Annual Status Report 2007

Neurobiology Research Unit

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

www.nru.dk

Table of Contents

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; approx. 500 square meters, 19 offices and a conference room with kitchen facilities is 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 in studies of cerebral blood flow. The unit has a close collaboration 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 and laboratory leader is PhD Susana Aznar.

In 2007 the research staff consisted of:

Senior Researchers:
Susana Aznar, Biologist, PhD
Paul Cumming, Biochemist, PhD
Amir Hashemi, Biologist, PhD
Steen Hasselbalch, MD, DMSc (half time)
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
Anders Ettrup, Human Biologist
Vibe Gedsø Frøkjær, MD
Jens Munk Hansen, Physicist
Steven Haugbøl, MD
Jan Kalbitzer, MD
Birgitte Rahbek Kornum, Human Biologist
Cecilie Löe Licht, Human Biologist
Karine Madsen, MD
Anders Bue Marcussen, Human Biologist
Lisbeth Marner, MD
Robin de Nijs, Physicist*
Mikael Palner, Engineer
Kåre Søndergaard, Chemist*
Viktorija Trajkovska, Human Biologist

Junior Researchers:
Haroon Arfan, MD
Anetta Claussen, Engineer
Ruben Christensen, Biologist
Celia Kjærby Hansen, Human Biologist
Klaus Holst, Biostatician
Daniel Tolnai, MD
Gry Zornhagen, Psychologist

Associated Researchers:
Barbara Lykke Lind, Human Biologist
Lars Hageman Pinborg, MD
Morten Ziebell, MD

Students:
Tine Arentzen, biochemist student
Lis Arneberg, biochemist student
Maria Christoffersen, medical student
Lærke Damgaard, medical student
Peter Vestergaard Jensen, biology student
Lisbeth Kirkegaard, biology student
Caroline Myosatis, psychology student
Rune Nielsen, psychology student
Mads Okholm, medical student
Andreas Schmith, biochemistry student

Technical Administrative Personnel:
Anita Dole, medical technologist
Pia Farup, secretary
Dorthe Givard, secretary
Mette Søgaard Hansen, medical technologist
Kirsten Hornsyld, 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
Rasmus Sichlau, research assistant
Glenna Skouboe, medical technologist
Gerda Thomsen, Chief technologist

* shared with another research group

Guest Researchers:
Michael Pedersen, MD, PhD-student, Department of Epidemiology, Rigshospitalet
Hans Rasmussen, psychologist, Glostrup Hospital
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 2007

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

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

Haugbøl S. PhD-afhandling: Imaging brain serotonin 2A receptors: Methodological and genetic aspects and involvement in Tourette's syndrome. København: Eget forlag 2007:1-79. Forsvaret d. 2. februar 2007 ved Københavns Universitet, Det Sundhedsvidenskabelige Fakultet.

Law I. Disputats: Human brain mapping under increasing cognitive complexity using regional cerebral blood flow measurements and positron emission tomography. København: Lægeforeningens Forlag 2007:1-94. Forsvaret d. 31. august 2007 ved Københavns Universitet, Det Sundhedsvidenskabelige Fakultet.

Møller K. Disputats: Cerebral blood flow and metabolism in adults with acute bacterial meningitis. København: Eget forlag 2007:1-64. Forsvaret d. 24. august 2007 ved Københavns Universitet, Det Sundhedsvidenskabelige Fakultet.

Strauss GI. Disputats: The effect of hyperventilation upon cerebral blood flow and metabolism in patients with fulminant hepatic failure. København: Lægeforeningens Forlag 2007:1-45. Forsvaret d. 30. marts 2007 ved Københavns Universitet, Det Sundhedsvidenskabelige Fakultet.

Trajkovska V. PhD-afhandling: Brain-derived neurotrophic factor (BDNF) and glucocorticoids: Influence on serotonin 2A receptors and relation to major depression. København: Eget forlag 2007:1-64. Forsvaret d. 5. oktober 2007 ved Københavns Universitet, Det Sundhedsvidenskabelige Fakultet.

Peer-review Full-length Publications

Cerebral Blood Flow and Metabolism

Pedersen M, Brandt CT, Knudsen GM, Ostergaard C, Skinhoj P, Frimodt-Moller N, Moller K. Cerebral blood flow autoregulation in early experimental S. pneumoniae meningitis. J Appl Physiol 2007;102(1):72-8.

