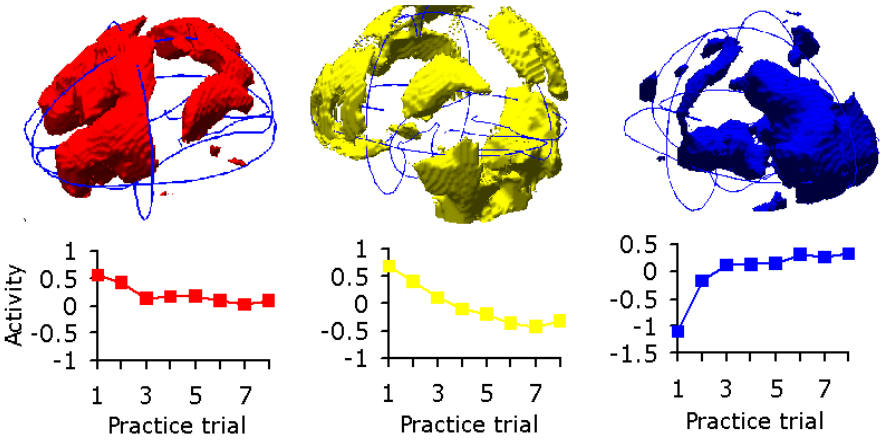
Annual Report 2002

Neurobiology Research Unit



Dept. Neurology, Neuroscience Centre
Rigshospitalet
The Health Science Faculty
Copenhagen University

www.nru.dk

Front page:
Representative spatial and temporal patterns of brain activity during motor learning extracted using K-means cluster analysis from voxel specific activity time-series acquired with positron emission tomography (PET) during practice trials with a novel tool. Upper row: surfaces through the voxels within each cluster in relation to 3 orthogonal planes through the anterior commissure. Bottom row: mean of activity time-series across the voxels assigned to each cluster, expressed in arbitrary units. The figure shows decrease of activity in a fronto-parieto-cerebellar network and increase of activity in the visual, somatosensory and motor areas over practice trials (Balslev et al., Hum Brain Mapp 2002;15:135).

Preface

We are happy to present you to a summary of the various events that took place within the Neurobiology Research Unit (NRU) in 2002. In the beginning of the year, Charlotte Videbæk defended her doctoral thesis on neuroreceptor mapping with SPECT, thereby completing more than ten years work originally initiated with late Niels A. Lassen as her supervisor. Her thesis is described in a separate section within this annual report.

Also in the beginning of the year, the renovation and installation of the new SPECT-scanner was completed, and the extensive work with validation of scanner equipment, set-up for clinical examinations as well as research projects was initiated. By the end of 2002, crucial work still remains to be done but the clinical routine scans are now running smoothly for the benefit of the patients at Rigshospitalet and other admitting hospitals. Also, several research projects are already being carried out.

In April, the Copenhagen Brain Research Center was inaugurated. The center consists of a multidisciplinary collaboration between several institutes in the Copenhagen area working with brain related research. Several prominent guests gave their view on the appropriate need and timing for constructing such a center. The Danish Minister for Science, Technology and Innovation Helge Sander expressed the importance of cross-disciplinary research at high international standard for the future of the society. The Rector of Copenhagen University Linda Nielsen and the Vice-rector for the Danish Technical University also expressed their best wishes for the center.

As part of Rigshospitalet Research Council's present schedule to evaluate all major research groups at Rigshospitalet, NRU had volunteered and was selected as one of the two first groups to be evaluated at Rigshospitalet. An ad hoc committee was appointed for the evaluation of NRU consisting of Professor Anthony Strong (Chair), King's College, London, Professor Marc Laruelle, Columbia University, New York, and Professor Hans Hultborn, University of Copenhagen. A summary of the evaluation report is given in this annual report. Briefly, the committee concluded that the quality of management and scientific supervision in the unit is outstanding and that the current scientific output is excellent in volume and relatively impressive in impact. They also did point out the relative lack of a clearly identified and promoted overarching strategy, and recommended research areas that they felt held particular promise for future growth. Currently, the Research Council is discussing the evaluation report along with the responses obtained from NRU. Going through such an evaluation represents, obviously, a work load but we sincerely believe that it will contribute substantially to improve the research quality.

Since 1997, NRU has continuously had a steady rise in the production of scientific papers. This year, the NRU publication list contained 22 peer-review original papers published in international scientific journals. In particular, a number of functional brain mapping papers have been completed. These results are described in separate sections within this report.

We hope that you will enjoy reading the Year 2002 Annual Report!

Olaf B. Paulson *Claus Svarer* *Gitte Moos Knudsen*

Table of Contents

1. Research Facilities 5
2. Organization and Staff 5
3. Collaborators in 2002 7
4. Doctoral and PhD theses 9
5. Research Topics 11
   5.1. Cerebral Blood Flow and Metabolism: Experimental Studies 11
   5.2. Cerebral Blood Flow and Metabolism: Clinical Studies 13
   5.3. Brain Mapping 17
   5.4. Cerebral Neuroreceptors: Radiosynthesis and Experimental Studies . . 21
   5.5. Cerebral Neuroreceptors: Clinical Studies 23
   5.6. Methods for Brain Data Analysis 25
6. Publications 28
7. Other Activities 30
   7.1. Congress Participation 30
   7.2. Congress Organizing 30
   7.3. Pre- and Postgraduate Teaching 30
   7.4. National and International Committees 31
   7.5. Awards 32
8. SPECT-Laboratory 33
9. Prospects 34
10. Acknowledgements 35
11. Site-Visit 36
12. Dansk Resumé 38

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.

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 Neuro-immunology Laboratory and with the Cardiovascular Laboratory. Four laboratory rooms are allocated for NRU, and it shares another three rooms and two offices with the above mentioned research groups.

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. Organization and Staff

NRU has its four main research themes within:

- Cerebral blood flow and metabolism (chair: Olaf B. Paulson and Gitte Moos Knudsen)
- Functional brain mapping (chair: Olaf B. Paulson)
- Neuroreceptor research (chair: Gitte Moos Knudsen)
- Image analysis and kinetics (chair: Claus Svarer)

The research personnel mainly work within a single research topic. There is, however, a substantial overlap between some of the different activities.

The research group is chaired by Professor Olaf B. Paulson, who since 1995 also has chaired the MR Department at Hvidovre Hospital. Research Professor, Consultant Gitte Moos Knudsen, DMSc, and Chief Engineer Claus Svarer, PhD, take part in chairing the research group. Gitte Moos Knudsen chairs the experimental laboratory in Building 93 and the SPECT laboratory. The Chief Technologist is Gerda Thomsen.

In 2002 the research staff consisted of:

Senior Researchers:
Susana Aznar, Biologist, PhD
Christian Gerlach, Psychologist, PhD
Steen Hasselbalch, MD (½ time)
Gitte Moos Knudsen, Professor, DMSc
Olaf B. Paulson, Professor, DMSc
Gitte I. Strauss, MD
Claus Svarer, Engineer, PhD

PhD-students:
Karen Husted Adams, Pharmacologist
Daniela Balslev, MD
Betina Elfving, Pharmacologist
Esben Høgh-Rasmussen, Engineer
Jacob Madsen, Chemist*
Lars Hageman Pinborg, MD
Kristin Scheuer, MD
Kåre Søndergaard, Chemist*

Junior Researchers:
Tim Dyrby, Engineer
Vibe Gedsø Frøkjær, MD
Steven Haugbøl, MD
Matthew Liptrot, Engineer
Lasse Søndergaard, Physicist
Peter Willendrup, Physicist

Associated Researchers:
Morten Blinkenberg, MD, PhD
Ian Law, MD, PhD
Bjørn Sperling, MD
Charlotte Videbæk, MD, DMSc

Students:
Haroon Arfan, medical student
Søren Christiansen, biology student
Heidi Kristiansen, biology student
Karine Madsen, medical student
Kirsten Nielsen, medical student
Anders Pryds, medical student*
Birgitte Rahbek, human biology student
Jan Tønnesen, biology student

Technologists:
Inge Møller
Anja Pedersen
Glenna Skouboe
Karin Stahr
Gerda Thomsen

Research Assistants:
Mads Dyrholm
Nikolaj Hjortholm
Simon Krabbe

Secretaries:
Pia Farup
Dorthe Givard

* shared with another research group

Guest Researchers:
Monica Fumagalli, MD, Department of Neonatology, Clinica Mangiagalli – I.C.P. Milan, Italy.
Per Hartvig, Adj. Professor, Department of Analytical Pharmaceutical Chemistry, University of Uppsala, Sweden
Mads Rasmussen, MD, PhD-student, Department of Neuroanaesthesiology, Aarhus Kommunehospital

3. Collaborators in 2002

Copenhagen Brain Research Center
www.cbrc.dk
The center was inaugurated in April. It consists of a multidisciplinary collaboration among institutes and departments in the Copenhagen area working with brain related research. These institutions are -

Department of Medical Chemistry, The Royal Danish School of Pharmacy
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

The center is based on an already existing collaboration between the institutes involved. It is the desire and the hope that the formal creation of the center will further strengthen the collaboration and improve the possibilities for frontline brain research.
At NRU, we are happy to be involved in this cross-disciplinary collaboration which already now have several PhD-students engaged.

