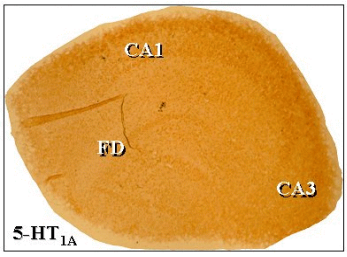
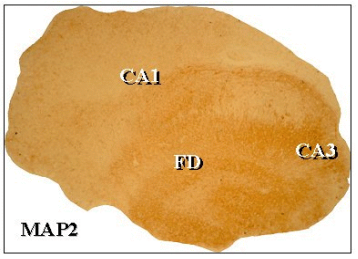
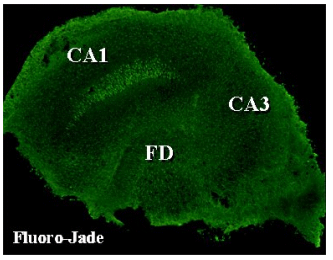
Annual Report 2001

Neurobiology Research Unit







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

http://nru.dk

Front page:
Sections immunostained for the 5-HT_{1A} receptor (left) and MAP2, which stains cell bodies and dendrites (middle) and histochemically stained for Fluoro-Jade, which marks degenerating neurons (right) of 2-week-old organotypic hippocampal cultures. Bar = 500 μM. The study shows that with increasing 5-HT levels, the 5-HT_{1A} receptors are down-regulated. This down-regulation is not caused by neuronal death (see also page 13).

Preface

For the Neurobiology Research Unit (NRU), 2001 has in several respects been a year of expansion. The more-than-20-year-old SPECT scanner was taken apart and an extensive renovation of the SPECT facilities has been conducted to house a new SPECT scanner. The old SPECT scanner, installed by professor Niels A. Lassen, was one of the first brain-dedicated scanners ever produced and it contributed to the publication of more than 150 scientific publications and 7 Doctoral/Ph.D. theses. Nevertheless, the replacement was highly needed, and due to generous funds from the Danish Research Agency and the Toyota Foundation, this has now been completed. We expect that the new scanner will continue to make substantial contributions to neuroscience within the coming years. The PET Unit at Rigshospitalet has also conducted major rebuilding in 2001 to allow for the installation of a new PET-CT scanner which was inaugurated in December. For NRU, this installation potentially allows for an expansion of the research activities. In March, the kick-off meeting for the EU 5th Framework concerted action, chaired by NRU between scientific partners in Sweden, The Netherlands, Italy, and Denmark took place. The objectives of this concerted action are to establish an early diagnosis of, and a prognosis for, the development of Alzheimer's disease. Mapping of brain receptors in normal aged individuals, in patients with mild cognitive impairment, and in those with Alzheimer's disease will be compared to neuropsychological and psychiatric variables to establish the interrelationships between the metrics.

In 2001, NRU has increased its research activities thanks to the ongoing support from many charitable trusts and foundations. As during the previous years, donations from the 1991 Pharmacy Foundation, the Lundbeck Foundation, and the Health Insurance Foundation have been of major significance. New grants supplied this year include, amongst others, the Danish Research Agency and NeuroSearch Innovation Post Doc Grant to Ph.D. Susana Aznar, Rigshospitalet's supply of a Ph.D.-position for MD Daniela Balslev, and a three year grant from the Danish Medical Research Council. It is particularly encouraging that an increasing number of pre-graduate students choose to conduct their dissertation projects in the laboratories at NRU. The recruitment of young medical investigators was further reinforced by a successful meeting organized in conjunction with other research groups for medical students at the Department of Neurology in September 2001.

Since 1997, NRU has had a steady rise in the production of scientific papers. This year, a number of projects within cerebral blood flow and metabolism have been completed and published. These include investigations of patients with multiple sclerosis, Alzheimer's disease, Huntington's disease, and liver- or heart-failure. The number of publications based on neuroreceptor studies show an increasing tendency, including the first results from the experimental laboratory. This annual report describes most of the results that we have published this year. We hope that you will enjoy reading it!

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

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.

The SPECT laboratory of NRU is located at the Department of Neurology on the 8th floor in the main complex of Rigshospitalet. During 2001, the laboratory has been rebuilt to include a room for the new SPECT scanner, a type B approved isotope laboratory, and a small office. Further office and laboratory facilities are shared with other users of 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 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, Ph.D., 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 2001 the research staff consisted of:

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

Ph.D.-students:
Karen Husted Adams, Pharmacologist
Betina Elfving, Pharmacologist
Trine Fischer Hansen, Biologist
Jacob Madsen, Chemist*
Lars Hageman Pinborg, MD
Kristin Scheuer, MD

Junior Researchers:
Robin Colwell, Bachelor Sci.
Esben Høgh-Rasmussen, Engineer
Matthew Liptrot, Engineer
Peter Willendrup, Physicist

Associated Researchers:
Morten Blinkenberg, MD, Ph.D.
Søren Kyllingsbæk, Psychologist
Ian Law, MD, Ph.D.
Charlotte Videbæk, MD

Students:
Daniela Balslev, medical student
Søren Christiansen, biology student
Heidi Kristiansen, biology student
Kirsten Nielsen, medical student
Marie-Louise Sveen, medical student

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

Research Assistants:
Karsten Harboe
Nikolaj Hjortholm
Morten Bonnin Larsen

Secretaries:
Pia Farup
Dorthe Givard

* shared with another research group

Guest Researchers:
Qian Zhaoxia, Dept. of Physiology, Hainan Medical College, Haikuo, Hainan, China
Robin de Nijs, Bosch Medicentrum, Groot Ziekengasthuis, Dept. Clinical Physiology, Hertogenbosch, The Netherlands

3. Collaborators in 2001

Departments within Rigshospitalet:
Deparment of Cardiology
Department of Clinical Physiology/Nuclear Medicine
Department of Hepatology
Department of Infectious Diseases
Department of Neurosurgery
Department of Neuroanesthesiology
Department of Pediatrics
Department of Psychiatry
PET and Cyclotron Unit

Research groups within H:S (Copenhagen Hospital Cooperation):
Danish Research Center for Magnetic Resonance, Hvidovre Hospital
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, Rome, 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 Psychology, University of Copenhagen Amager
Department of Pharmacology, Tours University Hospital, France
H. Lundbeck A/S
Informatics and Mathematical Modelling, Technical University of Denmark
MAP Medical, Helsinki, Finland
Memory Clinic, Basel, Schweiz
National Cardiovascular Research Center, Osaka, Japan
NeuroSearch A/S
PET Center, Aarhus Kommunehospital
The Royal Danish School of Pharmacy

4. Doctoral and Ph.D. theses

Apolipoprotein E (*APOE*) Genotype: Impact for the Pathophysiology and Disease Progression in AD and Multiple Sclerosis

Peter Høgh, MD, Ph.D.