Brain Mapping and Structure

Balslev D, Cole J, Miall RC. Proprioception contributes to the sense of agency during visual observation of hand movements: evidence from temporal judgments of action. J Cogn Neurosci 2007;19:1535-41.

Christensen MS, Lundbye-Jensen J, Geertsen SS, Petersen TH, Paulson OB, Nielsen JB. Premotor cortex modulates somatosensory cortex during voluntary movements without proprioceptive feedback. Nat Neurosci 2007;10:417-9.

Dyrby TB, Sogaard LV, Parker GJ, Alexander DC, Lind NM, Baare WF, Hay-Schmidt A, Eriksen N, Pakkenberg B, Paulson OB, Jelsing J. Validation of in vitro probabilistic tractography. Neuroimage 2007;37:1267-77.

Gerlach C. A review of functional imaging studies on category specificity. J Cogn Neuroscience 2007;19:296-314.

Kornum BR, Thygesen KS, Nielsen TR, Knudsen GM, Lind NM. The effect of the inter-phase interval in the spontaneous object recognition test for pigs. Behav Brain Res 2007;181:210-7.

Rowe JB, Sakai K, Lund TE, Ramsøy T, Christensen MS, Baare WFC, Paulson OB, Passingham RE. Is the prefrontal cortex necessary for establishing cognitive sets? J Neuroscience 2007;27:13303-10.

Starrfelt R, Gerlach C. The visual what for area: Words and pictures in the left fusiform gyrus. Neuroimage 2007;35:334-42.

Neuroreceptor Studies

Elfving B, Madsen J, Knudsen GM. Neuroimaging of the serotonin reuptake site requires high affinity ligands. Synapse 2007;61:882-8.

Hasselbalch SG, Hansen ES, Jacobsen TB, Pinborg LH, Lønborg JH, Bolwig TG. Reduced midbrain-pons serotonin transporter binding in patients with obsessive-compulsive disorder. Acta Psychiatr Scand 2007;115:388-94.

Haugbøl S, Pinborg LH, Regeur L, Hansen ES, Bolwig TG, Nielsen FA, Svarer C, Skovgaard LT, Knudsen GM. Cerebral 5-HT2A receptor binding is increased in patients with Tourette's syndrome. Int J Neuropsychopharmacol 2007 Apr;10(2):245-52.

Haugbøl S, Pinborg LH, Arfan HM, Frøkjær V, Madsen J, Dyrby TB, Svarer C, Knudsen GM. Reproducibility of 5-HT_{2A} receptor measurements and sample size estimations with [^{18}F]altanserin PET using a bolus/infusion approach. Eur J Nucl Med Mol Imaging 2007;34:910-5.

Olling JD, Ulrichsen J, Haugbøl S, Glenthøj B, Hemmingsen R, Woldbye DP. Decreased gene expression of neuropeptide Y and its receptors in hippocampal regions during ethanol withdrawal in rats. Neurosci Lett 2007;424:160-4.

Pinborg LH, Videbaek C, Ziebell M, Mackeprang T, Friberg L, Rasmussen H, Knudsen GM, Glenthoj BY. [123I]Epidepride binding to cerebellar dopamine D_2/D_3 receptors is displaceable: Implications for the use of cerebellum as a reference region. Neuroimage 2007;34:1450-3.

Severino M, Pedersen AF, Trajkovska V, Christensen E, Lohals R, Veng LM, Knudsen GM, Aznar S. Selective immunolesion of cholinergic neurons leads to long-term changes in 5-HT2A receptor levels in hippocampus and frontal cortex. Neurosci Lett 2007;428:47-51.

Trajkovska V, Marcussen AB, Vinberg M, Hartvig P, Aznar S, Knudsen GM. Measurements of brain-derived neurotrophic factor: Methodological aspects and demographical data. Brain Res Bull 2007;73:143-9.

Ziebell M, Thomsen G, Knudsen GM, de Nijs R, Svarer C, Wagner A, Pinborg LH. Reproducibility of [(123)I]PE2I binding to dopamine transporters with SPECT. Eur J Nucl Med Mol Imaging 2007;34:101-9.

