigshospitalet.

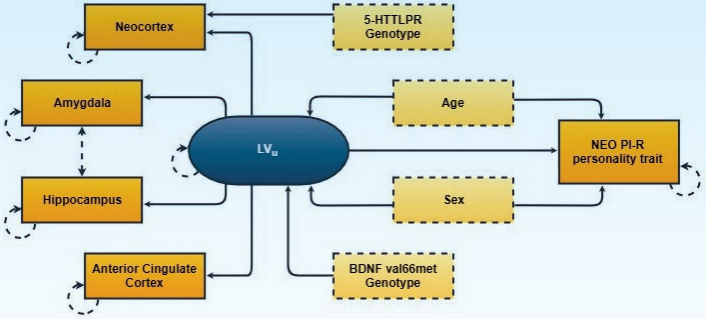


Figure 10: Latent variable model of the association between cerebral 5-HT4R binding and NEO personality traits. A separate model was determined for each of the five NEO traits: Neuroticism, Extroversion, Openness, Agreeableness and Conscientiousness. The blue circle represents the latent 5-HT4R variable (LVu), the light yellow boxes the observed predictors, and the dark yellow boxes, predicted by the latent variable, the observed log-transformed regional 5-HT4R binding potential (BPND) and NEO personality traits. The hatched line between amygdala and hippocampus reflects additional shared correlation, and circular hatched lines denote parameters estimated with error. No significant associations were observed between 5-HT4R BPND and any of the five NEO personality traits. From [39], Copyright © 2017 the authors.

We collaborate with Babylab, which is an experimental research unit at University of Copenhagen, connected to "Center for Spæd- og Småbørn", in a longitudinal study of mother, father and child stress responses in families, where mothers experienced Post-Partum Depression compared to families, where mothers did not. We also collaborate with the Psychedelic Research Group at Imperial College, London, and the Cambridge Cognition Group.

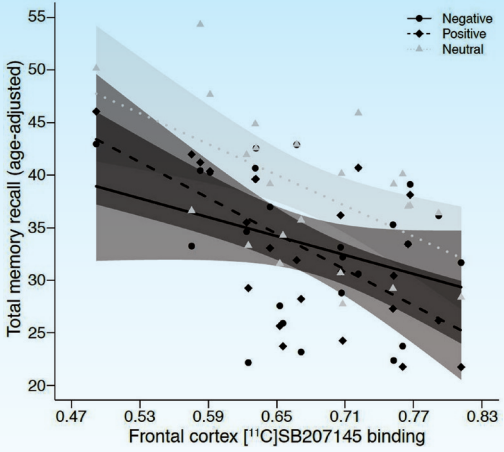


Figure 11: Grouped scatter plot of [11C]SB207145 5-HT4R binding potential values plotted against total words recalled (i.e., sum of immediate, short term, and long-term recall of positive, negative, and neutral words). Our data indicate an inverse relation between memory recall and 5-HT4R binding (positive words, p=0.0005, negative, p=0.07, and neutral, p=0.004). They also suggest a steeper slope for positive and neutral word recall compared to negative, and that the relative recall between positive and negative words changes with 5-HT4R binding such that more negative words relative to positive words are recalled with increasing binding and the opposite with decreasing binding. From [38], Copyright © 2017 the authors.

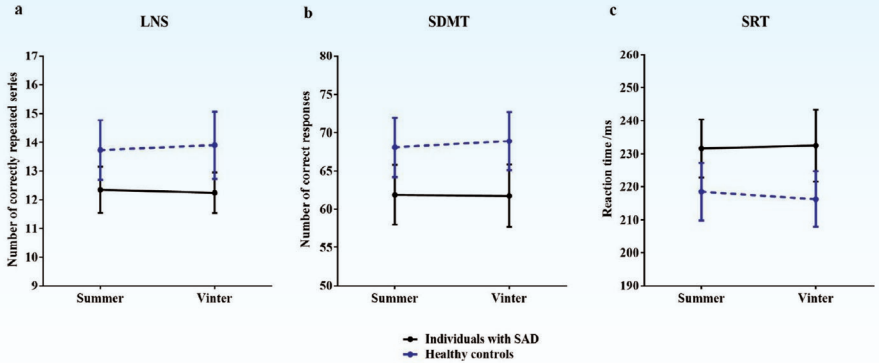


Figure 12: Cognitive performance scores for three cognitive tests for individuals with SAD (n=29) and healthy controls (n=30) in summer and winter. The graphs show raw scores on measures of (a) working memory (Letter-Number sequencing), (b) cognitive processing speed (Symbol Digit Modalities Test) and (c) motor speed (Simple Reactions Time). Error bars represent standard deviation. Compared to controls, individuals with SAD showed significant season-independent impairments in tasks measuring working memory (p=0.016), cognitive processing speed (p=0.004) and motor speed (p=0.009). From [19], Copyright © 2017 Elsevier B.V.