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

Research groups within H:S (Copenhagen Hospital Corporation)
Department of Clinical Physiology, Bispebjerg Hospital
Department of Neurology, Bispebjerg Hospital

EU 5th Framework Programs
Neuroreceptor Changes in Mild Cognitive Impairment (NCI-MCI), QLRT-2000-00502
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

Enhancement of Clinical Value of Functional Imaging Through Automated Removal of Partial Volume Effect (PVEOut), QLRT-1999-30594
Department of Clinical Neuroscience, Karolinska Hospital, Stockholm, Sweden
Inserm U320, Caen, France
National Council for Research (CNR), Centre for Nuclear Medicine, Napoli, Italy
PET Centre, Debrecen, Hungary
RASNA Imaging Systems, Firenze, Italy
Electric Engineering Laboratories, University of Kent at Canterbury, United Kingdom

The Human Brain Project
PET Imaging Service, University of Minnesota, Minneapolis
Research Institute for Brain and Blood Vessels, Akita, Japan

Others
Behavioural Brain Sciences, School of Psychology, University of Birmingham, UK
Department of Medical Biochemistry & Genetics (IMBG), University of Copenhagen
Department of Pharmacology, Tours University Hospital, France
MAP Medical, Helsinki, Finland
National Cardiovascular Research Center, Osaka, Japan
NeuroSearch A/S
PET Center, Aarhus Kommunehospital
Philips

4. Doctoral and PhD theses

Single Photon Emission Computer Tomography for Neuroreceptor Studies: Methodological Considerations

Charlotte Videbæk, MD, DMSc

The doctoral thesis is based on experimental animal studies and Single Photon Emission Computer Tomography (SPECT) studies in human performed at Department of Neurology and at the Neurobiology Research Unit, Rigshospitalet; SPECT studies performed at Department of Clinical Physiology, Bispebjerg Hospital; and in-vitro receptor studies performed at Novo-Nordisk.

Neurotransmitters interacting with neuroreceptors are effective messengers in the central nervous system and currently also the main target for development of substances used for treatment of CNS diseases. Therefore, it is highly important to study the interaction between ligand (neurotransmitter or drug) and receptors in-vivo. One of the new possibilities for this is SPECT. The studies behind this thesis analyse potentials and pitt-falls in neuroreceptor studies using SPECT and steady-state methodology. The importance of non-specific binding of tracer in the brain; blood-brain barrier transport; differences in plasma protein binding in-vitro and in-vivo; cerebral blood flow; and in-vitro binding pattern of ligands were studies for the methodology by use of animal studies and in-vitro receptor studies.

In humans, the steady-state method was successfully implemented to be used in SPECT for the benzodiazepine receptor (BZR) complex. It was possible to obtain robust in-vivo affinity measurements for unlabeled BZR ligands (flumazenil and midazolam) by use of the radioactive labelled BZR ligand ([^{123}I]Iomazenil). For the dopaminergic system, sources of errors were a bigger problem. It was though still possible by use of steady-state methodology to implement two different dopamine D2/D3 tracers for striatal and extrastriatal affinity measurements respectively. For striatum [^{123}I]IBZM was applied for measurement of haloperidol´s affinity to Dopamine D2/D3 receptors. For extrastriatal regions [^{123}I]Epidepride could be implemented as tracer for affinity measurements in-vivo.

In conclusion, there are many pit-falls in SPECT neuroreceptor imaging but it is possible to study many aspects of the human brain with this technology, if the possible errors are taken into careful consideration.

The thesis was accepted for evaluation at the Faculty of Health Sciences, Copenhagen University. The defence took place on January 25, 2002, at the Medical-Historic Museum, Copenhagen. The evaluators were Professor Lars Farde and Associate Professor Per Sejrsen.

Modulation of Cerebral Blood Flow and its Autoregulation by the Renin-Angiotensin System, in Nephrectomized Rats

Trine Fischer Pedersen, cand.scient., PhD

The cerebral blood flow (CBF) autoregulation is a physiological mechanism maintaining a constant blood flow in the brain during changes in the systemic blood pressure. The autoregulation mechanism protects the brain against ischaemia during decreases in blood pressure, and against capillary damage and edema during increases in blood pressure. A lower and an upper limit for the cerebral autoregulation mechanism have been defined. The lower limit is the systemic blood pressure, under which cerebral perfusion decreases, and the upper limit is the systemic blood pressure, above which cerebral perfusion increases. These limits are not entirely fixed but can be modulated by various factors including the renin-angiotensin system.

The aim of the present studies was to investigate the hypothesis that local rather than circulating renin and angiotensin modulates CBF autoregulation.

We established a nephrectomized rat model, in which all circulating renal renin was eliminated, to selectively investigate the influence of the local extrarenal renin-angiotensin system, on CBF and its autoregulation. The nephrectomized rats were held in a good general condition by treatment with continuous peritoneal dialysis, until circulating renin was eliminated, 48 hours after nephrectomy. The dialysis catheter and an automated dialysis system were developed in the laboratory for this study. To isolate the effects of surgery, dialysis and drug administration (anesthesia, analgesia and antibiotic) from those of elimination of circulating renal renin, three control groups were included. These three groups were sham nephrectomized, dialyzed rats, drug control rats, receiving the same drugs (anesthesia, analgesia and antibiotic) as nephrectomized and sham operated rats and diet control rats, given no drugs and no surgery.

In a separate study nephrectomized rats were submitted to converting enzyme inhibition (captopril i.v.), to investigate the existence and influence of a local renin-angiotensin system on CBF and its autoregulation.

CBF was measured under full halothane anesthesia using the intracarotid xenon injection method. Time course studies, where CBF and mean arterial blood pressure were measured over two hours, were conducted to confirm that the anaesthetized rats were stable. The lower limit of autoregulation was found as blood pressure was decreased by controlled bleeding.

The results of the present studies showed that baseline CBF was not influenced by nephrectomy, whereas blood pressure was significantly decreased. The lower limit of autoregulation was decreased by the same extent following nephrectomy and sham operation and we could not demonstrate any selective influence on CBF autoregulation of the circulating renal renin-angiotensin system. Captopril significantly decreased the lower limit of CBF autoregulation in nephrectomized rats, but did not influence blood pressure. The decrease of the lower limit in nephrectomized rats following captopril was of the same magnitude as has previously been found in normal rats. These effects of captopril on blood pressure and CBF appeared to depend on circulating and local renin and angiotensin, respectively. However, other effects of captopril, such as blockade of bradykinin degradation may also have contributed to the present results.

In conclusion, these studies provide evidence for the existence of a local extrarenal renin-angiotensin system influencing CBF autoregulation. It appears from these results that the modulation of CBF and its autoregulation is modulated by this local renin-angiotensin system, with a possible contribution of bradykinin, and not by the circulating renin-angiotensin system, which is an important factor in the regulation of systemic blood pressure.

The PhD thesis was accepted for evaluation at the Faculty of Health Sciences, Copenhagen University. The defence took place on June 10, 2002, Auditorium 93, Rigshospitalet, Copenhagen. Evaluators were Senior Lecturer, Consultant, DMSc Hans Ibsen, KAS Glostrup, Consultant, DMSc Hans Dieperink, Odense University Hospital, and Senior Registrar, MD, John Hauerberg, Rigshospitalet.

The PhD-project was completed with Professor, DMSc Olaf B. Paulson and Professor, DMSc Svend Strandgaard as supervisors.

5. Research Topics

5.1. Cerebral Blood Flow and Metabolism: Experimental Studies

Gitte Moos Knudsen, MD, Professor

Cerebral blood flow in the newborn rat. In collaboration with Dept. of Pediatrics, a newborn rat model has been established. The model has proven useful for studies of cerebrovascular functions, to mimick the situation in the pre-term baby. Studies are currently conducted to establish the effects of hyperoxygenation.

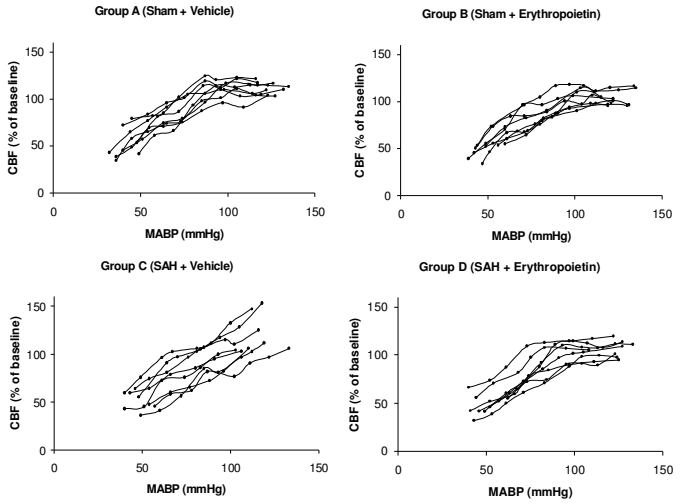
Olaf B. Paulson, MD, Professor

A *nephrectomized rat model* was developed where the rats could be kept awaked and peritoneal dialyzed in a good general condition for a period long enough (48 hours) to allow the elimination of all circulating renin. The model was successful and has been used in ongoing studies on the physiological effect on the cerebral circulation of the circulating versus the local renin angiotensin system.

Pedersen TF, Nielsen AH, Strandgaard S, Paulson OB. Nephrectomy and peritoneal dialysis eliminates circulating renin and controls uraemia in the rat. JRAAS 2002;3:130-4

Recombinant erythropoietin (EPO) administered systemically has been demonstrated to mediate neuroprotection. This effect of EPO may in part rely on a beneficial effect on cerebrovascular dysfunction leading to ischaemic neuronal damage. The in vivo effects of subcutaneously administered recombinant EPO on cerebral blood flow autoregulation after experimental subarachnoid haemorrhage was investigated in four groups of rats: group A, sham operation plus vehicle; group B, sham operation plus EPO; group C, SAH plus vehicle; group D, SAH plus EPO. SAH was induced by injection of 0.07 ml of autologous blood into the cisterna magna. EPO (400 iu kg(-1) s.c.) or vehicle was given immediately after the subarachnoid injection of blood or saline. Forty-eight hours after the

induction of SAH, CBF autoregulation was found to be preserved in both sham-operated groups whereas in the vehicle treated SAH-group, autoregulation was abolished. A subcutaneous injection of EPO given immediately after the induction of SAH normalized CBF autoregulation of CBF. These data indicate that early activation of endothelial EPO receptors may represent a potential therapeutic strategy in the treatment of cerebrovascular perturbations after SAH.