Textbooks and Reviews

Innis RB, Cunningham VJ, Delforge J, Fujita M, Gjedde A, Gunn RN, Holden J, Houle S, Huang S-C, Ichise M, Iida H, Ito H, Kimura Y, Koeppe RA, Knudsen GM, Knuuti J, Lammertsma AA, Laruelle M, Logan J, Maguire RP, Mintun MA, Morris ED, Parsey R, Price JC, Slifstein M, Sossi V, Suhara T, Votaw JR, Wong DF, Carson RE. Consensus nomenclature for in vivo imaging of reversibly-binding radioligands. J Cereb Blood Flow Metab, 2007:27;1533-9.

Knudsen GM. Emotioner og hjernens transmittersystemer. In: Jensen TW, Skov M, eds. Følelser og kognition. København: Museum Tusculanums Forlag, 2007:113-25.

Paulson OB, Balslev D, Gerlach C. Hvad er PET og fMRI? In: Jensen TW, Skov M, eds. Følelser og kognition. København: Museum Tusculanums Forlag, 2007:37-53.

Paulson OB, Parving HH. Niels A. Lassens banebrydende forskning. Ugeskr Laeger 2007;169:2899.

Ramsøy T, Balslev D, Paulson OB. Methods for observing the living brain. In: Baars BJ, Gage NM, eds. Cognition, brain and consciousness. Amsterdam: Academic Press, 2007:477-511.

Sigurdsson ST, Strandgaard S. Blood pressure lowering in acute ischaemic stroke: an update on the role of angiotensin receptor blockers. J Hypertens 2007;25:743-5.

Skov M, Stjernfelt F, Paulson OB. Language and the brain's mental cinema. In: Grundtvig B, McLaughlin M, Petersen LW, eds. Image, eye and art in Calvino. London: Modern Humanities Research Association and Maney Publishing, 2007:185-99.

Strandgaard S, Paulson OB. Hypertension and brain. In: Anand MP, Nadkar MY, eds. Hypertension. India: IJCP Group of Publications, 2007;137-42.

Strandgaard S, Paulson OB. Management of hypertension with cerebrovascular disease. In: Anand MP, Nadkar MY, eds. Hypertension. India: IJCP Group of Publications, 2007;268-72.

Other

Nielsen FÅ. Scientific citations in Wikipedia. First Monday, 2007;12(8).

5. Other Activities

5.1 Congress Participation

The staff of NRU has participated in 43 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/Symposium Organizing

Fall Symposium of the Danish Society of Neuroscience, October 4, 2007: Neurotrophins and Neuroplasticity in Neuropsychiatric Disorders (Gitte Moos Knudsen)

Meeting within Network of Excellence - Diagnostic Molecular Imaging (DiMI), October 13, 2007: Peripheral benzodiazepinetracers/Amyloid tracers (Gitte Moos Knudsen)

5.3 Pre- and Postgraduate Teaching

PhD-course: Kinetics and Modelling with particular emphasis on imaging, Copenhagen, 26.2. –2.3.2007 (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 7, 2007, NRU organized an open-to-the-public one day symposium where scientists from NRU presented their most recent data.

Pregraduate Supervision:

Master thesis: Barbara Lykke Lind, human biology student: A study of the mechanisms that leads from NMDA excitotoxic stimulation to pronounced lesion formation in mouse cortex (supervisor: Gitte Moos Knudsen)

Master thesis: Celia Kjærby Hansen, human biology student: Assessing the effect of alpha 7 nicotinic acetylcholine receptors in hippocampus - a discussion of the methodological approach (supervisor: Gitte Moos Knudsen)

Cell Biology Projekt II: Martin Andreas Santini, human biology student: The role of brain derived neurotrophic factor (BDNF) in depression and antidepressant treatment (supervisor: Gitte Moos Knudsen and Susana Aznar)

5.4 International Exchange

PhD-student Cecilie Löe Licht: Department of Pharmacology, Oxford.

PhD-student Anders Bue Marcussen: Sackler School of Graduate Medical Sciences, Tufts University, Boston.

PhD-student Mikael Palner: PET-center, Toronto, Canada.

