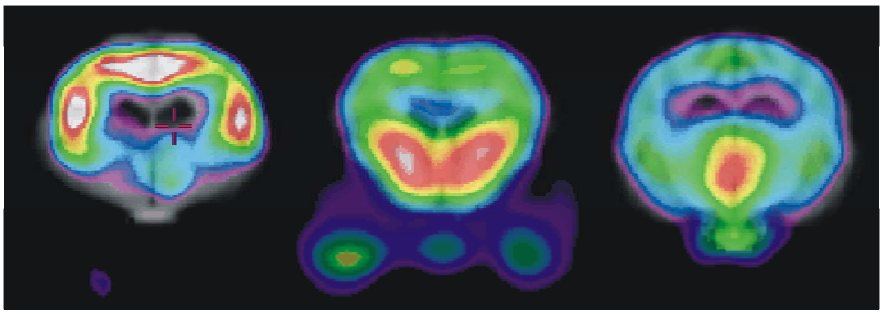
Annual Status Report 2006

Neurobiology Research Unit



Dept. Neurology, Neuroscience Centre
Rigshospitalet
Faculty of Health Sciences
Copenhagen University

www.nru.dk

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Front page: The Serotonergic transmitter system in the minipig brain: From left 5-HT_{2A} (^{18}F-altanserin, 5-HT_4 (^{11}C-SB207145), and SERT (^{11}C-DASB).

1. Research Facilities

Since June 1996 the Neurobiology Research Unit has been located at Juliane Maries Vej 24 in an old villa named Building 92 at the Rigshospitalet campus. In this house, NRU has offices and facilities for data analysis. During the summer of 2006, as a consequence of the establishment of Cimbi, the Director of Rigshospitalet has decided to allocate additional facilities for the center and the entire building 92 (approx. 500 square meters, 19 offices and a conference room with kitchen facilities) is now allocated for NRU.

The SPECT laboratory of NRU is located at the Department of Neurology on the 8th floor in the main complex of Rigshospitalet. The laboratory includes a room for the Philips IRIX SPECT scanner, a type B approved isotope laboratory, and a small office. Further office and laboratory facilities are shared with other employees at the department.

The NRU experimental laboratory resides in Building 93, Juliane Maries Vej 20, just opposite Building 92. The ground floor of Building 93 is shared with the Cardiovascular Laboratory. Four laboratory rooms (in total 92.5 m^2) are allocated for NRU, and it shares another three rooms and two offices with the above mentioned research group.

NRU conducts its PET research activities in close collaboration with the Department of Clinical Physiology/Nuclear Medicine, and has access to the three PET scanners in the PET Unit in the Finsen Building at Rigshospitalet. NRU has a close collaboration with the Department of Clinical Physiology/Nuclear Medicine in the research planning and developmental activities.

2. Objectives, Organization, and Staff

NRU has its main interest within neurotransmission brain research, with particular focus on neuroreceptor imaging. Traditionally, the research unit has also been involved with studies of cerebral blood flow. The unit has a close collaboratio with the Danish Research Centre for Magnetic Resonance (DRCMR), Hvidovre University Hospital. Finally, image analysis and tracer kinetics remain issues that receive high attention within the unit.

The research group is chaired by Professor Gitte Moos Knudsen. Professor Olaf B. Paulson, who since 1995 also has chaired the DRCMR at Hvidovre Hospital, Chief Engineer Claus Svarer, PhD, and Associate Professor Steen Hasselbalch are partners in the NRU steering group. The Chief Technologist is Gerda Thomsen.

In 2006 the research staff consisted of:

Senior Researchers:
Susana Aznar, Biologist, PhD
Amir Hashemi, Biologist, PhD
Steen Hasselbalch, MD, DMSc (half time)
Esben Høgh-Rasmussen, Engineer
Gitte Moos Knudsen, Professor, MD, DMSc
Finn Årup Nielsen, Engineer, PhD*
Olaf B. Paulson, Professor, MD, DMSc
Karam Sidaros, Engineer, PhD*
Claus Svarer, Engineer, PhD

PhD-students:
David Erritzøe, MD
Vibe Gedsø Frøkjær, MD
Steven Haugbøl, MD
Birgitte Rahbek Kornum, Human Biologist
Cecilie Löe Licht, Human Biologist
Anders Bue Marcussen, Human Biologist
Lisbeth Marner, MD
Robin de Nijs, Physicist*
Kåre Søndergaard, Chemist*
Viktorija Trajkovska, Human Biologist