Alzheimer's disease (AD) is a neurodegenerative disease characterised by specific neuropathological abnormalities. The diagnosis of AD, which clinically is determined on the basis of descriptive clinical criteria such as NINCDS-ADRDA, can be difficult to settle as a specific biological marker for the disease has yet to be identified. There is a consensus regarding the importance of structural imaging as an adjunct in the diagnostic classification. However, the significance of functional imaging methods, as well as the relevance of Apolipoprotein E (ApoE) genotyping in the diagnostic evaluation of patients with dementia is somewhat more controversial.

Multiple sclerosis (MS) is an inflammatory neurodegenerative disorder characterised by demyelinating lesions and axonal loss spread in the white matter of the central nervous system. The clinical course in patients with MS is highly variable and the prognostic determinants are generally not identified.

The aim of the present Ph.D. thesis was to examine the possible impact of the *APOE*-genotype on prognosis and course in AD and MS. In AD, we specifically examined whether the *APOE*-genotype had an independent influence on regional cerebral blood flow (rCBF) measured by Single Photon Emission Computer Tomography (SPECT).

We examined 49 patients with clinical AD and 26 healthy sex- and age-matched volunteers with SPECT and determined their *APOE*-genotypes. When rCBF was statistically compared in the 2 subgroups of *APOE* ε4-positive (n=33) and *APOE* ε4-negative (n=16) AD patients, rCBF was significantly reduced in multiple cortical regions of interest among the *APOE* ε4-positive patients. The difference between these two subgroups was most prominent in the frontal association cortex.

The *APOE*-genotype was determined from 240 blood samples from patients with clinical MS. The prevalences of the various genotypes were compared with the distribution of genotypes in a control population of 361 patients obtained from a cross-sectional population study (*Glostrupundersøgelsen*). The prevalence of the *APOE* ε4-homozygote patients was significantly higher in the MS patients compared to controls ($p<0.05$). MS patients with *APOE* ε4-homozygocy had a significantly faster clinical progression as compared to other *APOE*-genotypes ($p<0.05$).

In conclusion, the results from the present Ph.D. thesis support the hypothesis that the *APOE*-genotype has an independent impact on pathophysiology, prognosis and course in both AD and MS. While previously shown in AD, from our studies the *APOE* ε4-allele also appears to be a susceptibility gene in MS. In AD, the presence of the *APOE* ε4-allele determines a more severe affection of the frontal lobe, even in the early stages of the

disease.

The Ph.D.-defence took place on February 16, 2001, in Rigshospitalets auditorium 93. The evaluators were Professor Johannes Jakobsen, Aarhus University Hospital, Professor Lars-Olof Wahlund, Huddinge Hospital, Stockholm, and Professor Christian Krarup, Rigshospitalet.

The Ph.D.-project was completed with Professor Gunhild Waldemar, Professor Gitte Moos Knudsen, and Professor Olaf B. Paulson as supervisors.

Cerebral Blood Flow Autoregulation in Patients with Acute Bacterial Meningitis

Kirsten Møller, MD, Ph.D.

This Ph.D. thesis deals with the relation between cerebral blood flow (CBF) and mean arterial pressure (MAP) during acute bacterial meningitis. In healthy subjects, CBF autoregulation maintains the flow constant despite changes in MAP. Impaired autoregulation renders patients at increased risk of cerebral hypoperfusion and ischaemia if MAP is low, and of hyperperfusion and vasogenic oedema if MAP is high. Twenty adult patients were investigated during the early phase of meningitis (<24 hours after diagnostic lumbar puncture) to determine whether CBF autoregulation was intact. As autoregulation was generally found to be impaired, we studied whether and when autoregulation was recovered during the course of illness, and the effect of acute hypocapnia on autoregulation during the early phase.

In the initial study, autoregulation, as assessed by transcranial Doppler and the arterial-to- jugular oxygen difference method during a norepinephrine- infusion-induced-increase in MAP, was impaired in nineteen out of twenty patients. The time-course was studied in ten patients. In eight patients, autoregulation reappeared after a median of 7 (range 2-10) days. The effect of acute hypocapnia was studied in nine patients; all were mechanically ventilated. For the group, autoregulation was significantly improved by hyperventilation; it was intact in four patients during hyperventilation as compared to one during baseline ventilation. Thus, CBF autoregulation is impaired in the early phase of acute bacterial meningitis, but reappears with clinical recovery. Acute hypocapnia leads to partial recovery of autoregulation in the early phase. The findings may be of significance for optimal supportive therapy in such patients.

The Ph.D.-defence took place on August 23, 2001, in Auditorium 93, Rigshospitalet. The evaluators were Professor Olaf B. Paulson, NRU, Consultant Georg E. Cold, Aarhus University Hospital, and Professor Court Pedersen, Odense University Hospital.

The Ph.D.-project was completed with Professor Peter Skinhøj, Professor Gitte Moos Knudsen, and Ph.D. Fin Stolze Larsen as supervisors.

5. Research Topics

The Neurobiology Experimental Research Laboratory

The Neurobiology Experimental Research Laboratory has, during 2001, been chaired by Research Professor Gitte Moos Knudsen and the laboratory staff consisted of eight scientific employees and two technologists.

In the laboratory experimental research studies of cerebrovascular functions, neuroreceptors with ligand binding, bioavailability, metabolism, in situ hybridization, antibody detection of brain cells, autoradiography, and determination of specific and non-specific brain binding in animals are conducted. Furthermore, determination of receptors in subpopulations of brain cells in culture is performed.