Individual CBF autoregulation curves in four experimental groups. Group A and B represent control groups with intact autoregulation. Group C is a non-treated group with experimental subarachnoid haemorrhage with complete loss of autoregulation. Group D is a group with experimental subarachnoid haemorrhage treated with erythropoietin. Autoregulation of cerebral blood flow is restored

Springborg JB, Ma X, Rochat P, Knudsen GM, Amtorp O, Paulson OB, Juhler M, Olsen NV. A single subcutaneous bolus of erythropoietin normalizes cerebral blood flow autoregulation after subarachnoid hemorrhage in rats. Br J Pharmacol 2002;135:823-9

Beta-adrenergic blockade. It is well established that activation will increase cerebral blood flow and cerebral glucose uptake in excess of cerebral oxygen uptake. The purpose of the present study was to investigate the influence of beta-adrenergic blockade with propranolol on the activation induced uncoupling of cerebral glucose and oxygen metabolism. Studies were performed in awake rat and the mode of activation was a condition with arousal where the shelter of the box containing the rats were opened exposing the rat to the environment for 10 min. This mode of activation resulted in a significant decrease of the oxygen/glucose uptake ratio. This decrease was completely abolished following beta-adrenergic blockade, but the behavior and movement frequency of the animals remained unchanged. This result leads to speculations on whether the effect of beta-adrenergic blockade is on the cerebral metabolic pattern per se or whether it is more specifically related to the condition of arousal.

Schmalbruch IK, Linde R, Paulson OB, Madsen PL. Activation-induced resetting of cerebral metabolism and flow is abolished by β-adrenergic blockade with propranolol. Stroke 2002;33:251-5

5.2. Cerebral Blood Flow and Metabolism: Clinical Studies

Olaf B. Paulson, MD, Professor

Autonomic dysfunction. Whether cerebral blood flow autoregulation is maintained in this condition has been debated for a long time and the sparse data available are equivocal. The relationship between cerebral blood flow and mean arterial blood pressure was therefore tested in 8 patients with symptoms and signs of severe cardiovascular autonomic dysfunction. Three had Parkinson's disease, three diabetes, one multiple system atrophy and the remaining pure autonomic failure. The results indicated that autoregulation was preserved in 3 patients demonstrating constant cerebral blood flow in a physiological blood pressure range while the remaining 5 patients showed a more linear relationship between cerebral blood flow and blood pressure indicating an absence of autoregulation.

Hesse B, Mehlsen J, Boesen F, Schmidt JF, Andersen EB, Waldemar G, Andersen AR, Paulson OB, Vorstrup S. Regulation of cerebral blood flow in patients with autonomic dysfunction and severe postural hypotension. Clin Physiol & Func Im 2002;22:241-7

Gitte Moos Knudsen, MD, professor

By means of single photon emission tomography (SPECT) and the flow tracer ^{99m}Tc-HMPAO, the regional brain distribution of blood flow can be measured. The transcranial Doppler (TCD) technique enables a non-invasive monitoring of the linear blood flow in the basal arteries of the brain. During the last years, these methods have been used in clinical studies of patients with acute fulminant liver failure, meningitis, postoperative cognitive dysfunction, and in heart failure.

A high-altitude research project coordinated by Bengt Saltin, Rigshospitalet, was carried out in the summer 1998. Scientists from NRU joined the excursion. The effects of acclimatization to high altitude on cerebral blood flow and oxidative metabolism at rest and during exercise was investigated in nine healthy, native sea-level residents. The subjects were studied 3 weeks after arrival at Chacaltaya, Bolivia (5,260 m) and after reacclimatization to sea level. Global cerebral blood flow at rest and during exercise on a bicycle ergometer was measured by the Kety-Schmidt technique. Cerebral metabolic rates of oxygen, glucose, and lactate were calculated by the Fick principle. At high altitude at rest, arterial carbon dioxide tension, oxygen saturation, and oxygen tension were significantly reduced, and arterial oxygen content was increased because of an increase in hemoglobin concentration. Global cerebral blood flow was similar in the four conditions. Cerebral oxygen delivery and cerebral metabolic rates of oxygen and glucose also remained unchanged, whereas cerebral metabolic rates of lactate increased slightly but non significantly at high altitude during exercise compared with high altitude at rest. The data show that cerebral blood flow and oxidative metabolism are unaltered after high-altitude acclimatization from sea level, despite marked changes in breathing and other organ functions.

Møller K, Paulson OB, Hornbein TF, Colier W, Roach R, Knudsen GM. Unchanged cerebral blood flow and oxidative metabolism after acclimatization to high altitude. J Cereb Blood Flow Metabol 2002; 22:118-26

Acute bacterial meningitis. This study represents a follow-up on the PhD-thesis defended by Kirsten Møller in 2001. Nine-teen patients had their global cerebral blood flow, cerebrovascular CO_2-reactivity, and cerebral metabolic rates of oxygen, glucose, and lactate, measured and these measures were compared to those in 8 healthy control subjects. Cerebral blood flow did not differ significantly among groups, although a larger variation was seen in patients than in controls. CO_2-reactivity was also similar in both groups. At baseline, patients had significantly lower arterio-venous oxygen difference, cerebral oxygen, lactate, and glucose consumption. In hyperventilation cerebral oxygen consumption was unaltered, whereas the cerebral glucose consumption was significantly increased as compared to baseline values. It is concluded that in patients with acute bacterial meningitis, a ventilation strategy guided by jugular bulb oximetry and/or repeated CBF measurements may be more optimal in terms of cerebral oxygenation than a strategy aiming at identical levels of P_aCO_2 for all patients.

Møller K, Strauss GI, Thomsen G, Larsen FS, Holm S, Sperling BK, Skinhøj P, Knudsen GM. Cerebral blood flow, oxidative metabolism, and cerebrovascular carbon dioxide reactivity in patients with acute bacterial meningitis. Acta Anaesthesiol Scand 2002;46:567-78

The proinflammatory cytokine, tumor necrosis factor-alpha (TNF-alpha), has been suggested to mediate septic encephalopathy through an effect on CBF and metabolism. The effect of an intravenous bolus of endotoxin on global CBF, metabolism, and net flux of cytokines and catecholamines was investigated in eight healthy young volunteers, at baseline and 90 minutes after an intravenous bolus of a endotoxin. Arterial TNF-alpha peaked at 90 minutes, coinciding with a peak in subjective symptoms. At this time, CBF and Paco were significantly reduced compared to baseline; the CBF decrease was readily explained by hypocapnia. The cerebral metabolic rate of oxygen remained unchanged, and the net cerebral flux of TNF-alpha, interleukin (IL)-1beta, and IL-6 did not differ significantly from zero. Thus, high circulating levels of TNF-alpha during human endotoxemia do not induce a direct reduction in cerebral oxidative metabolism.

Møller K, Strauss GI, Qvist J, Fonsmark L, Knudsen GM, Larsen FS, Krabbe KS, Skinhøj P, Pedersen BK. Cerebral blood flow and oxidative metabolism during human endotoxemia. J Cereb Blood Flow Metab 2002;22:1262-70

Near-infrared spectroscopy (NIRS) enables continuous non-invasive quantification of blood and tissue oxygenation, and may be useful for quantification of cerebral blood volume (CBV) changes. In this study, changes in cerebral oxy- and deoxyhemoglobin were compared to corresponding changes in CBF and CBV as measured by positron emission tomography (PET). These changes were induced by voluntary hyperventilation and by inhalation of 6% CO_2. The resulting data subsequently entered a physiological model of cerebral oxygenation. The PET-measurements showed an average CBV of 5.5+/-0.74 ml 100 g(-1) in normoventilation, with an increase of 29% during hypercapnia, whereas no significant changes were seen during hyperventilation. CBF was 51+/-10 in normoventilation, increased by 37% during 6% CO_2 and decreased by 25% during hyperventilation. NIRS showed significant increases in oxygenation during hypercapnia, and a trend towards decreases during hyperventilation. Changes in CBV measured with both techniques were significantly correlated to CO_2 levels. However, the changes as

measured by NIRS was much smaller than those detected by PET, and measured NIRS parameters smaller than those predicted from the model. It is concluded that while qualitatively correct, NIRS measurements of CBV should be used with caution when quantitative results are needed.

Rostrup E, Law I, Pott F, Ide K, Knudsen G M. Cerebral hemodynamics measured with simultaneous PET and near-infrared spectroscopy in humans. Brain Res 2002;954:183-93

Postoperative cognitive dysfunction after cardiac surgery has been attributed both to embolic events and periods with reduced cerebral perfusion. In this collaborative study, it was investigated whether cognitive dysfunction after coronary surgery is associated with changes in regional cerebral blood flow, as measured with SPECT. Before surgery and at discharge, 15 coronary surgery patients were studied with SPECT and neuropsychological testing. Postoperative cognitive dysfunction was defined as a Z score above 2. The CBF data were compared to normative SPECT data from 26 healthy age-matched controls. Preoperative global CBF was significantly lower in patients compared with controls (53.7 versus 46.1 mL/100 g/min, $p = 0.006$). After surgery, global CBF significantly decreased in the patients (46.1 versus 38.6 mL/100 g/min, $p = 0.0001$, but no significant differences were detected in regional CBF. Cognitive dysfunction was identified in 4 of the 15 patients, but no correlation was found between the neuropsychological Z score and global or regional CBF. That is, we find that the significant decrease in CBF after coronary surgery is either a global phenomenon, or alternatively, patients show different patterns of CBF reductions. The global decrease was not correlated to postoperative cognitive dysfunction.