Clinical Psychiatry

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 [1] which is profoundly involved in mood disorders, schizophrenia, neurodegenerative disorders and their treatment. In particular, we are interested in serotonin brain biology as a driver of healthy adaptation to e.g. seasons, stressors, genetic make-up, personality [39,41], sex-steroid hormone milieu [33] and healthy navigation in social relations.

Aggressive behavior is an enormous societal challenge. We pursue an interest in the neural mechanisms involved in aggression [36] which may inform strategies for development of anti-aggressive treatments. In a seminal study of violent offender inmates, we have shown (**Figure 13**) that the availability of the 5-HT1B receptor (5-HT1BR) is associated with trait anger and level of psychopathy [4] and specifically that the anterior cingulate is involved in response inhibition in the context of angry facial expressions [5]. Further, we have shown that violent offenders display an abnormal sensitivity to provocations (**Figure 8**), i.e. they respond to provocations with high amygdala and striatal brain activity relative to controls [3].

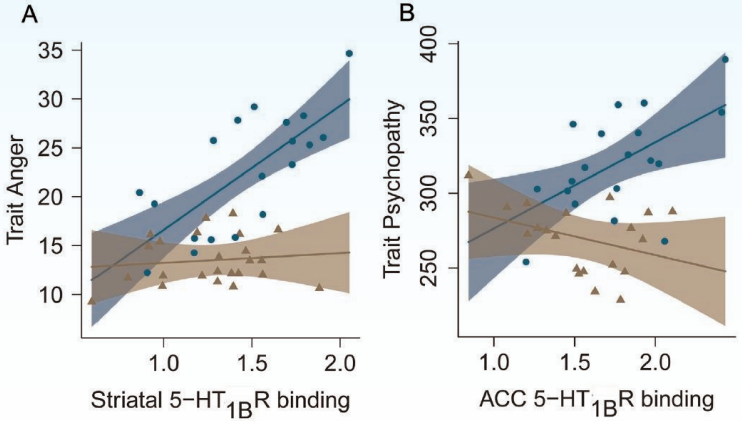


Figure 13: Interactions between group status and 5-HT1BR binding in predicting trait anger and trait psychopathy. (A) Association between striatal 5-HT1BR binding and trait anger is moderated by group status (test for difference in slopes, p = .004, $p_{corrected}$ = .04). (B) Association between anterior cingulate cortex (ACC) 5-HT1BR binding and trait psychopathy is moderated by group (test for difference in slopes, p = .007, $p_{corrected}$ = .08). Blue circles: violent offenders, brown triangles: healthy control subjects. Shades represent 95% confidence intervals. Plots are shown given a mean age, mean IQ, and mean injected mass per kilogram. From [4], Copyright © 2017 Elsevier Inc.

Healthy adaptation to seasonal changes is critical for mental health and Scandinavian populations provide a unique naturalistic model to study season related brain architecture. Recently, we have directly linked heightened 5-HTT binding, which tends to decrease serotonin tone, to symptom severity in SAD. Further, we have characterized depressed-state dependent [18] and season independent [19] cognitive bias and deficits, which suggest that while affective cognitive disturbances may be normalized by efficient treatments some cold cognitive features may sustain independent of season (**Figure 12**).

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 how hormonal transitions may trigger depressive episodes. We have recently provided direct evidence for sex-hormone manipulation to provoke subclinical depressive symptoms in about 12% of healthy women, in a manner dependent on serotonin signaling and to the magnitude of sex-steroid (estradiol) decline. In the same cohort, we have shown (**Figure 14**) that depressive responses to sex-hormone manipulation, i.e. estradiol, are linked to changes in functional connectivity of key limbic brain structures [10]. Based on a prestigious Sapere Aude grant from the Danish Research Council, Vibe Frøkjær will in future studies focus on illuminating if estradiol-linked risk and resilience mechanisms translate to clinical settings of women across pregnancy to postpartum transition in order to guide a targeted and personalized preventive strategy in high-risk groups.