Junior Researchers:
Haroon Arfan, MD
Anetta Claussen, Engineer
Martin Drews, Physicist
Jens Munk Hansen, Physicist
Rasmus Lohals Larsen, Biologist
Michael Palner, Engineer

Associated Researchers:
Lars Hageman Pinborg, MD
Morten Ziebell, MD

Students:
Lis Arneberg, biochemist student
Bjarni Bödvarsson, engineer student*
Ruben Christensen, biology student
Maria Christoffersen, medical student
Anders Ettrup, human biology student
Celia Kjærby Hansen, human biol.student
Louise Legaard, engineer student
Lisbeth Kirkegaard, biology student
Rune Nielsen, psychology student
Morten Skøtt Thomsen, human biol.student
Helle Tolstrup, biology student
Sanne Wulff, medical student

Technical Administrative Personnel:
Anita Dole, medical technologist
Pia Farup, secretary
Dorthe Givard, secretary
Mette Søgaard Hansen, medical technologist
Bente Høy, nurse
Liselotte Jacobsen, medical technologist
Christine B. Janssens, medical technologist
Thomas Jensen, IT supporter
Inge Møller, medical technologist
Anja Pedersen, medical technologist
Lene Rottensten, research assistant
Glenna Skouboe, medical technologist
Karin Stahr, medical technologist
Gerda Thomsen, Chief technologist

* shared with another research group

Guest Researchers:

Per Hartvig, Adj. Professor, Department of Analytical Pharmaceutical Chemistry, University of Uppsala, Sweden

Jan Kalbitzer, MD, Jülich, Germany

Anne van Oosten, Physicist, Amsterdam, The Netherlands

Michael Pedersen, MD, PhD-student, Department of Epidemiology, Rigshospitalet

Maurizio Severino, MD, Neuroscience Department, 'Federico II', Naples, Italy

Stina Syvänen, Chemical Engineer, Uppsala Imanet, Sweden

Sigurdur Sigurdsson, MD, Dept. of Nephrology, KAS Herlev

Petrine Wellendorph, Cand.Pharm.,PhD, Faculty of Pharmaceutical Sciences, Copenhagen

3. Collaborators in 2006

Center for Integrated Molecular Brain Imaging, Cimbi

www.cimbi.dk

Cimbi consists of a multidisciplinary collaboration among institutes and departments in the Copenhagen areaThese institutions include:

- Department of Medical Chemistry, The Danish University of Pharmaceutical Sciences
- Danish Research Center for Magnetic Resonance, Hvidovre Hospital
- The PET and Cyclotron Unit, Rigshospitalet
- Informatics and Mathematical Modelling, Technical University of Denmark
- Neurobiology Research Unit, Rigshospitalet
- Department of Psychology, Faculty of Humanities, University of Copenhagen
- Department of Medical Biochemistry & Genetics (IMBG), University of Copenhagen
- Dept. of Health Psychology, Copenhagen University

Copenhagen Brain Research Center, CBRC

www.cbrc.dk

CBRC consists of a multidisciplinary collaboration among institutes and departments in the Copenhagen area working with brain related research. These institutions include:

- Department of Medical Chemistry, The Danish University of Pharmaceutical Sciences
- H. Lundbeck A/S, Copenhagen

- Danish Research Center for Magnetic Resonance, Hvidovre Hospital
- The PET and Cyclotron Unit, Rigshospitalet
- Informatics and Mathematical Modelling, Technical University of Denmark
- Neurobiology Research Unit, Rigshospitalet
- Department of Psychology, Faculty of Humanities, University of Copenhagen

Additional departments within Rigshospitalet
Department of Cardiology
Department of Hepatology
Department of Infectious Diseases
Department of Neuroanesthesiology
Department of Neurosurgery
Department of Pediatrics
Department of Psychiatry

EU 5th Framework Program
Neuroreceptor Changes in Mild Cognitive Impairment (NCI-MCI), QLRT-2000-00502
www.mci.nru.dk
Department of Geriatrics, Huddinge Universitetssjukhus, Sweden
PET Centre, Free University Hospital, Amsterdam, The Netherlands
PET Center, Karolinska Institutet, Stockholm, Sweden
Uppsala University PET Centre, Uppsala, Sweden
University 'Federico II', Napoli, Italy

Development of New Radiotracers for the in-vivo Assessment of Biological Functions and Drug Interactions (COST).
Collaborators within COST, workgroup 1: Radioligands for Brain Receptors.
PET-centres in Orsay, Villigen-PSI, Jülich, Stockholm, London (Hammersmith), Turku, Kuopio, Uppsala, Brussels, Aarhus.