Abildstrom H, Hogh P, Sperling B, Moller JT, Yndgaard S, Rasmussen LS. Cerebral blood flow and cognitive dysfunction after coronary surgery. Ann Thorac Surg. 2002;73:1174-8

Betina Elfving, Pharmacologist, PhD-student

Monitoring of cerebral oxygenation in newborns. In the intensive care of seriously ill infants, the global oxygen reserve capacity is estimated by co-oximetry (co-ox) of blood sampled from central venous catheters. Introduction of a non-invasive alternative is desirable. Near infrared spectroscopy (NIRS) offers a technique for non-invasive bedside monitoring of tissue oxygen economy. The study indicates that NIRS is practical for monitoring relative changes in central venous saturation. This might be useful in the future clinical care of newborns.

Bay-Hansen R, Elfving B, Greisen G. Use of near infrared spectroscopy for estimation of peripheral venous saturation in newborns: comparison with co-oximetry of central venous blood. Biol Neonate 2002;82:1-8

Steen G. Hasselbalch, MD

Obsessive-compulsive disorder (OCD) is a common neuropsychiatric disorder affecting more than 1% of the population. The hallmark symptoms of OCD are recurrent intrusive thoughts (obsessions) and repetitive ritualistic behaviour (compulsions). Accumulating evidence suggest an association with dysfunction in specific brain regions. Further, the well-documented effect of serotonin reuptake inhibitors (SSRI) in the therapy of OCD suggests a biological origin of the disorder. Previous neuroimaging studies of patients with

OCD have pointed to basal ganglia and the frontal cortical regions being relevant for an understanding of the pathophysiology and therapy of OCD. In a search for the neural substrate underlying the therapeutic action of paroxetine in the therapy of OCD we measured regional glucose metabolism in a PET study of 20 OCD patients before and after at least 3 months of treatment. We used 18-fluoro-deoxyglucose PET-scanning to measure regional cerebral glucose metabolic rate (rCMRglc) in 20 non-depressed patients fulfilling DSM-IV criteria for OCD. Patients were studied before and after 12-20 wk of treatment with the serotonin re-uptake inhibitor paroxetine. Clinical assessment rating with the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) was performed before the first and after the second study. The PET data was analysed regionally using statistical parametric mapping (SPM-96). A clinical improvement was indicated by a mean decrease of 55% in the Y-BOCS score. There was no difference in global cerebral metabolism before and after treatment whereas a post-treatment reduction in normalized rCMRglc was found in the right caudate nucleus (see figure). This finding also showed a significant positive correlation with symptom severity. When the level of significance was reduced in order to reveal other brain areas of interest, a decreasing trend in rCMRglc was found in several brain regions, including the left inferior frontal cortex, the right dorsolateral prefrontal cortex, and the right insula. These regions have previous been found hyperactive or activated during symptom provocation in other PET studies. Further, another study found a significant activation of the right insula when normal controls perceived the facial expression of disgust. Thus, our results support hypotheses regarding a malfunction of the cortico-striato-thalamic system in the pathophysiology of OCD and particularly point to the caudate nucleus playing an important role for the therapeutic action of paroxetine in the treatment of OCD.

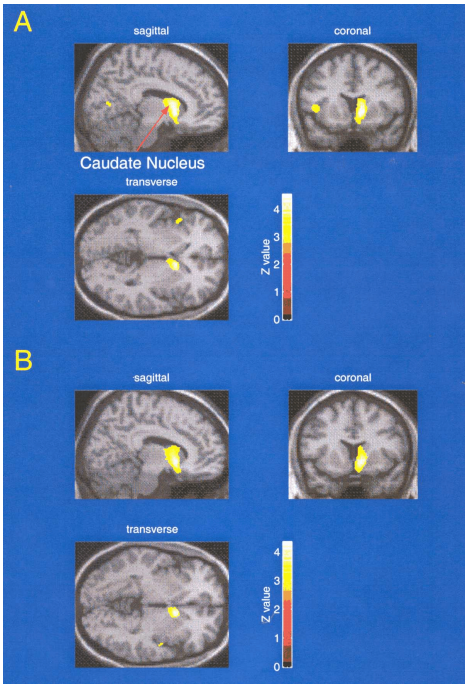


Figure A: The decreases in normalized rCMRglc following treatment with SSRI. the images are displayed in sagittal, coronal and transverse sections through the voxel of maximum change in the right caudate nucleus. For displaying purposes, the color scale has a threshold of Z >3.09, corresponding to p< 0.001, uncorrected.

Figure B: Positive correlations between normalized rCMRglc and symptom severity, measured by the Y-BOC scale. Note the close correspondence between brain areas in figure A and B

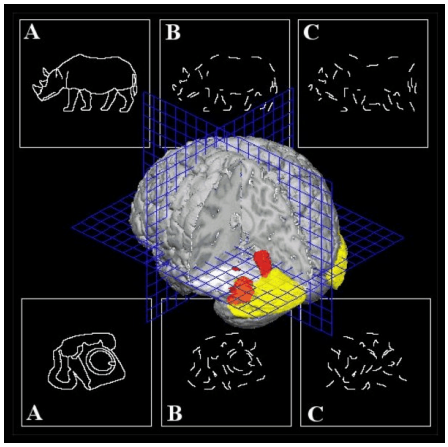
Hansen ES, Hasselbalch S, Law I, Bolwig TG. The caudate nucleus in obsessive-compulsive disorder. Reduced metabolism following treatment with paroxetine: a PET study. Int J Neuropsychopharm 2002;5:1-10

5.3. Brain Mapping

Christian Gerlach, Psychologist, PhD

With PET it is possible to measure rCBF with a high degree of spatial resolution. Because rCBF increases as neural activity increases, it is possible to use rCBF as an indirect measure of neural activity. Thus, by measuring rCBF while subjects are engaged in well-defined cognitive tasks, we can map the cognitive processes which underlie task performance. We have continued to use this technique in our effort to map different stages in visual perception. However, the projects listed below will probably be the last ones conducted with PET as we intend to use fMRI in future projects.

Visual Object Recognition - Perceptual Integration. Most theories of visual object recognition describe separate stores for the visual and functional attributes of objects and for their names, with object recognition and naming being realized by successive access to these stores. While imaging studies have supported such models, they have not considered in detail the cerebral organization of the processes that operate prior to the activation of stored memories of objects, such as those processes underlying the integration of visual elements into perceptual wholes. We studied these processes by presenting subjects with pictures of objects that were presented as either full line drawings or fragmented line drawings (both recognizable and unrecognizable) (see figure). We found that whereas early visual areas (shown in yellow) are involved in the integration of visual elements into perceptual wholes, regardless of whether the elements form recognizable objects or not, the posterior and lateral aspects of the fusiform gyri (shown in red) are involved in higher level integration, being more activated during the integration of elements from recognizable objects. Our findings thus indicate that wholistic integration also involves top-down processing, being affected by access to stored knowledge of visual shape, and they have strong implications for the debate concerning whether perceptual integration is mediated by ventral or dorsal pathways in the brain (Gerlach et al., 2002a).

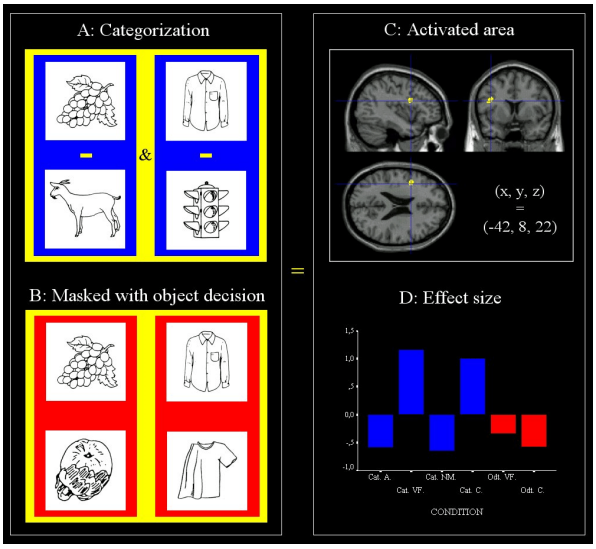


We have just completed a follow-up study where we, in addition to manipulating the degree of fragmentation across objects, also have manipulated object category to examine whether different categories of objects are integrated in the same manner.

Gerlach C, Aaside CT, Humphreys GW, Gade A, Paulson OB, Law I. Brain activity related to integrative processes in visual object recognition: Bottom-up integration and the modulatory influence of stored knowledge. Neuropsychologia 2002a;40:1254-67

Visual Object Recognition - Category-specific Processing. Following brain damage people may occasionally be unable to recognize objects - a disorder known as visual agnosia. In rare cases the agnosia may be restricted to specific categories of objects yielding a so-called category-specific agnosia. Usually these category-specific disorders involve impaired recognition of natural objects (e.g., animals, fruits and vegetables) with relatively spared recognition of man-made objects (e.g., furniture, tools, vehicles etc.) or vice versa.

While natural objects may be more visually similar than man-made objects and thus harder to recognize perceptually, it has been suggested that recognition of man-made objects, may rely on motor-based knowledge of object utilization (action knowledge). This hypothesis has been supported by studies which have demonstrated increased rCBF in the premotor cortex during the processing of man-made objects. We recently questioned this hypothesis by showing that the premotor cortex is not activated by all kinds of tasks requiring the comprehension of man-made objects (Gerlach et al., 2002b). Thus, we found activation of the premotor cortex during categorization of man-made objects, as opposed to natural objects, but not during naming of the same man-made objects. Because categorization is based on object equivalence, we proposed that the premotor activation reflected that man-made objects in general are more manipulable than natural objects and thus caused greater access to action knowledge during categorization. On this account one might expect to find activation of the premotor cortex during categorization of manipulable objects regardless of whether these are natural or man-made. We found support for this prediction in a new study where we showed increased activation of the premotor cortex during categorization of both articles of clothing and vegetables/fruits relative to both non-manipulable man-made objects and animals (Gerlach et al., 2002c) (see figure). Thus, the category-specific effects previously reported for man-made objects in the premotor cortex are probably not category-specific in a true lexical sense but rather may reflect that categories differ in manipulability.