5.1. The Renin-Angiotensin System and Cerebral Blood Flow

Olaf B. Paulson, MD, Professor

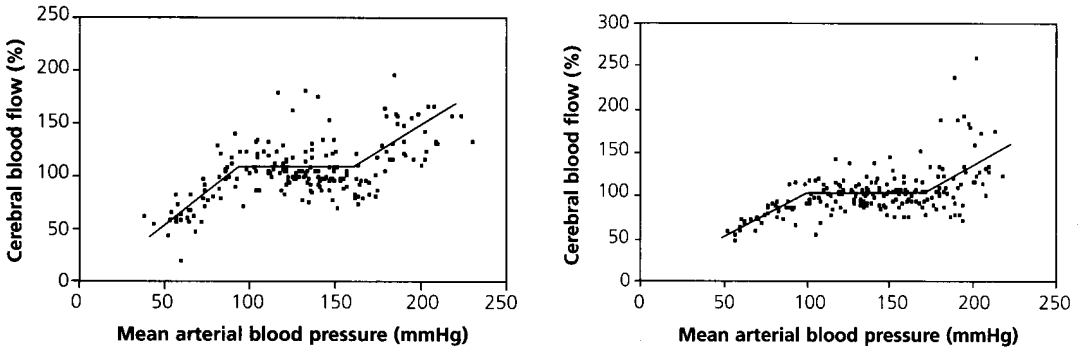
The renin angiotensin system has a marked regulating effect on the cerebral blood flow. Autoregulation of the cerebral circulation is a term that describes how the cerebral blood flow is kept constant despite wide variations in the cerebral perfusion pressure, normally determined by the arterial blood pressure alone. Both a lower and an upper limit of the autoregulation exist; when blood pressure falls below the lower limit, cerebral blood flow decreases and above the upper limit, forceful vasodilatation and a blood flow increase takes place. It has previously been shown in our laboratory that blockade of the renin angiotensin system by angiotensin converting enzyme (ACE) inhibitors as well as with an angiotensin AT_1 antagonist shifts the limit of autoregulation towards a lower blood pressure. We have shown that intravenous administration of the ACE inhibitor captopril changes the cerebral autoregulation. This change is not seen, however, when captopril is administered directly into the cerebral ventricles and is allowed to diffuse into the brain tissue.

In order to further investigate the role of the renin angiotensin system for the regulation of the cerebral circulation, two additional studies have been carried out. First, we wanted to determine whether renally produced renin is mandatory for the role of the renin angiotensin system in the cerebral autoregulation. Secondly, we wanted to determine whether the effect of angiotensin is carried out solely by the AT_1 receptors, or whether the AT_2 receptors also play a role.

For the study on the role of renally produced renin, a model of nephrectomised dialysed rats was adapted and further developed in order to keep the animals in a reasonable physiological condition for several days until all renal renin was eliminated (Pedersen et al). Cerebral autoregulation was then investigated in various groups of rats including captopril treated rats. None of the procedures influenced baseline CBF but the lower limit of autoregulation was lower both in nephrectomised and in sham operated rats, as

compared to control rats. Following captopril treatment the lower limit was significantly lower in the nephrectomised as well as in control rats. Thus, following removal of the circulating renin the lower limit of autoregulation was unchanged. Captopril, however, was able to lower the lower limit even in the absence of the circulating renin, and hence appeared to exert its blocking effect on compounds of the renin angiotensin system in the vessel wall, possibly with a contribution of bradykinin accumulation. These studies form the basis of Trine Fischer Pedersen's Ph.D. thesis to be defended at the University of Copenhagen during 2002.

The role of the AT_2 receptor was investigated using the AT_2 receptor antagonist PD123319 in spontaneously hypertensive rats. It was found that PD 123319 did neither influence baseline cerebral blood flow, nor did it affect the limits of cerebral blood flow autoregulation (Estrup et al). By contrast, it was previously shown that AT_1 receptor blockade leads to a left shift of the autoregulation limits.



The pooled autoregulation curve showing the lower and upper limit in (left) control group and (right) PD123319 treated rats. Cerebral blood flow values are given as percentages of baseline values.

Knowledge on the autoregulation of cerebral blood flow is essential for the understanding and treatment of essential hypertension. A review on the cerebrovascular effects of hypertension and the management thereof, with particular emphasis on the cerebral blood flow autoregulation, has been published (Strandgaard and Paulson).

Estrup TM, Paulson OB, Strandgaard. No effect of angiotensin II AT2 receptor antagonist PD123319 on cerebral blood flow autoregulation. JRAAS 2001;2:188-92

Pedersen TF, Paulson OB, Nielsen AH, Strandgaard S. Effect of nephrectomy and captopril blockade on autoregulation of cerebral blood flow in rats (submitted)

Strandgaard S, Paulson OB. Management of hypertension with cerebrovascular disease. In: Anand MP, Billimoria AR, eds. Hypertension. An International Monograph 2001. India: IJCP Group; 2001. p. 271-3

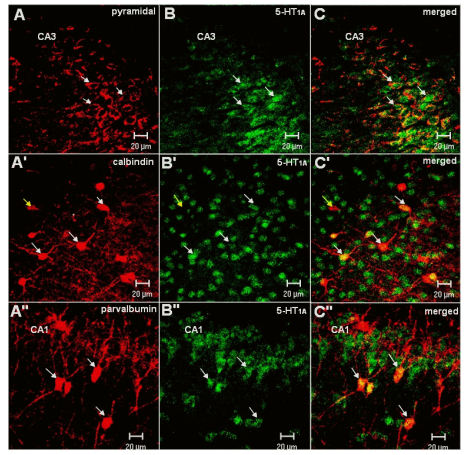
5.2 Experimental Receptor Studies

Susana Aznar, Ph.D.

One of our research themes are studies that 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 in vivo experimental studies where we apply neuronal tracing and double and triple immunostaining techniques. Parallel culture studies are used to address more functional questions. For example, using organotypic hippocampal cultures we have investigated how postsynaptic 5-HT_{1A} receptors are influenced by serotonin. This is important for understanding what effect serotonin reuptake inhibitors, which are widely used for the treatment of depression and act by increasing serotonin levels in the synaptic cleft, have on postsynaptic 5-HT_{1A} receptors. The 5-HT_{1A} receptor is a well-characterized serotonin receptor that plays a role in many central nervous functions and is involved in depression. Our results show that postsynaptic 5-HT_{1A} receptors are downregulated when serotonin levels are increased, indicating that the density of 5-HT_{1A} receptors is influenced by serotonin (see also the front page illustration). This finding may help explain how 5-HT_{1A} levels are affected in patients with mental disorders where serotonin transmission is impaired, as well as in patients receiving antidepressive drugs.

Aznar S, Knudsen GM. Serotonin induces decrease of 5-HT_{1A} immunoreactivity in organotypic hippocampal cultures. NeuroReport 2001;12:3909-12

Furthermore, we have investigated the localization and distribution of the 5-HT_{1A} receptor in different neuronal subtypes throughout the rat forebrain. This is important for understanding of both the role of this receptor in neuronal circuitries and the effect 5-HT_{1A} receptor activation has 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 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.



Aznar S, Qian Z, Shah R, Knudsen GM. The 5-HT_{1A} receptor is located on calbindin- and parvalbumin-containing neurons in the rat brain (submitted)

In a more recent study we have characterized in detail the projection of raphe fibers to these types of inhibitory interneurons in areas involved in controlling and maintaining hippocampal activity. 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 also are involved.