EU 6th Framework Program
DiMI - Diagnostic Molecular Imaging (LSHB-CT-2005-512146)
The goal of the Network of Excellence "Diagnostic Molecular Imaging" (DiMI) - Molecular Imaging for Diagnostic Purposes - is to integrate multidisciplinary research for the development of new probes and multimodal non-invasive imaging technology for early diagnosis, assessment of disease progression and treatment evaluation.
The general objectives of DiMI are to coordinate and efficiently integrate more than 50 research groups from various disciplines to study non-invasively gene expression and function in major diseases such as neurodegeneration, stroke, heart failure, atherosclerosis and autoimmune diseases.

For further information, please visit www.dimi-net.org.
NRU is training platform for image and data analyses for DiMI partners.

European Network of Excellence for Brain Imaging under the umbrella of the EANM
SPECT Centers from Italy, Germany, Belgium, Netherlands, Austria, Denmark, United Kingdom, France, and Spain.

Others
Glaxo SmithKline Beecham, London, UK
H. Lundbeck A/S
Language Section, National Institutes of Health, Bethesda, Maryland, USA
Mannheim Central Mental Institute, University of Heidelberg
MAP Medical, Helsinki, Finland
NeuroSearch A/S
Philips Medical Systems

4. Publications

PhD-theses

Høgh-Rasmussen E. PhD-afhandling: Tomographic reconstruction using anatomy and regularization. Copenhagen: Eget forlag 2006:1-184. Defended Februar 17, 2006 at the Danish Technical University.

Søndergaard K. PhD-afhandling: Synthesis, binding studies and PET studies of 2-substituted apomorphines. Copenhagen: HCØ Tryk 2006:1-88. Defended January 26, 2006 at the Danish Pharmaceutical University.

Peer-review Full-length Publications

Cerebral Blood Flow and Metabolism

Andersen PB, Blinkenberg M, Lassen U, Kosteljanetz M, Wagner A, Poulsen HS, Sørensen PS, Paulson OB. A prospective PET study of patients with glioblastoma multiforme. Acta Neurol Scand 2006;116:412-8.

Frøkjær VG, Strauss GI, Mehlsen J, Knudsen GM, Rasmussen V, Larsen FS. Autonomic dysfunction and impaired cerebral autoregulation in cirrhosis. Clin Auton Res 2006;16:208-16.

Kondziella D, Brenner E, Eyjolfsson EM, Markinhuhta KR, Carlsson ML, Sonnewald U. Glial-neuronal interactions are impaired in the schizophrenia model of repeated MK801 exposure. Neuropsychopharmacology 2006;31(9):1880-7.

Linde R, Hasselbalch SG, Topp S, Paulson OB, Madsen PL. Global cerebral blood flow and metabolism during acute hyperketonemia in the awake and anesthetized rat. J Cereb Blood Flow Metab 2006;26:170-80.

Mathiesen HK, Jonsson A, Tscherning T, Hanson LG, Andresen J, Blinkenberg M, Paulson OB, Sorensen PS. Correlation of global N-acetyl aspartate with cognitive impairment in multiple sclerosis. Arch Neurol 2006;63:533-6

Pedersen M, Brandt CT, Knudsen GM, Østergaard C, Skinhøj P, Frimodt-Møller N, Møller K. Cerebral blood flow autoregulation in early experimental S. pneumniae meningitis. J Appl Physiol 2006 [Epub ahead of print].

Brain Mapping

Balslev D, Nielsen FAa, Lund TE, Law I, Paulson OB. Similar brain networks for detecting visuo-motor and visuo-proprioceptive synchrony. Neuroimage 2006;31:308-12.

Gerlach C, Law I, Paulson OB. Shape configuration and category-specificity. Neuropsychologia 2006;44:1247-60.

Nielsen K, Rostrup E, Frederiksen JL, Knudsen S, Mathiesen HK, Hanson LG, Paulson OB. Magnetic resonance imaging at 3.0 Tesla detects more lesions in acute optic neuritis than at 1.5 Tesla. Invest Radiol 2006;41:76-82.

Scheuer KH, Nielsen JE, Krabbe K, Paulson OB, Law I. Motor activation in SPG4 linked hereditary spastic paraplegia. J Neurol Sci 2006;244:31-9.