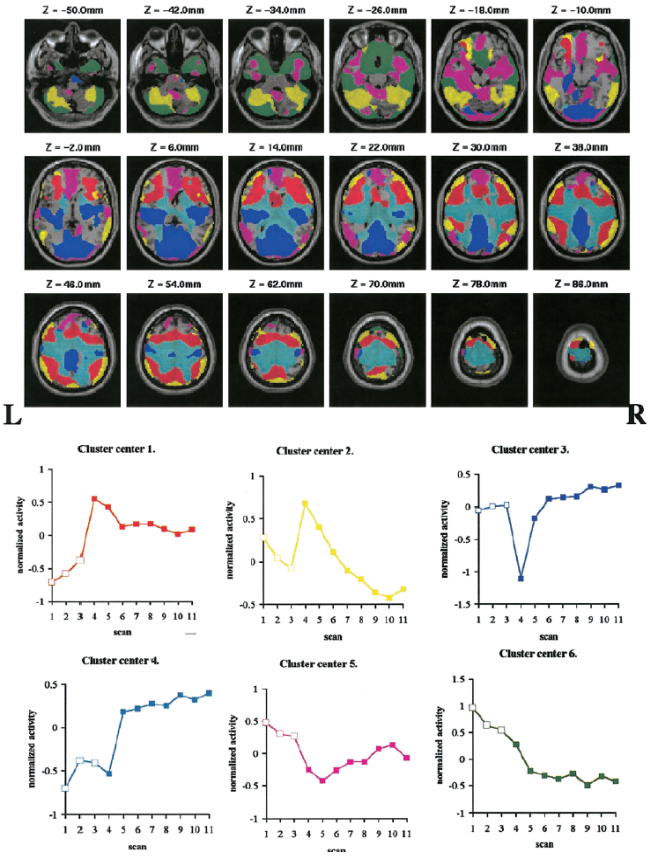


Gerlach C, Law I, Gade A, Paulson OB. The role of action knowledge in the comprehension of artefacts - A PET study. NeuroImage 2002b;15:143-152

Gerlach C, Law I, Paulson OB. When action turn into words: Activation of motor-based knowledge during categorization of manipulable objects. J Cogn Neurosci 2002c;14: 1230-39

Daniela Balslev, MD, PhD-student

Cluster Analysis of Activity-Time Series in Motor Learning. Neuroimaging studies of learning focus on brain areas where the activity changes as a function of time. To circumvent the difficult problem of model selection, we used a data-driven analytic tool, cluster analysis, which extracts representative temporal and spatial patterns from the voxel-time series. The optimal number of clusters was chosen using a cross-validated likelihood method, which highlights the clustering pattern that generalizes best over the subjects. Data were acquired with PET at different time points during practice of a visuomotor task. The results from cluster analysis show practice-related activity in a fronto-parieto-cerebellar network, in agreement with previous studies of motor learning. These voxels were separated from a group of voxels showing an unspecific time-effect and another group of voxels, whose activation was an artifact from smoothing.



Overview over the spatial clusters (top) and the corresponding temporal patterns of activity, the cluster center (bottom), calculated as the average of time series from the individual voxels within a cluster. The spatial extent of each cluster and the cluster center are shown in the same color. The voxels assigned to the clusters are superposed on a single MRI template, in coregistration with the standard anatomical space; z is the vertical displacement relative to the AC–PC line (– below this line). The activity of the time series was normalized to 0 mean. Tracing scans (empty squares). Mirror tracing scans (filled squares).

Balslev D, Nielsen FAA, Frutiger SA, Sidtis JJ, Christiansen TB, Svarer C, Strother SC, Rottenberg DA, Hansen LK, Paulson OB, Law I. Cluster analysis of activity-time series in motor learning. Human Brain Mapping 2002;15:135-45

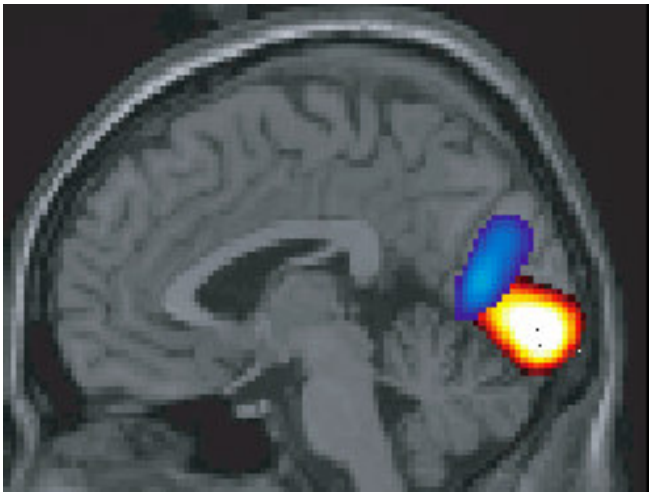
Ian Law, MD, PhD

The effects of attending to different features of an image. One strategy to extract relevant information from the complex visual scenes that meet our eyes is by attending to features that are important in that particular context.

In this study we have investigated the effects of attending and passing judgement on either the shape of figures or the colours of those same figures. Widespread effects were found during the shape-matching task involving the frontal lobes the thalamus and the primary visual cortex, which may have been generated by feedback signals preserving visual representations of selected stimuli in short-term memory.

Bundesen C, Larsen A, Kyllingsbæk S, Paulson OB, Law I. Attentional effects in early visual pathways: A whole-brain PET study. Exp Brain Res 2002;147(3):394-406

Can the brain be externally activated during sleep? Previous studies have shown that sleeping and sedated young children respond to visual stimulation with a visual cortex blood oxygenation level dependent (BOLD) functional magnetic resonance imaging (fMRI) signal decrease; this is in contrast to a signal increase in the visual cortex of alert adults. However, it is still unclear if this response pattern is caused by age, or by the influence of sleep or a sedative agent, and whether it represents a true change in rCBF. In this study we utilized our access to both fMRI and positron emission tomography (PET) in spontaneously sleeping adult volunteers. The response pattern is similar to that found in children (see figure), and is thus a true rCBF signal decrease and an effect of sleep rather than cerebral maturation. Possible mechanisms for the paradoxical response pattern during sleep include an active inhibition of the visual cortex or a disruption of an energy consuming process.



Response to visual stimulation during sleep (blue – decrease) and waking (Hot metal – increase)

Born AP, Law I, Lund TE, Rostrup E, Hanson LGP, Wildschiødtz G, Lou HC, Paulson OB. Cortical deactivation induced by visual stimulation in Human Slow-Wave Sleep. Neuroimage 2002;17(2): 1325-35

The cerebral activation pattern during light sleep. In this paper we investigated the changes in the cerebral activation pattern in stage-1 sleep. We saw relative flow increases in the occipital lobes and relative bilateral flow decreases in cerebellum, the posterior parietal cortex, and in the right premotor cortex and the left thalamus. The topography of the occipital activation during stage-1 sleep supports a hypothesis of this state being a state of imagery. The rCBF decreases in premotor cortex, thalamus and cerebellum could be indicative of a general decline in preparedness for goal directed action during stage-1 sleep. This is the first report on the distribution of regional cerebral blood flow (rCBF) changes during stage-1 sleep or somnolence.

Kjær T, Law I, Wildschiødtz G, Paulson OB, Madsen PL. Regional cerebral blood flow during light sleep - A $H_2{}^{15}O$-PET study. J Sleep Res 2002;11:201-7

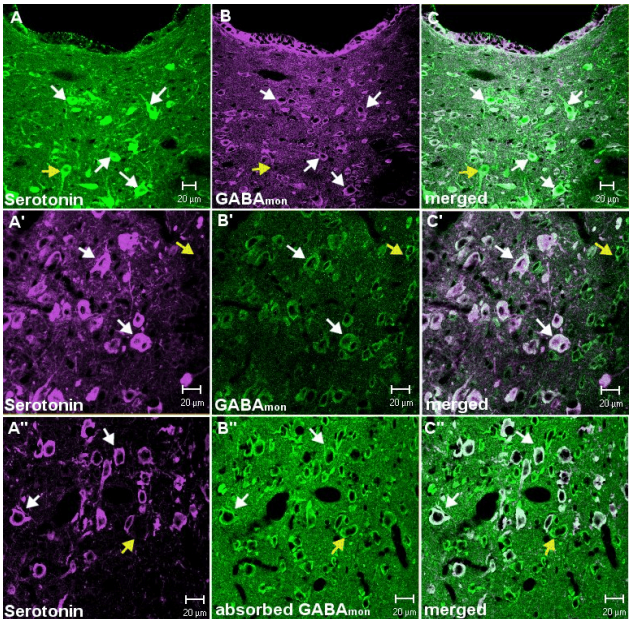
5.4. Cerebral Neuroreceptors: Radiosynthesis and Experimental Studies

Susana Aznar, Biologist, PhD

Experimental neuroreceptor studies are conducted in order to characterize and describe, from an anatomical and cellular point of view, the localization and role of the different serotonin receptors in the brain as well as its interaction with other receptor systems. Primarily, we make use of an in vivo experimental set-up where we apply neuronal tracing and double and triple immunostaining techniques.

The localization and distribution of the 5-HT_{1A} receptor was investigated in different neuronal subtypes throughout the rat forebrain knowing this distribution is important to understand both the role of this receptor in neuronal circuitries and the effect of 5-HT_{1A} receptor activation on brain activity. With the help of immunocytochemical double-labeling techniques, we have shown that the 5-HT_{1A} receptor is present on both pyramidal and principal cells and on different subtypes of inhibitory interneurons. Our finding that the receptor is present in certain groups of parvalbumin-containing interneurons that are involved in controlling neuronal firing activity suggests an important role of the 5-HT_{1A} receptor in modulating specific brain functions.