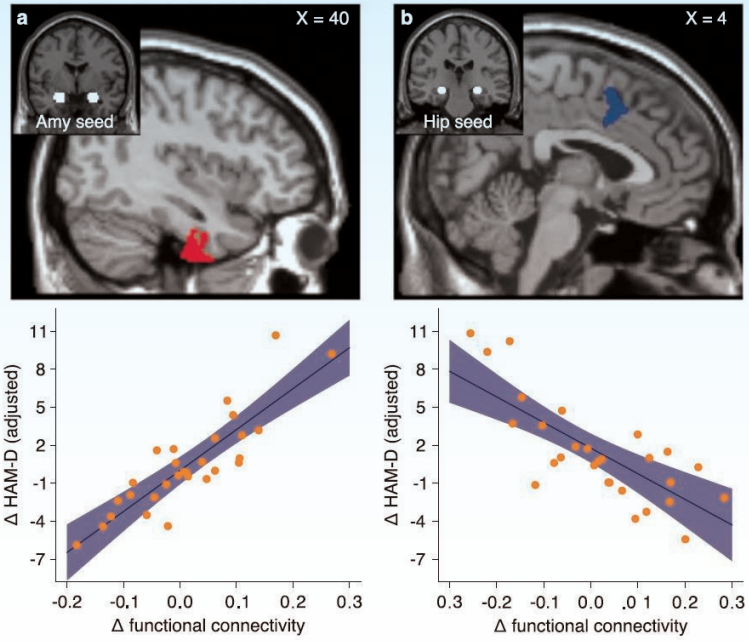


Figure 14: Change in brain network communication associated with emergence of depressive symptoms following sex hormone intervention. (Upper panel) Statistical parametric maps showing (A) right temporal cortex and (B) cingulate gyrus/pre-SMA where change in resting-state functional connectivity with respective seed (Amygdala/Hippocampus) was significantly associated with change in depressive symptoms. Red and blue denote a positive and negative correlation, respectively. (Lower panel) Plot of mean change in respective functional connectivity estimates against change in Hamilton 17-item depression score. From [10], Copyright © 2017 American College of Neuropsychopharmacology.

Clinical Neurology

Epilepsy surgery registry data

Patients with medically intractable epilepsy with a focal start in the brain are possible candidates for epilepsy surgery. In Denmark, this 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 and leading the research initiatives in epilepsy patients.

Supported by the Danish Council for Independent Research, the construction of a prospective database at Rigshospitalet for patients enrolled in the Danish Epilepsy Surgery program is close to completion. It has been closely coordinated with the European Database for Epilepsy (eCRF, E-pilepsy) and implemented on the same platform (REDCap).

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 renders free of disabling seizures.

NRU PhD student Mette Thrane Foged has in collaboration with associate professor Sándor Benickzy from the Epilepsy Hospital Filadelfia continued to record high density EEG (HD-EEG with 256 channels) in epilepsy surgery candidates. The aim is to estimate the added value of HD-EEG source localization in the epilepsy surgery evaluation process. This study will be completed in 2018.

Mette Thrane Foged also performed concurrent EEG and fMRI studies in epilepsy patients and healthy subjects. We have shown that temperature increase beneath the electrodes is quite modest and not a concern, and that the fMRI signal is to some extent influenced by the electrodes but does not affect the interpretation of the results [12].

The 7 Tesla MR scanner at Hvidovre Hospital is finally running. Setup for evaluation of epilepsy patients have been completed and investigation of patients just started (**Figure 15**). Giske Opheim has been appointed as PhD student on the project.