Neuroreceptor Studies

Glenthoj BY, Mackeprang T, Svarer C, Rasmussen H, Pinborg LH, Friberg L, Baaré W, Hemmingsen R, Videbaek C. Frontal dopamine $D_{2/3}$ receptor binding in drug-naive first-episode schizophrenic patients correlates with positive psychotic symptoms and gender. Biol Psychiatry 2006;60:621-9.

Husum H, Aznar S, Høyer-Hansen S, Larsen MH, Mikkelsen JD, Møller A, Mathé AA, Wörtwein G. Exacerbated loss of cell survival, neuropeptide Y-immunoreactive (IR) cells, and serotonin-IR fiber lengths in the dorsal hippocampus of the aged flinders sensitive line "depressed" rat: Implications for the pathophysiology of depression? J Neuroscience Res 2006;84:1292-1302.

Kornum BR, Weikop P, Møller A, Ronn LCB, Knudsen GM, Aznar S. Serotonin depletion results in a decrease of the neuronal activation caused by rivastigmine in the rat hippocampus. Brain Research 2006;1073-1074:262-8.

Kornum BR, Licht CL, Weikop P, Knudsen GM, Aznar S. Central serotonin depletion affects rat brain areas differently: A qualitative and quantitative comparison between different treatment schemes. Neurosci Lett 2006;392:129-34.

Nielsen K, Brask D, Knudsen GM, Aznar S. Immunodetection of the serotonin transporter protein is a more valid marker for serotonergic fibers than serotonin. Synapse 2006;59:270-6

Other

Lindberg C, Koefoed P, Hansen ES, Bolwig TG, Rehfeld JF, Mellerup E, Jorgensen OS, Kessing LV, Werge T, Haugbol S, Wang AG, Woldbye DP. No association between the -399 C > T polymorphism of the neuropeptide Y gene and schizophrenia, unipolar depression or panic disorder in a Danish population. Acta Psychiatr Scand 2006;113:54-8.

Textbooks and Reviews

Hasselbalch SG, Knudsen GM. Imaging of neurotransmitter systems in dementia. In: Herholz K, Perani D, Morris C, eds. The Dementias. Early Diagnosis and Evaluation. New York: Taylor and Francis Group 2006:253-77.

Other

Knudsen GM (Ed.). Conference proceedings on Neuroreceptor Mapping 2006. Neuroimage 2006;31, suppl.2:T1-186.

5. Other Activities

5.1 Congress Participation

The staff of NRU has participated in 27 international and national meetings and congresses related to their research fields. Staff members have participated as evaluators of abstracts and as chairmen at scientific sessions.

5.2 Congress Organizing

NCI-MCI Final Workshop: Molecular brain imaging in very early Alzheimer's disease, February 2-3, 2006 (Gitte Moos Knudsen).

The annual meeting of the Danish Society of Neuroscience, May 7-9, 2006: 'Neurobiology of Depression: From basal research to clinical application' (Susana Aznar).

NRM06 – 6th Neuroreceptor Mapping Symposium, Copenhagen, July 6-8, 2006 (Gitte Moos Knudsen).

5.3 Pre- and Postgraduate Teaching

PhD-course: Basic Kinetic Modeling in Molecular Imaging, Copenhagen, 27.2. –3.3.2006 (Gitte Moos Knudsen)

XVII PET Pharmacokinetic Course, Copenhagen, July 9-11, 2006 (Gitte Moos Knudsen)

NRU organizes every other week seminars open to the public within the areas of NRU research interests. The meetings are announced on the homepage http://nru.dk/meetings/FIG.

On December 8, 2006, NRU organized an open-to-the-public one day symposium where scientists from NRU presented their most recent data.

Pregraduate Supervision:

Thomas Rune Nielsen, psychology student: Cognitive testing of the Göttingen minipig (supervisor: Birgitte Kornum)

Ruben Christiansen, biology student: The serotonergic neurotransmittersystem in an in vivo model of Alzheimer´s disease. Master thesis defended February 2006. (supervisor: Susana Aznar)

Helle Tolstrup, biology student: Interactions between the serotonergic and the dopaminergic transmittersystem. Master thesis defended April 2006. (supervisor: Susana Aznar)

Morten Skøtt Thomsen, human biology student: Effects of BDNF in organotypic

hippocampal cultures. Focus on the 5-HT2A receptor. Master thesis defended August 2006. (supervisors: Susana Aznar and Gitte Moos Knudsen)

Cecilie Löe Licht, human biology student: The 5-HT4 receptor in depression related states. Master thesis defended September 2006 (supervisor: Gitte Moos Knudsen).