The projection of raphe fibres to these types of inhibitory interneurons in areas involved in controlling and maintaining hippocampal activity have also been characterized in detail. The hippocampus is important for spatial and memory formation. By using neuronal tracing techniques we found that these neurons receive a significant non-serotonergic raphe projection besides the well described serotonergic projection. These results indicate that the control that raphe nuclei exert on hippocampal and septal activity may not be exclusively through a serotonergic pathway, but that other neurotransmitter systems may be involved. In a complementary study we have shown that there is a GABAergic projection from the raphe nucleus to these areas and that a subgroup of neurons in the raphe nucleus contain both GABA and serotonin.



Colocalization of GABA and serotonin in raphe neurons. Double immunostaining for serotonin (A) and GABA (B) show colocalization of GABA and serotonin in DR neurons, as shown in C. In B' immunostaining for GABA is performed using the avidin-biotin method and Bodipy is used as the fluorochrome. In B'' immunostaining for GABA is performed after absorbing the antibody with 500 μM serotonin. In C' and C'' colocalized neurons are shown. White arrows indicate colocalization and yellow arrows non-colocalized neurons.

Aznar S, Qian ZX, Knudsen GM. Non-serotonergic dorsal and median raphe projection on parvalbumin- and calbindin-containing interneurons in hippocampus and septum. Presented at the 3rd Forum of European Neuroscience Societies 2002, Paris, France.

Aznar S, Knudsen GM. GABA containing neurons in dorsal and median raphe nucleus project to hipppocampus and medial septum/diagonal band of Broca complex. Presented at the 32nd Society for Neuroscience Congress 2002, Orlando, USA.

The serotonergic and the cholinergic systems interaction with each other is an ongoing field of research. Preliminary results indicate that α7 nicotinic receptors, which are very important in relation to Alzheimer's disease, are present in serotonergic neurons projecting to hippocampal and septal areas. Further studies will reveal whether in these areas the receptors are located presynaptically on serotonergic terminals. In a parallel study, where acetylcholine levels were increased after administration of acetylcholinesterase inhibitors in rats, a reduced neuronal activation was observed when at the same time the serotonergic system was inhibited. These preliminary results indicate that the cholinergic system exert its neuronal activation at least partly through activation of the serotonergic system.

Betina Elfving, Pharmacologist, PhD-student

(S)-citalopram and ligand properties. Based on current knowledge, radiolabeled (S)-citalopram was anticipated to be a suitable PET ligand for the 5-HT reuptake site. In humans [11C]-(S)-citalopram does not, however, yield a sufficient target-to-background ratio. In this study we have investigated whether the positron emission tomography signal of radiolabeled (S)-citalopram could be improved by predosing with the unlabeled distomer

(R)-citalopram. The non-specific binding of radiolabeled (S)-citalopram could not be reduced possibly due to the pool of non-specific sites being too large for blocking.

Elfving B, Bjørnholm B, Knudsen GM. Predosing with the unlabeled inactive enantiomer as a tool for improvement of the PET signal. Synapse 2002;46:125-127

Jacob Madsen, Chemist, PhD-student

Radiolabelled derivatives of citalopram and escitalopram have been developed in order to investigate the binding to the serotonin reuptake site in the monkey and rat brain.

In collaboration with H. Lundbeck A/S deuterium labelled analogues of escitalopram have been synthesized, labelled with carbon-11 and the regional brain distribution have been examined in rats. Iodine-125 labelled derivatives of citalopram and escitalopram were also prepared. Initial biological studies look promising and an iodine-123 labelled derivative will be further evaluated in a SPECT study.

Derivatives of citalopram have been synthesized and labelled with carbon-11 utilising palladium mediated reactions. One of these compounds was evaluated in the monkey brain using PET in collaboration with the radiochemistry unit in Uppsala. A manuscript describing this work has been submitted.

Madsen J, Elfving B, Martiny L, Andersen K, Knudsen GM. Iodine-125 labeled citalopram analogue as a potential SPECT radioligand for visualization of the serotonin transporter. Turku PET Symposium, May 25-28, 2002

Madsen J, Elfving B, Andersen K, Knudsen GM, Martiny L. Gas phase production of [^{11}C]CD_3I. Synthesis and biological evaluation of S-[–methyl-D_3-^{11}C]citalopram and S-[N-methyl-^{11}C]citalopram. Neuroimage 2002;16:S16

5.5. Cerebral Neuroreceptors: Clinical Studies

Gitte Moos Knudsen, MD, Professor

Through several years, NRU has conducted a number of both experimental and clinical SPECT neuroreceptor studies. Since 2000, the research unit has - in collaboration with the PET and Cyclotron Unit at Rigshospitalet - conducted a number of PET-studies with ^{18}F-altanserin, a $5HT_{2A}$-receptor ligand.

NRU coordinates a concerted action within the European Commission 5th framework dealing with neuroreceptor imaging in patients with *mild cognitive impairment* with the objective to be able to establish an early diagnosis and a prognosis for the development of Alzheimer's disease. More information is provided on the website www.mci.nru.dk.

In the EU-funded study of the *dopamine transporter SPECT ligand 123I-PE2I*, produced by MAP Medical, Finland, NRU has evaluated the tracer for use in humans. A method for accurate quantification of binding data following a bolus injection of 123I-PE2I. Distribution volumes (DVs) were calculated using compartment analysis, area under the curve analysis and Logan analysis. Logan analysis is preferred since stable DV values were already obtained 120 min after injection. Mean striatal DV was high, almost 40 ml ml(-1), and mean occipital cortex DV, as a marker of non-specific binding, was only about 6 ml ml(-1). We find that in the absence of local pathology in reference tissue, Logan analysis

without blood sampling is an attractive method for accurate quantification of 123I-PE2I binding.

Pinborg LH, Videbæk C, Svarer C, Yndgaard S, Paulson OB, Knudsen GM. Quantification of [123I]PE2I binding to dopamine transporters with SPET. Eur J Nucl Med 2002;29:623-31

NRU PhD-student Karen Husted Adams (previously Husted Kjaer) conducted during her exchange visit to the MRC Cyclotron Unit, Hammersmith Hospital, London, in collaboration with particularly Dr. Paul Grasby, several studies. In one of these, *PET studies of 5-HT1A receptor function* were conducted in humans by means of the radiotracer [(11)C]WAY-100635. In a large normal database of 61 healthy men, the variability of 5-HT1A in different brain regions as well as test-retest studies was described and correlated to several independent measures, such as radiochemical, demographic, physiological, and behavioral variables. The sensitivity of [(11)C]WAY-100635 binding to manipulations of endogenous 5-HT was also tested. The regional distribution of [(11)C]WAY-100635 binding in healthy human brain was similar to that reported in vitro. The test-retest variability was approximately 12%. The binding of [(11)C]WAY-100635 was insensitive to changes in brain 5-HT induced by tryptophan infusion and depletion. Although BP values varied greatly across subjects (range 2.9-6.8), there were no significant correlations of regional and global BP with common radiochemical, demographic, physiological, and personality variables. Specifically, in contrast with two recent small studies, no decline of [(11)C]WAY-100635 binding with age was found. The large between-subject variability observed could not be explained by common methodological, physiological, or behavioral factors and hence the biological basis of this variability remains to be clarified.

Rabiner EA, Messa C, Sargent PA, Husted-Kjaer K, Montgomery A, Lawrence AD, Bench CJ, Gunn RN, Cowen P, Grasby PM. A database of [11C]WAY-100635 binding to 5-HT1A receptors in normal male volunteers: Normative data and relationship to methodological, demographic, physiological, and behavioral variables. Neuroimage 2002;15:620-32

SPECT-study of benzodiazepine receptor density was conducted to evaluate the extent of neuronal damage induced by cardiac surgery. The study was performed in collaboration with the Dept. Anaesthesia and Dept. Cardiology, Rigshospitalet. Cerebral dysfunction is common after cardiac surgery, and this is probably related to embolic phenomena. Fifteen elderly patients undergoing coronary artery bypass surgery were included. The patients were tested with a neuropsychological test battery before surgery and postoperatively at discharge from hospital and after 3 months. SPECT was performed before surgery and after 3 months using the iomazenil bolus/infusion technique, and the benzodiazepine receptor density was calculated for the frontal, parietal, temporal, and occipital cortex. The data showed that cognitive dysfunction was found in 46.7% at discharge from hospital and in 6.7% after 3 months. A significant decrease in the estimated density of neurons was found in the frontal cortex, but no significant correlation was found between cognitive dysfunction and SPECT findings.

Rasmussen LS, Sperling B, Abildstrom HH, Moller JT. Neuron loss after coronary artery bypass detected by SPECT estimation of benzodiazepine receptors. Ann Thorac Surg 2002;74:1576-80

5.6. Methods for Brain Data Analysis

Matthew G. Liptrot, MSc., Peter Willendrup, MSc., Tim Dyrby MSc., Esben Høgh-Rasmussen, MSc., Lasse R. Søndergaard MSc., and Claus Svarer, PhD, MSc.

In January 2002 NRU had a new Marconi/ Philips SPECT scanner installed. The data analysis section has been involved in optimisation of the SPECT scanning protocols for getting the best obtainable signal-to-noise ratio in the images. Especially, the scanning parameters: injected doses, acquisition-time and –matrix, and reconstruction method have been optimised for clinical as well as experimental dynamic scanning protocols.