New insights and innovative treatment strategies for epilepsy

In 2017 we have started new research projects aiming at gaining new insights into epilepsy based upon tissue resected during epilepsy surgery. We collaborate with associate professor Lasse K. Bak from Dept. of Drug Design and Pharmacology at University of Copenhagen (UCPH) to better understand mechanisms of anti-epileptic drug response and identify possible new targets for

anti-epileptic drugs. We collaborate with associate professor Konstantin Khodosovich from Biotech Research & Innovation Centre, UCPH using unique techniques to identify mechanisms underlying seizure activity in epilepsy and potential biomarkers and targets for diagnostics and disease treatment. We have continued our collaboration with professor Merab Kokaia's group at Lund University and associate professor David Woldbye's group at UCPH to pave the way for new innovative gene therapeutic treatment strategies for drug-resistant epilepsy patients.

Brain Tumor project

A brain tumor 7T MR project was started by Olaf B. Paulson in collaboration with neurosurgeon Jannick Brennum in the fall of 2017 and setup is now essentially completed. The aim is to assess the diagnostic add-on value of the higher resolution in structural imaging as compared to 3T MR. Further, the high fMRI resolution combined with diffusion tensor imaging will be used to evaluate eloquent cortical areas and fiber bundles proximal to the tumor growth, and thereby contribute to surgical planning. Nizar Hamrouni has been appointed scholar student on this project.

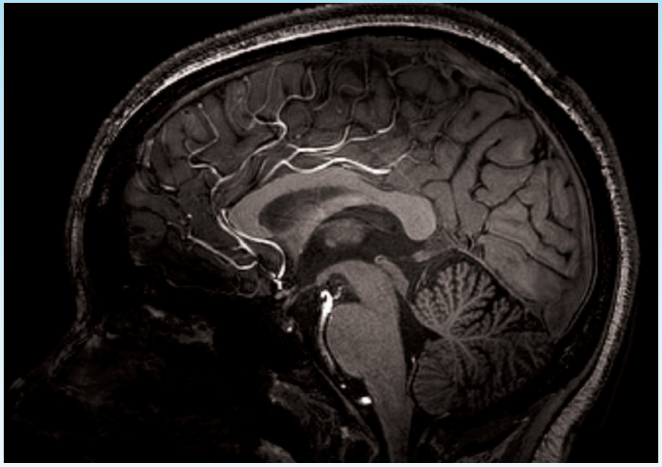


Figure 15: Example T1-weighted 7T MR scan (sagittal view) of a 25 year old female epilepsy surgery candidate patient. Courtesy of Giske Opheim.

Imaging of neuroinflammation

Molecular imaging of neuroinflammatory changes in the brains of patients with neurological, neurosurgical and psychiatric disorders is a method of great potential for research and clinical application. In the brain, TSPO is preferentially present on microglia. Imaging of TSPO in the human brain is believed to be important for demonstrating the role of microglial activation 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 and new treatment strategies.

In 2017 Per Jensen successfully defended his PhD thesis on the role of neuroinflammation in stroke, glioblastoma and autoimmune encephalitis. Sebastian Ebert, supported by a scholar stipend from the Danish Council for Independent Research, completed enrolment of patients in his study on the role of neuroinflammation in brain concussion.

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, Hillerød, and other hospitals in Denmark.

One of the diagnostic investigations performed by the SPECT-lab, is clinical DAT-SPECT scans, i.e. striatal DAT imaging with the SPECT ligand [^{123}I]FP-CIT. It is a robust technique for early detection of nigrostriatal dopaminergic output neurons loss and relevant to the differential diagnosis in patients with possible movements disorder and/or dementias. In 2017 we performed a total of 120 clinical DAT-SPECT investigations.

We also perform blood flow imaging with the SPECT ligand [^{99m}Tc]HMPAO. We mostly use the technique to localize the epileptic focus in patients with drug-resistant epilepsy. We are the only laboratory in Denmark to conduct ictal-interictal SPECT imaging with co-registration to MRI (SISCOM) (**Figure 16**). In 2017 the SPECT-lab performed a total of 35 [^{99m}Tc]HMPAO investigations and 20 SISCOM-analyses.