5.4 National and International Committees

National Committees:

Chairman, Department of Clinical Neuroscience and Psychiatry, University of Copenhagen (Olaf B. Paulson)

Member of the Medical faculties committee for clinical medicine in the regional hospitals (UKM) (Olaf B. Paulson)

Chairman of the Research Committee of the Neuroscience Centre at Rigshospitalet (Olaf B. Paulson)

Member of the Research Committee of Hvidovre Hospital (Olaf B. Paulson)

President of the Danish Society of Neurology (Olaf B. Paulson)

Board Member of the Danish Neuroscience Society (Gitte Moos Knudsen)

Board Member of the Danish Alzheimer Association (Olaf B. Paulson)

Chairman of the Research Committee of the Danish Alzheimer Association and Member of the Danish Alzheimer Research Foundation (Olaf B. Paulson)

Member of the Neurology Committee of the Copenhagen Hospital Corporation (Olaf B. Paulson)

Member of the board of directors of the Elsass Foundation (Olaf B. Paulson)

Board Member of the NeuroCluster, Health Science Faculty, Copenhagen University (Gitte Moos Knudsen)

International Committees:

International scientific advisor for Brain Imaging Centre West, Jülich, Germany (Gitte Moos Knudsen)

Member of the Steering Group Committee for the EU 6th Framework Network of Excellence, Diagnostic Molecular Imaging (DiMI) (Gitte Moos Knudsen)

Evaluation:

Evaluator of PhD thesis: Lars Christian Storr: Rehabilitation of people with multiple sclerosis in Denmark, University of Copenhagen (Gitte Moos Knudsen)

Evaluator of PhD thesis: Nicholas Seneca: PET Imaging of two monoaminergic neurotransmitter systems in brain: Studies of the norepinephrine transporter and dopamine D2 receptor, Karolinska Institutet (Gitte Moos Knudsen)

Member of the Editorial Board of the Journal of Cerebral Blood Flow and Metabolism (Gitte Moos Knudsen)

Expert Evaluator at the Norwegian Research Council and at EU, Brussels (Gitte Moos Knudsen)

External examiner at the Technical University of Denmark (Claus Svarer)

Finally, staff members of NRU regularly conduct peer-reviews for several international journals and at international congresses.

6. SPECT Laboratory

A total of 412 clinical scans have been performed in 2006, 88 of these with the dopamine transporter ligand 123I-PE2I, the remaining with 99mTc-SHMPAO.

Two physics students, Anders Torp and Louise Legaard have been working in the SPECT laboratory for the conduction of their master thesis. Anders Torp has worked with the Polaris System for correction of head movements while scanning and defended his master thesis in May 2006

Another physics student, Anna van Oosten from Amsterdam, have been connected to the SPECT laboratory for the conduction of her minor internship, practical training. Anna van Oasten has worked with attenuation correction in SPECT.

Research projects carried out in 2006

- Reproducibility of 123I-PE2I binding to dopamine transporter with SPECT following bolus/infusion (paper in press)
- Investigations of the serotonin transporter with 123I-ADAM (paper in preparation)
- 123I-PE2I SPECT as a diagnostic tool in clinically uncertain parkinsonian syndromes
- High energy photon correction for I-123 in SPECT-studies
- The clinical application of arterial spin labelling in dementia evaluation (article in preparation)
- Implementation of a system for correcting SPECT acquisitions for head movements during scanning using a Polaris Accedo System
- Validation of FAN beam collimator
- Attenuation correction in SPECT.
- The time delay from injection to data acquisition using 99mTc-SHMPAO SPECT
- Automatic delineation of VOI's on HMPAO SPECT images

7. Acknowledgements

The Neurobiology Research Unit has received generous support from a number of public and private research funds.

Augustinusfonden

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Danish Agency for Science, Technology and Innovation

Danish Medical Research Council

H:S - Copenhagen Hospital Corporation

Ludvig og Sara Elsass Fond

Novo Nordisk Fonden

Rigshospitalets Jubilæumsfond

Savværksejer Jeppe Juhl og hustru Ovita Juhls Mindelegat

The Health Insurance Foundation

The Lundbeck Foundation

The Research Council of Rigshospitalet

University of Copenhagen, Faculty of Health Sciences and the Neuro Cluster

International research funding:

EU 5th Framework program

EU 6th Framework program