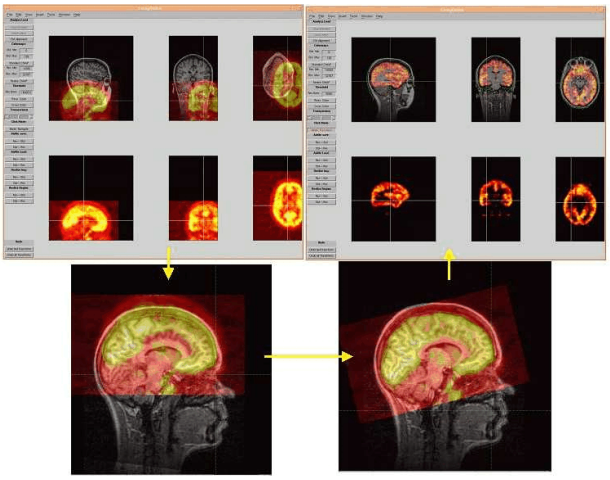
Furthermore, the data analysis section is still involved in a number of common European projects. In the NCI-MCI project five different centres within the EU collaborate in acquiring functional PET or SPECT images from patients with Mild Cognitive Impairment. Each centre is performing studies of ligand binding to different neuroreceptor systems. Data sets from all centres will be analysed in a common and standardised way using automatic tools for applying regions of interest to 'new' subjects. The principle for applying the regions to the 'new' subjects will be based on individual high-resolution structural MR images.

The other EU project the data-analysis section is involved in is the PVEOut project. In this project a method for correcting the relatively low resolution of functional PET/SPECT images (> 6 mm) will be developed. The idea is to use high resolution (< 1.5 mm) MR images to correct for the low-resolution data, e.g. by using deconvolution techniques. The data analysis section is mainly involved in development of visual based methods for rigid alignment of structural and functional scans, including testing of the precision that it is possible to achieve using the methods on functional neuroreceptor images with binding limited to certain regions. Furthermore, the data analysis section will be involved in development of a common user interface for the PVEOut software package.

Another way to handle partial volume correction is to include the correction process in the reconstruction algorithm. NRU has started a PhD project where it will be investigated if it is possible to get even better PVE correction results including the high-resolution structural information in the reconstruction process leaving out the traditional low-pass filtering.

Furthermore, the data analysis section is involved in developing methods for identifying input curves for kinetic modelling directly from image data. The idea is to have an alternative to manually/automatically sampled arterial or venous blood data. A clustering method is very well suited for tasks like this: identification of voxels in the brain that behave in a significantly different manner compared to cortex voxels.

Alignment of structural and functional images. One of the basic problems doing a partial volume correction of functional images based on a structural image is to have the two images aligned. For many image modalities automatic methods are available and have been published in the literature. In this study two manual methods have been implemented and examined based on either identification of corresponding points in the image modalities or surface/overlay plots. It has been shown that these methods are especially well fitted for receptor studies with limited binding of the receptor ligand in many areas of the brain.

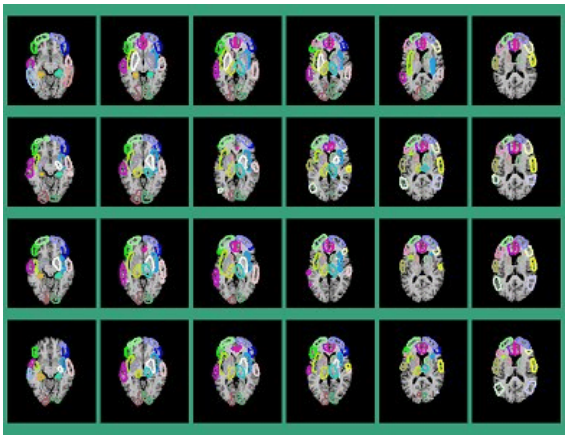


Interactive image overlay alignment program. In this program alignment are done manually based on either surfaces or image overlays

Willendrup P , Svarer C, Hasselbalch SG, Knudsen GM. Comparison of Coregistration Techniques for Neuroreceptor PET images. Society of Nuclear Medicine. Reston, VA, USA: Society of Nuclear Medicine 2002;49:S853

Willendrup P , Svarer C, Hasselbalch SG, Knudsen GM. Precision of Coregistration Techniques for F18-Altanserin PET Images. Cunningham VJ, Myers R. The Fourth International Symposium on Functional Neuroreceptor Mapping of Living Brain. San Diego, CA, USA: NeuroImage 2002;16(3):S85

Algorithm for automatic application a template set of regions of interest to new functional data sets. In this study a method for automatic application of a template ROI set to new subjects is developed and examined. This method uses high resolution (< 1.5 mm) structural MR scans for identifying co-registration parameters between the subject's own space and a standard space such as Talairach space. In the template space a set of template ROIs are defined. This standard set of ROIs can then be transferred to the subject's own space using the identified parameters. Both linear and non-linear co-registration techniques are used. Data will be extracted from the functional scans based on these ROIs. Using a method like this, the ROI set will not be as operator- and site-dependent as would be the case if the ROIs were defined on each subject's own MR image.

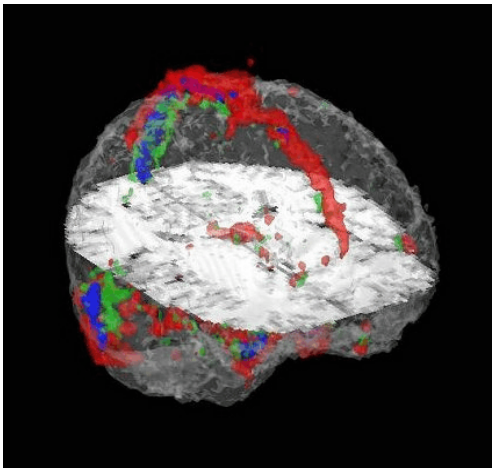


In this figure four different template ROI sets are shown (each row). All of them have been defined on other template MR images and have automatically been transferred to this new subject. The robustness of the ROI transformation method is documented due to the overlap seen between the ROI sets

Svarer C, Willendrup P, Adams KH, Knudsen GM. Region of Interest Analysis: All for One. Society of Nuclear Medicine. Reston, VA, USA: Society of Nuclear Medicine 2002;49:S363

Svarer C, Willendrup P, Adams KH, Knudsen GM. Region of Interest Analysis: One for All. Cunningham VJ, Myers R. The Fourth International Symposium on Functional Neuroreceptor Mapping of Living Brain. San Diego, CA, USA: Neuroimage 2002;16(3):S87

Identification of input curves for kinetic modelling using cluster analysis. In emission tomography, quantification of tracer uptake, metabolism or binding requires knowledge of the cerebral input function. Traditionally, this is achieved with arterial blood sampling. In this work a non-invasive alternative is proposed. The input curve is extracted directly from the PET scans by cluster analysis. The proposed alternative input curves were then used as the input to the Logan plot, and compared with arterial and venous blood samples. This work acts as a proof-of-principle that the use of cluster analysis on a PET data set could obviate the requirement for arterial cannulation when determining the input function for kinetic modelling of ligand binding.



This 3D plot illustrates the identified vascular cluster (red, green and blue voxels). The time activity curve for these voxels is extracted and used as an input curve for kinetic modelling

Liptrot MG, Adams KH, Svarer C, Knudsen GM. Cluster Analysis As A Replacement For Arterial Sampling In Kinetic Modelling. Society of Nuclear Medicine. Reston, VA, USA: Society of Nuclear Medicine 2002;49:S360

Liptrot MG, Adams KH, Svarer C, Knudsen GM. Cluster Analysis In Kinetic Modeling: Better Than Arterial Sampling? Cunningham VJ, Myers R. The Fourth International Symposium on Functional Neuroreceptor Mapping of Living Brain. San Diego, CA, USA: Neuroimage 2002;16(3):S78

6. Publications

Peer-review Full-length Publications

Cerebral Blood Flow and Metabolism

Abildstrom H, Hogh P, Sperling B, Moller JT, Yndgaard S, Rasmussen LS. Cerebral blood flow and cognitive dysfunction after coronary surgery. Ann Thorac Surg 2002;73:1174-8

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7. Other Activities

7.1. Congress Participation

The staff of NRU has participated in 30 international meetings and congresses related to their research fields. Staff members have participated as evaluators of abstracts and as chairmen at the scientific sessions.

7.2. Congress Organizing

The research unit organized the Symposium: *Partial Volume Effects in Emission Tomography* at the European Winter Brain Research Conference, Arc 1800, March 2002.

NRU also organized the 15th Nordic Symposium on Cerebral Blood Flow and Metabolism, in Snekkersten, Denmark, May 2-3, 2002.

7.3. Pre- and Postgraduate Teaching

In 2002 the research group organized the following courses:

Neurodegenerative diseases, April 23-25, 2003, under the auspices of the Copenhagen Neuroscience School.

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

On December 20, 2002, NRU organized an open-to-the-public one day symposium where scientists from NRU presented their most recent data.

Pregraduate Supervision:

OSVAL 1: Medical student Anders Donatsky Kristensen: Bestemmelse af stoffers frie fraktion og dennes betydning for PET. En undersøgelse af interaktionen mellem [18F]altanserin og human albumin. Supervisor: Gitte Moos Knudsen.

OSVAL 1: Medical student Morten Scheibye-Knudsen. Neurofysiologisk gennemgang af søvn-cyklusen: Fokus på hukommelseskonsolidering og drømme. Supervisor: Gitte Moos Knudsen.

OSVAL 1: Medical student Adam Nissen: SPECT-metoden og dens muligheder indenfor diagnosticering af demens. Supervisor: Olaf B. Paulson.

OSVAL 2: Medical student Marie-Louise Sveen: Effect of MDMA on Cell Death and 5-HT_{2A} Receptor Density in Organotypic Hippocampal Cultures. Supervisor: Gitte Moos Knudsen and Susana Aznar.

Cell Biology Project: Human biology student Betina Heinsbæk Thuesen: The potential role of apoptosis in delayed neuronal death following focal cerebral ischemia - apoptosis-regulating proteins as therapeutic targets. Supervisor: Gitte Moos Knudsen.

Cell Biology Project: Human biology student Birgitte Rahbek: Abnormal protein folding. Supervisor: Gitte Moos Knudsen.

Bachelor thesis student Søren Christiansen: Functional and anatomical characterization of the relationship between the serotonergic and the cholinergic receptor systems: Implications for Alzheimer's disease. Supervisors: Susana Aznar and Gitte Moos Knudsen.