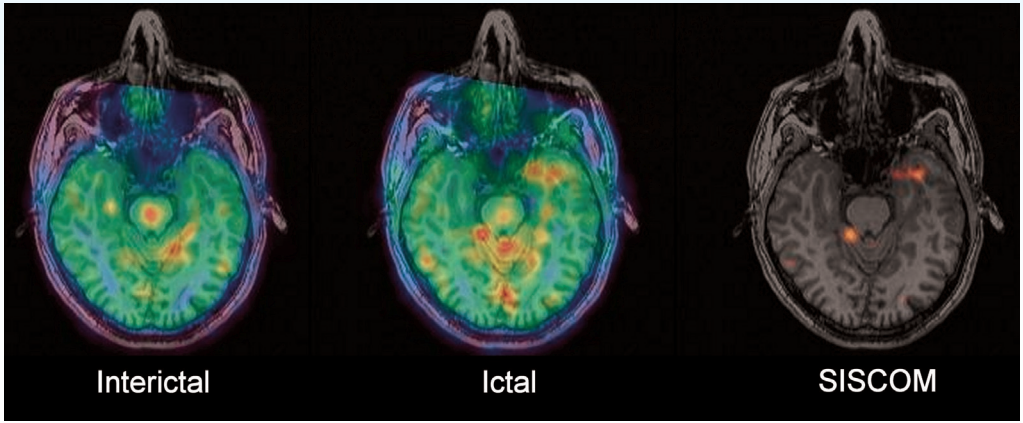


Figure 16: (Left) Interictal and (middle) ictal [^{99m}Tc]HMPAO SPECT imaging with co-registration to MRI, and (right) the SISCOM image. Courtesy of SPECT-lab.

Research projects

In the past year the SPECT-lab has again been actively engaged in several of the ongoing research projects at NRU. We have concluded our active engagement in the EU-funded INMiND project in which several [^{123}I]CLINDE-SPECT investigations in both healthy subjects and in patients expected to show microglial activation have been performed. Some of these data have been used in Per Jensen's PhD thesis.

Based on [^{123}I]FP-CIT SPECT data from the European Normal Control Database of DaTSCAN (ENCDAT database), which we together with several EU collaborators collected data for in the period 2008-10, we have shown that the clinical use of the database requires consistency in image processing and analysis and that caution must be taken when comparing data from different centers [7,40].

In collaboration with professor Anders Fink Jensen from the Psychiatric Centre Copenhagen we have initiated a large-scale data acquisition in two new research projects involving dopamine transporter (DAT) SPECT scans. The first project investigates if an acute infusion with Byetta® (exenatide), i.e. a Glucagon Like Peptide 1 (GLP-1) receptor agonist, induces acute changes in the striatal DAT availability in healthy individuals, while the second project investigates the placebo-controlled effects of Bydureon® (exenatide), another GLP-1 receptor agonist, on alcohol intake in patients with a diagnosis of alcohol dependence.

Radioligand Development

In the Cimbi radioligand development group we combine biology, chemistry, radiochemistry and neuroimaging to develop new PET radioligands. 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 also carry out preclinical studies for industrial partners.

For decades, scientists have searched for PET radiotracers that are sensitive to acute changes in brain 5-HT levels. In 2017 we reported that that the 5-HT2A receptor agonist radioligand [^{11}C]Cimbi-36, is indeed sensitive to pharmacologically induced changes in 5-HT in both non-human primates [44] and pigs [22].

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-HT1A, 5-HT1B, 5-HT2A, and 5-HT4 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 2017 we had in total 15 requests for data.

Innovation Fund Denmark

NeuroPharm

Center for Experimental Medicine Neuropharmacology

Center for Experimental Medicine Neuropharmacology (NeuroPharm) is funded by the Innovation Fund Denmark and resides at NRU. National partners include the pharmaceutical company H. Lundbeck A/S and four academic partners: one from UCPH and three from university hospitals in the Capital Region of Denmark, while international partners include Massachusetts General Hospital/Harvard and the British-based small-medium sized enterprise, Imanova Ltd (acquired by Invicro LLC in August 2017). 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.

NP1: Treatment outcome in Major Depressive Disorder (led by Vibe G. Frøkjær, NRU)

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

We will enroll a total of 100 MDD patients and examine how these markers 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. The imaging program is repeated at week 8 in a subgroup of 40 patients with variable antidepressant response. In 2017, a total of 42 patients have been enrolled.