Aznar S, Qian Z, Knudsen GM. Non-serotonergic dorsal and median raphe projection on parvalbumin- and calbindin-containing neurons in hippocampus and septum (submitted)

Betina Elfving, Ph.D.-student

When developing ligands for emission tomography studies, one of the major obstacles lies in the selection of ligand candidates. A previously unattended factor such as the influence of temperature on ligand affinity is likely to play a role. By use of rat brain homogenates, the binding characteristics of [^{3}H]-(S)-citalopram and [^{3}H]-(+)-McN5652 and 17 selective serotonin reuptake inhibitors were compared at 21˚C and 37˚C. Ligand logP values were also calculated. It was found that temperature affects the affinity differently and that in vitro dissociation may help to predict whether a given ligand may be useful in PET studies. LogP values did not per se predict the potential of a given ligand as an emission tomography tracer (Elfving et al, 2001a).

Based on current knowledge, radiolabeled (S)-citalopram was anticipated to be a suitable PET ligand for the 5-HT reuptake site. In man, however, [^{11}C]-(S)-citalopram does not yield a sufficiently specific PET signal. Inhibition of a possibly significant cerebral metabolism of radiolabeled (S)-citalopram by predosing with the MAO inhibitors selegiline and/or chlorgyline was attempted, but the effects of inhibited metabolism could not be separately evaluated since selegiline and chlorgyline turned out to be competitive inhibitors of (S)-citalopram to the 5-HT reuptake site. Further, it was tested whether the non-specific binding of radiolabeled (S)-citalopram could be reduced by prior injection of the non-radioactive inactive enantiomer (R)-citalopram (Elfving et al., 2001b). It was found, however, that the affinity difference between the S- and R-citalopram was not sufficiently high to attain the goal. Emission tomography studies carried out with animals, when developing new ligands, are mostly performed under anesthesia. We have demonstrated that ketamine, isoflurane and halothan interfere with the 5-HT reuptake site (Elfving et al., 2001c). That is, the type of anaestheisa in PET neuroreceptor studies should be carefully evaluated.

Elfving B, Bjørnholm B, Ebert B, Knudsen GM. Binding characteristics of selective serotonin reuptake inhibitors with relation to emission tomography studies. Synapse 2001a;41:203-11

Elfving B, Bjørnholm B, Knudsen GM. Evaluation of (S)-citalopram as a PET radiotracer. J Cereb Blood Flow Metab 2001b;21(suppl 1):S557

Elfving B, Bjørnholm B, Knudsen GM. Ketamine binds to the serotonin reuptake site and may interfere with evaluation of PET- og SPECT ligands. J Nucl Med 2001c;42 (suppl.):214P

In collaboration with Lundbeck A/S and the radiochemistry unit in Uppsala, we have produced ^{11}C-citalopram and other radiolabeled derivatives and investigated the binding to the serotonin reuptake site in the monkey and rat brain. These data are currently being analysed and manuscripts are in preparation.

Madsen J, Andersen K, Knudsen GM, Martiny L. Gas phase production of $^{11}CD_3I$ and synthesis of *S*-[*N*-D_3-Methyl-^{11}C]citalopram. Poster at Seventh International Symposium on: The synthesis and applications of isotopes and isotopically labelled compounds. Dresden, June 2001

5.3. Studies of the Cerebral Blood Flow with PET, SPECT, and TCD

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. Studies of cerebral blood flow in Alzheimer patients have been completed and entered in Peter Høgh's Ph.D.-thesis, as described above. Studies of cerebral blood flow and metabolism in patients with acute bacterial meningitis have been completed and entered Kirsten Møller's Ph.D.-thesis, as described above.

Cerebral Blood Flow and Metabolism in Fulminant Hepatic Failure

Gitte I. Strauss, MD

Cerebral oedema and intracranial hypertension frequently complicate the clinical course of fulminant hepatic failure (FHF). The pathophysiological background for the development of cerebral oedema and intracranial hypertension is not completely solved, but changes in cerebral blood flow (CBF) as well as changes in cerebral metabolism seem to be of importance. Institution of acute mechanical hyperventilation is one of the treatment modalities during episodes of intracranial hypertension, however, it may critically reduce CBF.

In eight patients with FHF, we evaluated the efficacy of Transcranial Doppler Sonography (TCD) and the internal jugular bulb saturation ($svJO_2$) to determine relative changes in CBF during mechanical hyperventilation (CO_2-reactivity). We found that TCD and $svJO_2$ could be used to evaluate relative changes in CBF during hyperventilation, however the TCD method was less accurate to determine CO_2-reactivity compared with the $svJO_2$ and Kety-Schmidt method.

Strauss GI, Møller K, Holm S, Sperling B, Knudsen GM, Larsen FS. Transcranial doppler sonography and internal jugular bulb saturation during hyperventilation in patients with fulminant hepatic failure. Liver Transplantation 2001;7:352-8

Arterial levels of the astroglial marker S-100b and Neuron-Specific Enolase (NSE) were evaluated as a marker for cerebral herniation in thirty-five patients with FHF. For comparisons, we also determined arterial levels of S-100b and NSE in six patients with acute or chronic liver disease (AOCLD), in thirteen patients with cirrhosis without HE, and in eight healthy subjects. We found that S-100b was elevated in almost all patients with FHF and AOCLD, but unrelated to cerebral herniation, whereas NSE tended to be higher in patients with FHF who subsequently died of cerebral herniation as compared to patients who survived.

Strauss GI, Christiansen M, Møller K, Clemmesen JO, Larsen FS, Knudsen GM. S-100b and Neuron-Specific Enolase in patients with fulminant hepatic failure. Liver Transplantation 2001;7:964-70

Calcitonin gene-related peptide (CGRP) and vasoactive intestinal peptide (VIP) are prominent vasodilators that are stored in perivascular nerves. Conversely, Neuropeptide Y (NPY) induces vasoconstriction. Since wide variations in CBF are observed in patients with FHF, we evaluated the relationship between high CBF and circulating levels of CGRP, VIP and NPY, respectively. The arterial levels of the vasodilatory peptides, CGRP and VIP, were elevated, whereas the arterial level of NPY was normal. However, none of the neuropeptides were correlated to CBF.