5.5 National and International Committees

National Committees:

Vice Chairman, Department of Neurology, Psychiatry and Sensory Sciences, 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)

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)

Steering group member of the Danish Society for Neuroscience since 1997 (Gitte Moos Knudsen)

Chairman for the steering group for research laboratories at Rigshospitalet from 1999 (Gitte Moos Knudsen)

Member of the Steering Group for the Neurocluster, Health Science Faculty, since 2004 (Gitte Moos Knudsen)

HR representative committee member of Biologue since 2007 (Gitte Moos Knudsen)

Formand for neurogruppen vedr Forskningsindikatorer, Forskning- og innovations-styrelsen 2008 (Gitte Moos Knudsen)

Medlem af Sundhedsstyrelsens specialarbejdsgruppe for neurologi (Olaf B. Paulson).

International Committees:

Member of the Editorial Board of the Journal of Cerebral Blood Flow and Metabolism from 2000 (Gitte Moos Knudsen)

Member of the Steering Group for the Network of Excellence Diagnostic Molecular Imaging (DiMI) since 2005 (Gitte Moos Knudsen)

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

Scientific Advisory Board Member, Health Science Faculty, University of Lund since 2008 (Gitte Moos Knudsen)

Member of the Scientific Programme Committee for Brain09 and BrainPET09, July 2009, Chicago (Gitte Moos Knudsen)

Member of the Scientific Programme Committee for ECNP Congress, 12-16 September 2009 (Gitte Moos Knudsen)

Evaluation:

Evaluator of PhD-thesis: Elzbieta Maria Kalowska: Cerebral blood flow in patients with stroke in progression (Gitte Moos Knudsen)

Evaluator of PhD-thesis: Marianne Hald Larsen: Biomarkers in stress-related diseases (Gitte Moos Knudsen)

Evaluator of PhD-thesis: Alexandra C. Soliman, McGill University, Canada: Stress, dopamine and vulnerability: A functional neuroimaging investigation of stress in schizotypy (Gitte Moos Knudsen)

Evaluator of PhD-thesis: Trine Rasmussen Nielsen, Copenhagen University: Epstein-Barr virus and multiple sclerosis (Gitte Moos Knudsen)

Evaluator of Doctoral Thesis: Thomas Christensen, Copenhagen University: Experimental focal cerebral ischemia - Pathophysiology, metabolism and pharmacology of the ischemic penumbra (Gitte Moos Knudsen)

Expert Evaluator at the Norwegian Research Council (Gitte Moos Knudsen)

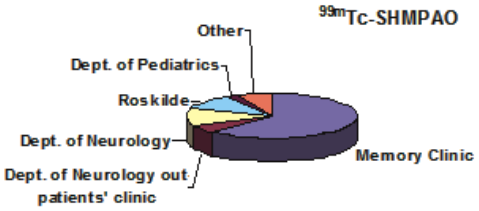
Evaluation Site-Visit, INSERM-CNRS-Université: Imaging and Brain (Gitte Moos Knudsen).

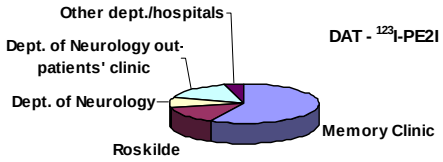
External examiner at the Technical University of Denmark and Aalborg University (Claus Svarer)

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

6. SPECT Laboratory

A total of 376 clinical scans have been performed in 2007, 91 with the dopamine transporter ligand 123I-PE2I, the remaining with 99mTc-SHMPAO. The admission pattern is shown below.





The following clinical diagnostic tools have been fully implemented in the SPECT laboratory during 2007 and start of 2008:

- Cerebral blood flow (rCBF), described both visually and with semiquantitative analysis correlated to age-matched healthy subjects database
- Subtraction of interictal from ictal SPET images with subsequent coregistration with MRI (SISCOM) as a useful diagnostic tool for identifying the epileptogenic region, fully standardized and quality assured

Research projects carried out in 2007

- 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 press)
- 123I-PE2I SPECT as a diagnostic tool in clinically uncertain parkinsonian syndromes
- High energy photon correction for I-123 in SPECT-studies
- Attenuation correction in SPECT.
- The time delay from injection to data acquisition using 99mTc-SHMPAO SPECT

7. Acknowledgements

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

Danish Agency for Science, Technology and Innovation

Danish Medical Research Council

H:S - Copenhagen Hospital Corporation

Rigshospitalets Jubilæumsfond

Savværksejer Jeppe Juhl og hustru Ovita Juhls Mindelegat

Speciallæge i neurologi Jørgen Wendelboe-Jørgensen og Laura Wendelboe-Jørgensens Fond

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 6th Framework program