NP2: 5-HT_{2A}R modulation effects on neurobiology, cognition and mood (led by Patrick Fisher, NRU)

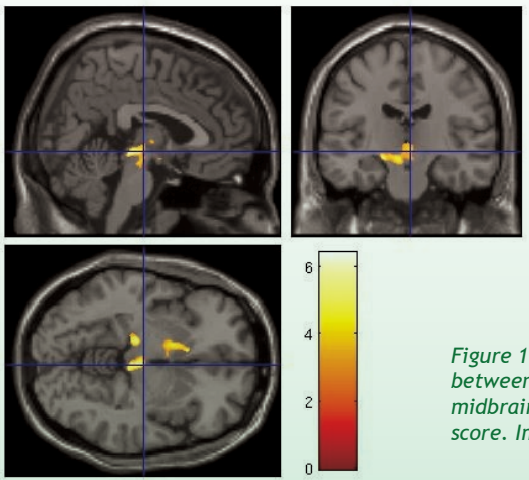
The goal of NP2 is to apply an experimental medicine strategy coupled with human functional neuroimaging to elucidate the effects of 5-HT2AR modulation on brain function and mood in healthy individuals. We are comparing psilocybin (5-HT2AR agonist) and ketanserin (5-HT2AR antagonist) effects on brain 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.

In late 2016 and through 2017 we have completed targeted data collection for the first component of NP2, wherein we have measured 5-HT2AR receptor occupancy (i.e., change in [^{11}C]Cimbi-36 PET signal) in the human brain following administration of a single dose of either ketanserin or psilocybin. Preliminary results are very encouraging with measurable receptor occupancy by both drugs. In early 2018, we will examine the link between receptor occupancy and measured drug levels in blood.

The second component of NP2 will start in early 2018, examining the prolonged effects of a single psilocybin dose on 5-HT2AR levels. Component three of NP2 is scheduled to start in Fall 2018 wherein we will examine the dose-dependent effects of 5-HT2AR modulation on brain connectivity, cognition and mood.

NP3: Novel neuroimaging methods for an experimental medicine approach (led by Hanne D. Hansen, NRU)

As described earlier (page 16), we have in 2017 published our investigations of the hemodynamic effects and occupancy changes of functionally different compounds (agonists, partial agonists, antagonists) using simultaneous PET-MRI [15]. We are now working on translating the experimental design from non-human primates into a clinical setting, and the first pilot studies have been conducted.



NP3 also includes the investigation of the serotonergic system in migraine patients. We have studied episodic migraine patients and found that the 5-HT1B receptor binding was lower in these patients than in healthy controls [6]. More specifically we also found clusters in the brain that had a positive correlation between 5-HT1B receptor binding and days since the last attack (**Figure 17**). The same patient group and a group of chronic migraine patients has been scanned with the 5-HT4 receptor radioligand [^{11}C]SB-207145 to settle a long-debated issue, to establish if migraine patients have reduced brain 5-HT levels.

Figure 17: Whole-brain voxel-based analysis in the migraine patients showing a positive correlation between 5-HT1B receptor binding and days since the last attack in a cluster in the brainstem and midbrain ($k = 3589$, $t(11) = 6.41$, $p < 0.05$ corrected, $x = 15$, $y = 22$, $z = 8$). Color bar indicates t-score. Image shown at $z = 5.84$. From [6], Copyright © International Headache Society 2016.

NP4: Bioinformatics, statistical and predictive models (led by Brice Ozenne, UCPH)

Latent variable models (LVM) have shown their efficacy for analysing complex neuroimaging data in the CIMBI project. In order to be applied on the data collected in NP1-3, we have in two recent different projects extended LVM to better handle challenges in these data. In the first project, we have developed statistical methods providing more accurate inference for LVM in presence of small sample sizes (**Figure 18**) and when the LVM can only be partially defined a priori. A software package called *lavaSearch2* that implements these developments is available on CRAN (https://cran.r-project.org) and we will seek to publish both methods soon. In the second project we focused on non-linear LVMs. A new estimation algorithm was developed and studied, and the work has been documented in a manuscript that has been submitted for publication.

In future works, an LVM which is able to predict treatment response (e.g. to SSRI) will be built upon these developments and compared to machine learning technics.