Strauss GI, Edvinsson L, Larsen FS, Møller K, Knudsen GM. Circulating levels of neuropeptides (CGRP, VIP, NPY) in patients with fulminant hepatic failure. Neuropeptides 2001; 35:174-80

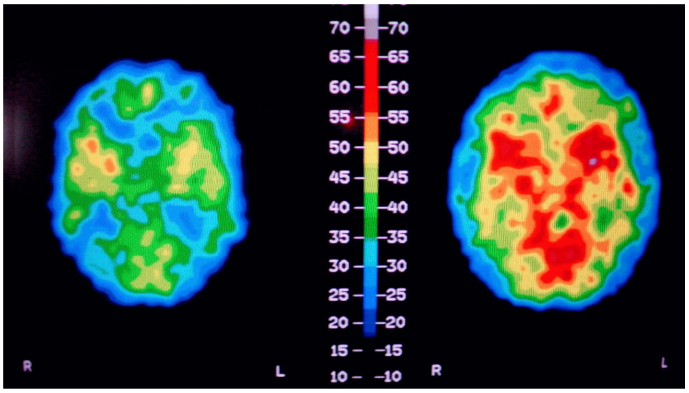
Hyperammonemia is a consistent finding in patients with FHF. Ammonia is detoxified in the astrocytes by the formation of glutamine. According to the glutamine hypothesis, glutamine accumulates within the astrocytes, which results in a shift of water from the extracellular space into the astrocytes. In the present study the net brain flux of ammonia and amino acids, with special emphasis on glutamine, were determined and related to cerebral herniation in patients with FHF. We found an increased cerebral ammonia net uptake and increased cerebral glutamine efflux in patients with FHF. Subsequent development of cerebral herniation in patients with FHF was associated with the highest cerebral ammonia uptake and glutamine efflux.

Strauss GI, Knudsen GM, Kondrup J, Møller K, Larsen FS. Cerebral metabolism of ammonia and amino acids in patients with fulminant hepatic failure. Gastroenterology 2001;121:1109-19

Cerebral Blood Flow in Heart Failure

Gitte Moos Knudsen, MD, Professor

Arterial blood pressure and cardiac output are often reduced in patients with chronic heart failure (CHF). Counter-regulatory mechanisms with increased neurohormonal activation and changes in the distribution of cardiac output are assumed to secure vital organ perfusion. However, clinical examination of patients with CHF frequently reveals neurological symptoms with dizziness and memory problems, suggesting altered brain perfusion. In this study we determined whether cerebral blood flow (CBF) as measured with SPECT and TCD is reduced in patients with New York Heart Association (NYHA) functional class III and IV (n=12) compared with healthy control subjects (n=12) (Gruhn et al.). Furthermore, we examined whether heart transplantation (n=5) could restore CBF. In the CHF patients we found a 31% reduction in CBF as compared with the control group. After heart transplantation, CBF normalized from within the first postoperative month. Our finding that CBF is substantially, but reversibly, reduced in patients with NYHA class III/IV heart failure suggests that redistribution of cardiac output leads to a reduction in brain perfusion in these patients.



Regional cerebral blood flow (CBF) in a patient before (left) and after heart transplantation (right). Note the normalization of the globally decreased blood flow. The scale gives CBF in ml/100g/min.

It is unknown whether patients resuscitated from cardiac arrest have preserved CBF autoregulation. In another study, CBF autoregulation was investigated in 6 healthy volunteers and in eighteen patients within the first 24 hours after resuscitation from cardiac arrest by TCD during a stepwise rise in mean arterial blood pressure by use of norepinephrine infusion (Sundgreen et al.). We found that 8 out of 18 patients had impaired CBF autoregulation, and in 5 of the 10 patients with preserved CBF autoregulation, where the lower limit of autoregulation could be identified it was substantially higher than in the control group. That is, in a majority of patients in the acute phase after cardiac arrest, cerebral autoregulation is either absent or right-shifted. These results indicate that in order to secure cerebral perfusion, blood pressure should be kept at a higher level than commonly accepted.

Gruhn N, Larsen FS, Boesgaard S, Knudsen GM, Mortensen SA, Thomsen G, Aldershvile J.

Cerebral blood flow in patients with chronic heart failure before and after heart transplantation. Stroke 2001;32:2530-3

Sundgreen C, Larsen FS, Herzog TM, Knudsen GM, Boesgaard S, Aldershvile J. Autoregulation of cerebral blood flow in patients resuscitated from cardiac arrest. Stroke 2001;32:128-32

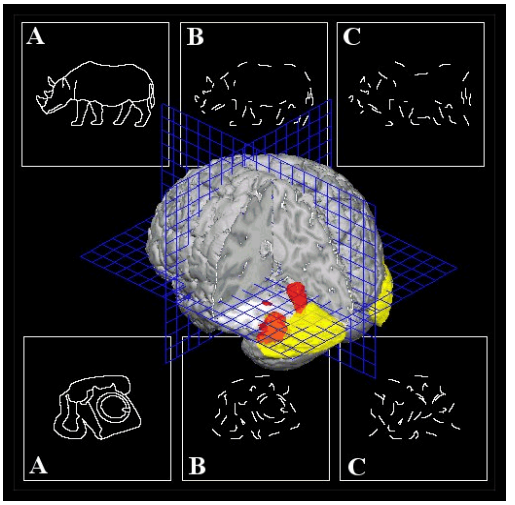
5.4. Brain Mapping

Psychologist, Ph.D., Christian Gerlach

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 but have also used it to study human memory.

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 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 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 (in press)

Parallel to the PET studies we are also conducting a large consecutive study of patients with infarcts in the arteria posterior cerebri (the artery supplying the posterior parts of the brain important for visual perception). This study is conducted in collaboration with partners from the Department of Psychology, Copenhagen University and the Behavioural Brain Sciences, School of Psychology, University of Birmingham, United Kingdom. While this study is still in progress some of the patients from this sample have been selected for comprehensive in-depth study. We have described one such patient who, following an infarct in the right occipital lobe, was left with an impairment of intermediate visual processing. On object naming tasks, the patient performed normally. However, on more demanding tests of visual object recognition the patient performed poorly. Based on these findings, we have suggested that normal object recognition does depend on intact intermediate processing (e.g., integration processes), but that object recognition abilities may deceivingly appear intact on standard object naming tests because these tests are not as sensitive as commonly conceived. As such, these data support models in which early, intermediate and late stages in visual object recognition are serially organized.

Gerlach C, Marstrand L, Gade A, Udesen H. Impaired shape integration following infarction of the right occipital lobe: Implications for models of visual object recognition (submitted)

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.

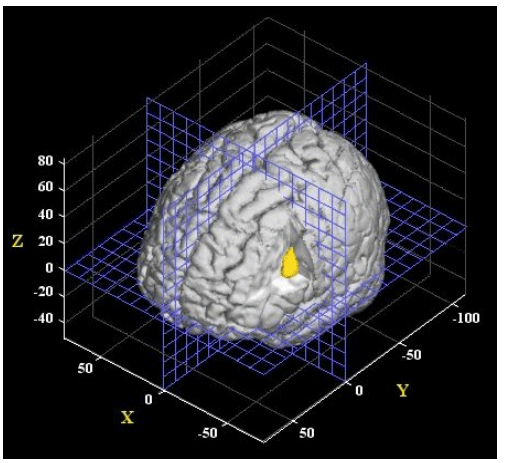
It has been suggested that category-specific disorders for natural objects may reflect that these objects are more visually similar than man-made objects and therefore more difficult to recognize perceptually. Although this hypothesis has been supported by many studies, it has been argued that these studies have failed to take into account that natural objects are usually more visually complex and familiar than man-made objects. To settle this matter we conducted a study in which pictures of natural and man-made objects were matched for various nuisance parameters. We found that the disadvantage claimed for natural objects persisted on matched sets of natural and man-made stimuli, but only on tasks that required a high degree of perceptual differentiation. This latter finding may explain the diverging results obtained in previous studies.