7.4. National and International Committees

National Committees:

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

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

Secretary of the Danish Society of Neuroscience (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 Health Science Faculty Research Council, Copenhagen University (Gitte Moos Knudsen)

Board Member of the Copenhagen Neuroscience School (Gitte Moos Knudsen)

Member of Rigshospitalets Medical Council (Gitte Moos Knudsen)

International Committees:

Past President of the International Society of Cerebral Blood Flow and Metabolism (Olaf B. Paulson)

Secretary of the International Society of Cerebral Blood Flow and Metabolism (Gitte Moos Knudsen).

Member of the European Federation of Neurological Societies Working Group on Brain Imaging (Olaf B. Paulson)

Evaluation:

Member of the European Commission 6th Framework "Expression of Interest" expert panel 2002, Brussels (Olaf B. Paulson)

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

Evaluator of two PhD-theses: Hanne Christensen, MD, and Rachid Beck, MD (Gitte Moos Knudsen)

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

Evaluator for a position as Research Professor of psychiatry at Copenhagen University (Gitte Moos Knudsen)

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

7.5. Awards

Technologist Karin Stahr received the Abbott-prize for her work with different methods to determine the free fraction of radiolabeled tracers for PET studies.

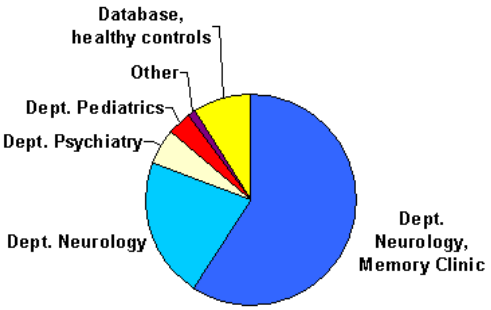
Professor Olaf B. Paulson received the William Nielsens Fonds Hæderspris 2002 for outstanding research.

Psychologist, PhD, Christian Gerlach received the prize from the Medical Faculty at the University of Copenhagen for the best article published from the Faculty by a young scientist.

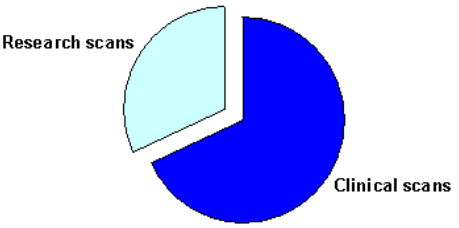
8. SPECT-Laboratory

Due to the exchange of the old SPECT-scanner with a new one, for the SPECT-laboratory 2002 has been a busy year. A full-time physicist has been engaged for implementation of the scanner. The renovation of the SPECT-facilities have ensured up-to-date laboratories that can be approved by modern standards.

The first scan with the new IRIX camera was performed on February 28, 2002, and during the rest of 2002 a total of 225 scans were performed. Admission patterns are shown below.



Admission pattern 2002



Fraction of SPECT-investigations related to research (AD2000-project from the Memory Clinic included)

Research projects carried out in 2002

- Database, healthy controls with and without transmission scan correction
- Development of steady-state quantification of dopamine receptors with ^{123}I-PE2I
- Cerebral blood flow changes in a patient cohort from the Memory Clinic

In order to validate the new IRIX scanner the following phantom studies have been conducted

- Head holder attenuation
- Scanner resolution
- Attenuation correction (uniform vs. transmission scan)

A collaboration agreement with Philips was signed in December 2002, for further evaluation of off-center fan beam collimators.

9. Prospects

In 2003, there will continue to be new tasks and challenges for NRU. The substantial work with improval of data analysis and presentation for use in both a clinical context as well as for research projects for the SPECT-scanner will be implemented. The research and development agreement with Philips will, according to the recently signed collaboration contract, begin in January. The PET-unit at Rigshospitalet has planned a substantial expansion of their radiochemistry facilities, to be completed during Summer 2003. Fortunately, the Lundbeck foundation has generously supported purchase of radiochemistry equipment essential for the full implementation of the radiochemistry laboratory. This is major step for matching the increasing demands on research and development and the expansion is sincerely welcomed.

The number of pregraduate students conducting their dissertation projects at NRU has been increasing and it is anticipated that their association will be of increasing importance in the coming years. The recruitment of young researchers is of the utmost importance for NRU to remain as an active and dynamic research unit in the future.

In the coming year we also expect that some of our recently developed data analysis tools (methods for a precise co-registration of functional and structural images, methods that automate the process of extracting region-of-interest data from new functional scans, and others that perform kinetic analysis of these data) that arise from our involvement in the two EU-projects PVEOut and NCI-MCI, will be made available for research projects and possibly even for clinical purposes.

Several of our scientific staff members will, in 2003, complete their term at NRU. In January, Betina Elfving will defend her PhD thesis entitled 'Characterization of serotonin transporter ligands in relation to emission tomography', and Steen G. Hasselbalch is anticipated to defend his doctoral thesis 'Quantitation of brain metabolism in humans using PET-FDG: levels and limitations' in April. Another two PhD-theses will be submitted during 2003.

The recommendations given in the evaluation report for NRU, based on the site-visit in September 2002, provide an exciting challenge for the leaders of NRU.

Finally, we are looking forward to reinforce our collaboration both with previous and new international collaborators and with research colleagues in the Copenhagen Brain Research Center.

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11. Site-Visit

Background

As part of the Research Council´s present schedule to evaluate all major research groups at Rigshospitalet an ad hoc committee was appointed for the evaluation of the Neurobiology Research Unit. The ad hoc committee consisted of:

Professor Anthony Strong (Chair), King´s College, London

Professor Marc Laruelle, Colombia University, New York

Professor Hans Hultborn, University of Copenhagen

The ad hoc committee convened in Copenhagen September 9-12 for a site visit at the NRU, and the final report was submitted to the Research Council of Rigshospitalet two months later.

The main conclusions of the report was as follows

- The quality of management and scientific supervision in NRU is outstanding
- The current scientific output is excellent in volume and relatively impressive in impact
- The volume of external funding generated in relation to the salary resources received from internal resources is substantial
- The balance of age and experience in the group is too heavily weighted towards young investigators, imposing an unreasonable supervisory and training load on senior group members
- There is a lack of a clearly identified and promoted overarching strategy
- Nevertheless, a very solidly based framework has been established on which an outstanding, internationally competitive neuroreceptor/molecular imaging group can develop and flourish in the future
- Factors have been identified which are impeding progress of the neuroreceptor programme and require immediate attention.

The panel members recommend (with particular emphasis by the external assessors)

- Concentration of work in NRU on neuroreceptor ligand development, in vivo pharmacology, molecular imaging, and related kinetics and modelling
- An immediate improvement in access to scanning time and radioligand generation in the Rigshospitalet PET Centre

- Continuing review and careful selection of areas of basic and clinical neuroscience, psychiatry and medicine in which the potential output of a world class molecular PET unit can be applied
- Funding of a radiochemist within the staffing structure of NRU, and development of an organic chemistry laboratory
- Funding of a network and computing systems support engineer to relieve the data analysis group of non-specific routine support tasks in NRU
- Funding of a new brain-dedicated PET camera, such as the HRRT
- Continued collaboration with the fMRI programme at Hvidovre Hospital
- Continuation of NRU's role in more general, collaborative but also innovative, studies with sister departments in Rigshospitalet
- Quantitative research (as opposed to clinical service work) should wherever possible be transferred from the SPECT to PET environment
- A planned programme of (1) reciprocal sabbatical visits between tenured and post-doctoral/tenure track NRU staff and their counterparts from sister units outside Denmark, and (2) invited ad hoc visiting lecturers to NRU

Upon receipt, the evaluation report was discussed within the Research Council of Rigshospitalet and with the involved parts. The Research Council is currently preparing a letter of recommendation for the Management of Rigshospitalet.

12. Dansk Resumé

En omfattende modernisering af SPECT-skannerrummet på neurologisk afdeling er afsluttet, og implementeringen af den nye skanner vil fortsætte i det kommende år. Igen i år har mange fonde bidraget til, at forskningsaktiviteterne fortsat vil kunne gennemføres. En samlet stor bevilling fra Apotekerfonden, Lundbeckfonden og Sygekassernes Helsefond har som tidligere været af uvurderlig værdi. Af de nye fondsbevillinger, der er doneret i løbet af 2002, skal særligt fremhæves Forskningsstyrelsens rammebevilling til receptorforskning og Lundbeckfondens støtte til indkøb af radiokemisk udstyr, doneret til vores samarbejdspartnere ved PET- og Cyklotronenheden. Statens Sundhedsvidenskabelige Forskningsråd har desuden bevilget en 3-årig rammebevilling til neuroreceptorforskning. Det er desuden særligt glædeligt, at et stigende antal specialestuderende inden for bl.a. humanbiologi har fundet interesse i at gennemføre deres afsluttende speciale i NRU's laboratorier.

Publiceringsmæssigt har NRU siden 1997 haft en støt stigende produktion. I år er det særligt en række tidligere projekter inden for Brain Mapping, der har kunnet afsluttes. Dette har bl.a. drejet sig om undersøgelser af hjernens aktivering ved motorisk indlæring, under søvn og ved synsindtryk.

Vi ser nu frem mod et nyt år. Også 2003 vil være præget af nyinstallationer og ombygninger, idet PET-enheden da vil gennemføre en tiltrængt udvidelse af deres radiokemilaboratorier. Dette hilses velkomment, idet radiokemikerne i tiltagende grad er blevet væsentlige samarbejdspartnere til NRU, og da de trange forhold i radiokemi-laboratoriet reelt har været begrænsende for udviklingsmulighederne. Vi kan endvidere se frem til, at en af NRU's mangeårige medarbejdere vil forsvare sin disputatsafhandling og yderligere 3 deres PhD-afhandling.

NRU staff December 2002