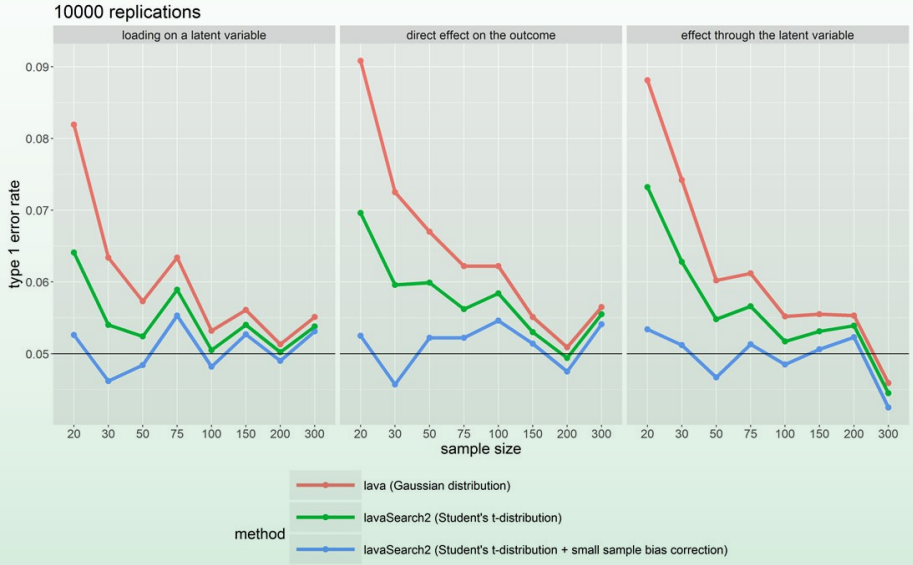


Figure 18: Type 1 error across the sample size for several coefficients of a latent factor model. Ideally the type 1 error should be of 5% regardless of the sample size. The new procedure provides a better control of the type 1 error, especially in small samples (n<50). Courtesy of Brice Ozenne, NRU.

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.