Gerlach C. Structural similarity causes different category-effects depending on task characteristics. Neuropsychologia 2001;39:895-900

While natural objects may be more visually similar than man-made objects, 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. 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.

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

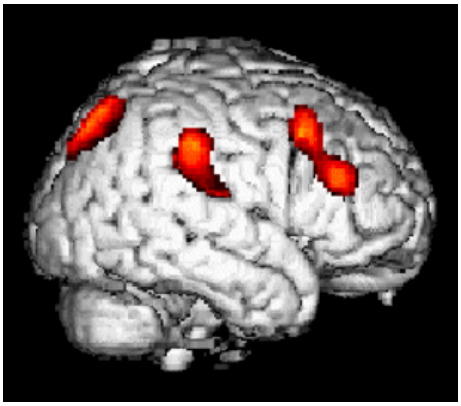
On the account suggested above one might expect to find activation of the premotor cortex during categorization of manipulable objects regardless of whether these are natural or man-made. We found support for this prediction in a new study where we showed increased activation of the premotor cortex during categorization of both articles of clothing and vegetables/fruits relative to both non-manipulable man-made objects and animals (see Figure). Thus, the category-specific effect previously reported for man-made objects in the premotor cortex is probably not category-specific in a true lexical sense but rather may reflect that categories differ in manipulability.



Gerlach C, Law I, Paulson OB. When action turn into words (submitted)

The Neural Correlates of Episodic Memory Retrieval

Functional imaging studies have relatively consistently revealed activation of the right frontal cortex, the right parietal cortex and the medial temporal lobes during retrieval from episodic memory. While damage to medial temporal and limbic regions leads to dramatic impairments of episodic memory, lesions in the frontal and parietal cortex have not been linked with such profound deficits, suggesting that these latter areas are not directly important for the long-term storage of or access to episodic memories. Accordingly, a growing number of studies converge on the notion that the ventrolateral frontal cortex (VLFC) may be involved in pre-retrieval processing (e.g. setting up search parameters for retrieving information from long-term memory) whereas the dorsolateral frontal cortex (DLFC) and the parietal cortex may be involved in post-retrieval processing, that is in the monitoring and on-line storage of retrieved information. In a PET study on episodic memory retrieval in both normal subjects and amnesics we found evidence supporting this broad division. Thus, we were able to show: (i) that rCBF increased in the right DLFC and parietal cortex as a monotonic function of the number of judgements passed by subjects across three different recognition memory conditions (see Figure), and (ii) that this parameter had no effect on rCBF in the VLFC although this area was activated by all three recognition memory conditions. In addition, we found no evidence that these areas (DLFC, VLFC, parietal cortex and the anterior frontal cortex) were affected by whether the information retrieved was veridical or false or concerned new or old events. These observations are compatible with the notion that these areas will be activated together and to the same extent regardless of the specific memory conditions employed, unless these conditions differ with respect to e.g. monitoring demands or rehearsal, which was not the case in the present study.



Gerlach C, Mortensen HV, Gade A, Aaside CT, Law I, Paulson OB. Distinguishing between pre- and post-retrieval processes in episodic memory (submitted)

$^{10}CO_2$, A New PET Tracer for Functional Brain Imaging

Ian Law, MD, Ph.D.

The most widely used PET tracer for functional mapping is $H_2{}^{15}O$. The tracer halflife (2 min) limits the number of attainable PET scans within 2 hours to approx. 12 scans. The PET and Cyclotron Unit at Rigshospitalet has, in collaboration with the University of Wisconsin, developed an ultra-shortlived PET tracer, $^{10}CO_2$, for human use. The tracer half-life is 19.3 sec., which enables up to 64 independent PET scans during different

behavioural conditions in the same time period and within the same subject radiation exposure as for a standard $H_2{}^{15}O$ session. The new tracer was validated indirectly by using a well-established stimulation paradigm using an annular reversing checkerboard at stimulation reversal frequencies of 0.03 to 30 Hz. The expected second order polynomial response function in the visual cortex was found, and it is concluded that $^{10}CO_2$ is a very promising tracer for human brain mapping experiments.

Law I, Jensen M, Holm S, Nickles RJ, Paulson OB. Using $^{10}CO_2$ for single subject characterization of the stimulus frequency dependence in visual cortex - A novel PET tracer for human brain mapping. J Cereb Blood Flow Metab 2001;21:1003-12

Using Cluster Analysis to Understand Motor Learning

Daniela Balslev, MD, Ph.D.-student

In cognitive activation studies using positron emission tomography or functional magnetic resonance imaging, data are usually analyzed using the general linear model. The general linear model requires an a priori model for the variation of activity over the scans. This is particularly a problem for neuroimaging studies in which the subjects are scanned successively while learning a new task, because the variation of activity over time is difficult to predict and varies from brain region to brain region. In this study we demonstrate the use of a data-driven analytic tool, cluster analysis, which extracts representative temporal and spatial patterns from the activity 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.

Balslev D, Nielsen FÅ, 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 (in press)

Modified Motor Activation in Autosomal Dominant Pure Spastic Paraplegia (ADPSP) Using PET

Kristin Scheuer, Ph.D.-student

Functional reorganization of adult sensorimotor cortex, e.g. after spinal cord injury or limb amputation, is a well-known phenomenon. However, cortical plasticity in neurodegenerative diseases with spinal cord degradation has not previously been reported. Autosomal Dominant Pure Spastic Paraplegia (ADPSP) is such a disorder, mainly leading to progressive spasticity and weakness of the lower limbs. Symptoms are presumably due to axonal degeneration of the sensory and motor tracts of the spinal cord causing impaired

afferent and efferent neural transmission in the central nervous system. This condition is in theory capable of generating plastic changes in the cerebral cortex, thus ADPSP patients may also possess this ability. Furthermore, according to the theory of representational plasticity, we would expect to see an expansion of the cortical upper limb area and a corresponding reduction in the cortical lower limb area. To investigate this, patients and healthy controls were divided into two groups and PET-scanned during a) upper limb movement, b) lower limb movement and c) rest. Subsequently, an interaction effect of activation response and group membership was calculated to compare the difference in activation patterns between patients and healthy controls. During both tasks the patient group exhibited more widespread cortical activation compared to the control group. Significant differences were found not only in the sensorimotor cortex, but also in the cerebellum. Lower limb movements also exhibited significantly more activation in the parietal cortex. Our results suggest that motor activation is altered in ADPSP, however our hypothesis of representational plasticity is not confirmed as both lower limb and upper limb activation exhibit expansion of the activated sensorimotor cortical areas.