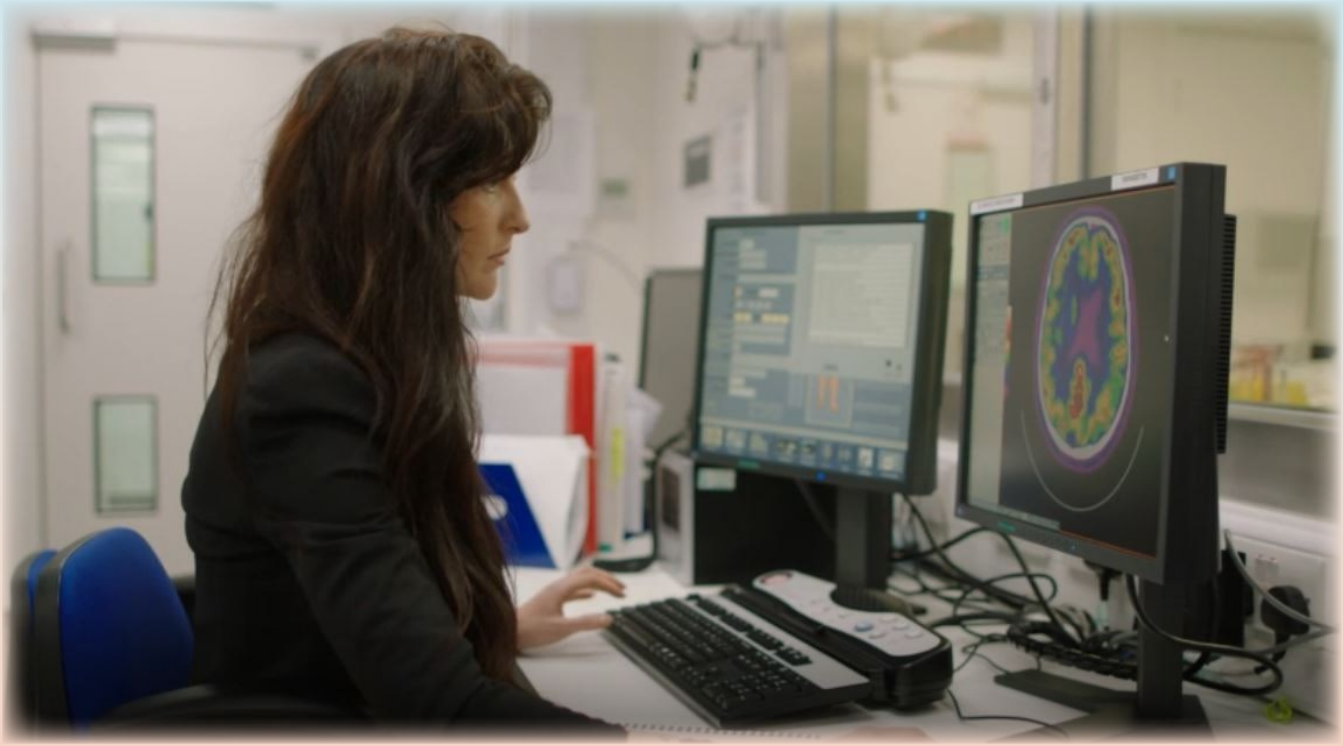
Psychiatric Centre Copenhagen

NRU has a close collaboration with Psychiatric Centre Copenhagen, in particular with professor Martin Balslev Jørgensen who is directly involved in NP1 of NeuroPharm, with professors Lars Vedel Kessing and Kamilla Miskowiak and the Neurocognition and Emotion in Affective Disorders (NEAD) group which carries research out in depression and bipolar disorder, as well as with professors Anders Fink Jensen and Birte Glenthøj. We highly appreciate this collaboration and look forward to continued joint research activities in the future.

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 two retreat meetings (the first one in Boston in 2012 and the second one in Copenhagen in 2014), 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 NeuroPharm Center grant (2015-22) from the Innovation Fund Denmark, as well as bilateral exchange of scientists in order to conduct 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 2017

NRU has in 2017 published a total of 2 PhD dissertations, 8 Master's or Bachelor theses, and 44 scientific peer-reviewed papers.

PhD dissertations

- Bettina Hornbøll. Functional brain imaging under serotonergic challenges. University of Copenhagen, Faculty of Health and Medical Sciences. Defended May 08, 2017
- Per Jensen. Translocator protein imaging with 123I-Clinde SPECT - Method development and clinical research. University of Copenhagen, Faculty of Health and Medical Sciences. Defended Sep 09, 2017

Theses and reports

The following list of NRU-affiliated students have successfully defended their theses or research year reports during 2017:

- Agata Casado-Sainz, "*Sensorimotor gating in Long Evans rats after selective chemogenetic manipulation of the nigrostriatal dopaminergic pathway*", Master's thesis in Molecular Biomedicine, Faculty of Health and Medical Sciences, UCPH
- Beatriche L.E Henriksen, "*Serotonin Receptor and Transporter Composition Peripartum, and in a rat Postpartum Depression Model*", Master's thesis in Medicinal and Molecular Biology, Roskilde University
- Ditte Christensen, "*Estimating the Reproducibility of an 'Emotional Faces' fMRI Paradigm*", Bachelor thesis in Biomedical Engineering, DTU/ UCPH
- Maja Højvang Sørensen, "*The pharmacology of a7 nAChRs in cultured primary microglia cells*", Master's thesis in Biochemistry, Faculty of Health and Medical Sciences, UCPH
- Mark Juul, "*Evaluating changes in same-subject multiple MR images over time*", Master's thesis in Biomedical Engineering, DTU/ UCPH
- Nizar Hamrouni, "Clinical Pathological Correlation", Bachelor thesis in Medicine, Faculty of Health and Medical Sciences, UCPH
- Simone Larsen Bærentzen, "*Magnetic Resonance Spectroscopy in Long Evans Rats Following Selective Chemogenetic Modulation of the Nigrostriatal Pathway with DREADDs*", Master's thesis in Human Biology, Faculty of Health and Medical Sciences, UCPH
- Siv Thorlund Peitersen, "*PET & Epigenetics - In vivo and in vitro evaluation of the PET tracer 11C-Martinostat's ability to quantify HDAC levels in pig brain*", Master's thesis in Biology, Faculty of Science, UCPH

Papers in peer-reviewed journals

1. Beliveau V, Ganz M, Feng L, Ozenne B, Højgaard L, Fisher PM, Svarer C, Greve DN, Knudsen GM. A High-Resolution In Vivo Atlas of the Human Brain's Serotonin System. J Neurosci. 2017 Jan 4;37(1):120-128

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NRU research is often being presented at conferences and meetings world-wide. Here, PhD students Martin Nørgaard (left), Liv V. Hjordt (middle) and Lene L. Donovan (right) are sharing their exciting results.

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