Scheuer KH, Nielsen JE, Krabbe K, Sørensen SA, Paulson OB, Law I. Modified motor activation in autosomal dominant pure spastic paraplegia (ADPSP) using PET. NeuroImage 2001;12:S834

5.5. FDG-PET Measurements of Brain Glucose Consumption

Quantitation of Brain Glucose Metabolism

Steen Hasselbalch, MD

Because glucose is the major energy ressource for the brain, cerebral neuronal activity is tightly coupled to cerebral glucose metabolism (CMRglc). Quantitation of CMRglc thus offers a unique possibility to study the functional activity of the brain. The study of CMRglc in vivo in humans became possible with the development of the fluorodeoxyglucose (FDG) method. FDG is a glucose analogue, which is not fully metabolized in the brain, but accumulates in brain tissue in proportion to the rate of glucose metabolism. Adding a radioactive isotope to FDG, the tracer activity in brain can be detected by positron emission tomography (PET). Since the uptake and metabolism of FDG differs from glucose, these differences are incorporated into one correction term, known as the lumped constant (LC). Thus, in order to quantitate glucose brain metabolism, knowledge of the exact value of this constant is essential.

Few studies have attempted a direct estimation of LC, and several previous studies from our group have suggested that the accepted "gold standard" for LC may be underestimated. This value stems from one single study with several methodological problems. In order to further evaluate these problems, we have replicated that study and were able to determine a LC value very close to the original value (Hasselbalch et al., 2001). However, we showed that a crucial assumption underlying this value was not met, and therefore, the method critically underestimates LC. In a second series of experiments, we used a different methodology independent of the previous erroneous assumption, and found evidence for

a resetting of LC towards a higher value. This resetting provides a physiological meaningful estimate for CMRglc determined with PET-FDG and allows for comparison of CMRglc values between different methodologies.

Since glucose is the major metabolic fuel in the brain, adequate glucose supply is essential for maintenance of cerebral energy production. For this reason, adaptation of glucose transport across the blood-brain barrier with changes in blood glucose levels has been extensively studied. Whereas data supports the notion that a sustained decrease in blood glucose induces an increase in BBB transport capacity, studies in chronic or acute hyperglycemia have shown conflicting results. In humans using the intravenous double-indicator method, we studied possible changes in BBB glucose transport during acute hyperglycemia. Furthermore, using PET-FDG we tried to elucidate whether rCMRglc is affected by marked acute elevations in blood glucose levels. We found no evidence for any adaptational changes in the transport capacity during 2 hours of acute hyperglycemia, and similarly CMRglc did not change. Our study thus indicates that in case of an excess of glucose supply, no immediate downregulation seems to take place in order to protect the brain from high glucose concentrations, which under certain circumstances may be harmful to the brain tissue.

Hasselbalch SG, Holm S, Pedersen HS, Svarer C, Knudsen GM, Madsen PL, Paulson OB. The ^{18}F-fluorodeoxyglucose lumped constant determined in human brain from extraction fractions of ^{18}F-fluorodeoxyglucose and glucose. J Cereb Blood Flow Metab 2001;21:995-1002

Hasselbalch SG, Knudsen GM, Capaldo B, Postiglione A, Paulson OB. Blood-brain barrier transport and brain metabolism of glucose during acute hyperglycemia in humans. J Clin Endocrinol Metab 2001;86:1986-90

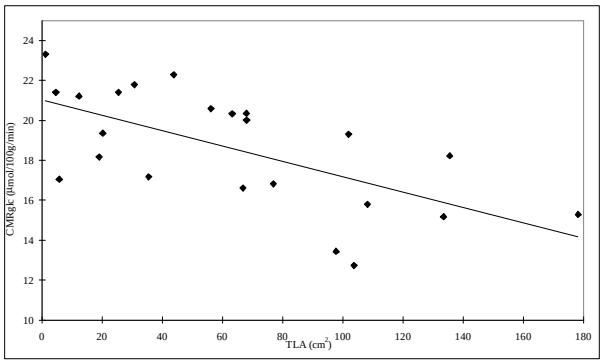
Cerebral Glucose Metabolism in Multiple Sclerosis

Morten Blinkenberg, MD

The pathological changes seen on MRI in Multiple Sclerosis (MS) consists of white matter hyperintensities on T2 weighted images. T2-MRI is often used in clinical phase III treatment trials as a secondary outcome measure, but still little is known about the clinical impact of the MS lesions.

Our two recent studies show that the T2 total lesion area (TLA) correlates to cerebral metabolic reductions seen on PET, and that both TLA and PET changes correlate to cognitive dysfunction (Blinkenberg et al). Furthermore, a population-based MRI study shows a correlation between TLA and clinical disability (Schreiber et al).

We conclude that MS lesions seen on T2-MRI have a deteriorating effect on cortical cerebral neural function, and that TLA plays an important role as a surrogate marker of disease in clinical trails.



Measurements of global cortical cerebral metabolic rate of glucose (CMRglc; mmol/100g/min) versus total MRI T2 weighted lesion area (TLA; cm2) of the MS patients (n=23). The figure is showing a significant correlation between global CMRglc and TLA (rho=-0.66; p=0.001).

Blinkenberg M, Rune K, Jensen CV, Ravnborg MH, Kyllingsbæk S, Holm S, Paulson OB, Sørensen PS. Reduceret cerebralt stofskifte korrelerer med MRI-forandringer og kognitiv dysfunktion hos patienter med dissemineret sklerose. Ugeskr Læg 2001;163:3788-92

Schreiber K, Sorensen PS, Koch-Henriksen N, Wagner A, Blinkenberg M, Svarer C, Petersen HC. Correlations of brain MRI parameters to disability in multiple sclerosis. Acta Neurol Scand 2001;104:24-30

Cerebral Glucose Metabolism in Brain Tumors

Morten Blinkenberg, MD

In this study, we evaluated treatment efficacy in patients with malignant brain tumors using tumor metabolism and size as outcome measures. Our results showed that chemotherapy, but not radiotherapy, treatment had a beneficial effect on glioblastoma. This finding, however, should be cautiously interpreted since the effect of the primary surgical treatment was not measured in this study. Furthermore, the study shows that PET is a useful secondary measure of treatment efficacy in prospective studies of patients with glioblastoma.

Andersen PB, Blinkenberg MB, Lassen U, Kosteljanetz M , Wagner A, Poulsen HS, Paulson OB. A prospective PET study of postsurgery chemotherapy and radiotherapy in patients with glioblastoma. Book of abstracts, 12th World Congress of Neurosurgery 2001

5.6. Implementation of Methods for Analysis of Brain Data

Matthew Liptrot, MSc., Peter Willendrup, MSc., and Claus Svarer, Ph.D., MSc.

The data analysis section has been involved in a number of new projects. One of them is the NCI-MCI project. In this 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. To be able to compare results from all centres a standardised and automatic way of analysing the data has to be developed. This includes methods for defining regions of interest (ROIs) within the images and methods for kinetic modelling of ROI data and image data (voxel based analysis).

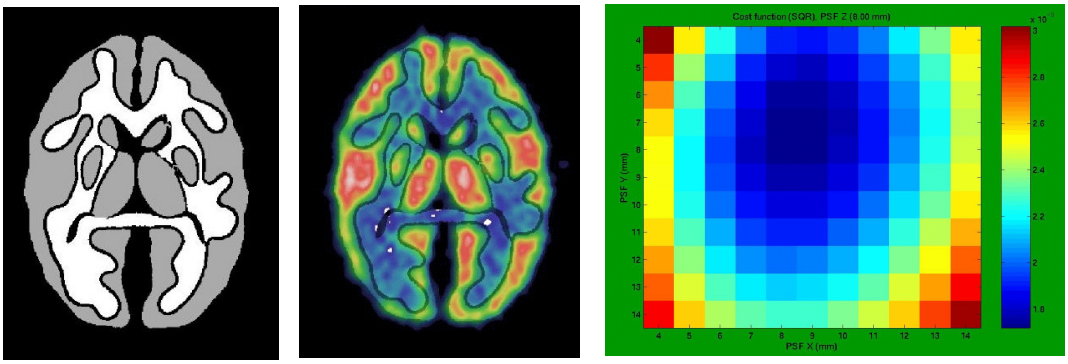
NRU are specifically involved in development of an automated method for applying a standard set of ROIs to new subjects. This method uses high resolution (< 1.5 mm.) structural MR scans for identifying co-registration parameters between the subject's own space and a standard space such as Talairach space. In the standard space a set of standard 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 will be 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.

Another project that NRU are 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. One of the essential steps in developing a method like this is to have the MR and PET/SPECT images co-registered very precisely. NRU are involved in developing and testing methods for implementing this co-registration.

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. Clustering methods are available in the Lyngby toolbox (see below).

Partial Volume Correction Combining Functional and Structural Images

A serious problem in emission tomography scans is underestimation of the real voxel values due to the limited scanner resolution – this is called the partial volume effect. A method for correcting this has been proposed and tested on real phantom data (Svarer et al). The method is based on deconvolution of the "low" resolution images using a segmented "high" resolution image.

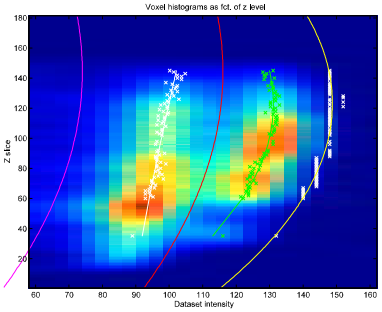


A gray-white matter segmented CT image (left panel) has been used to correct the FDG PET image (middle panel) for Partial Volume Effects. In the right panel the squared cost-function (difference between estimated and measured PET image) is shown with varying filtering in X and Y axis directions. It illustrates that it is essential to have a good estimate of the scanner PSF to be able to use this multi-modality correction method.

Svarer C, Willendrup P, Holm S, Knudsen GM. Partial volume correction of PET scans using a segmented high resolution CT or MR scan. J Nucl Med 2001; 42:5(supplement):826

Combined Inhomogeneity Correction and Tissue Segmentation

One of the basic problems in segmentation of the brain into white and grey matter is the tissue inhomogeneity change in image space. This is aggravated by the fact that white and grey matter do not necessarily change in the same way. In this abstract a simple method for handling this problem with varying contrasts is described.



The image shows voxel value histograms vs. axial slice value. The white and green curves are fitted 2nd order polynomials through max. values for gray and white matter. The other curves represent tissue class boundaries.

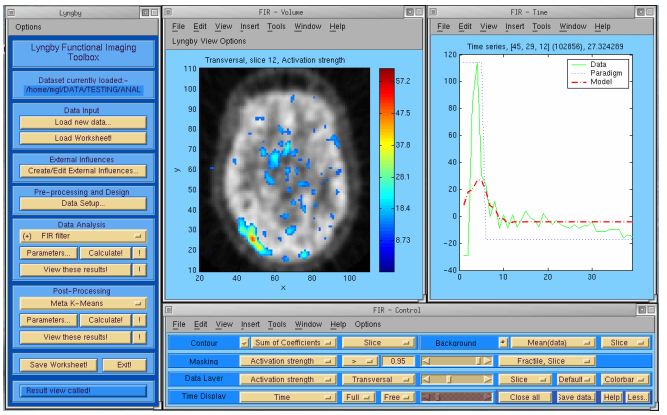
Willendrup P, Svarer C, Hanson LG, Paulson OB. A simple approach to combined inhomogeneity correction and tissue segmentation of MR MPRAGE images. BrainPET'01. J Cereb Blood Flow Metab 2001;21(suppl.1):S580

Spatio-temporal Analysis of Functional Neuroimages

In a collaboration with the Section for Signal Processing, IMM, DTU a "Modeller's Toolbox" for spatio-temporal analysis of functional neuroimages has been developed. The toolbox allows researchers to directly compare how well both simple and complicated leading-edge modelling algorithms fit the time-series data. As such, it includes many

models, such as K-Means clustering, FIR Filter, Lange-Zeger, neural networks, t-tests etc. Furthermore, it allows researchers to include their own models in the toolbox framework. The toolbox is downloadable at the internet address:

http://hendrix.imm.dtu.dk/software/lyngby/



The figure illustrates the user interface to the Lyngby toolbox in a typical analysis situation.

Hansen LK, Nielsen F, Liptrot MG, Goutte C, Strother SC, Lange N, Gade A, Rottenberg DA, Paulson OB. lyngby 2.0 -- A modeler's Matlab toolbox for spatio-temporal analysis of functional neuroimages. NeuroImage 2001;11:S917

5.7. Clinical Receptor Studies

Lars Pinborg, MD and 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 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. This project is conducted in collaboration with Swedish, Dutch, and Italian collaborators and the work was initiated at the kick-off meeting in March 2001. The objectives are to be able to establish an early diagnosis and a prognosis for the development of Alzheimer's disease. Mapping of brain receptors in normal, aged individuals, in patients with mild cognitive impairment, and in Alzheimer's disease will be compared to neuropsychological and psychiatric measures to establish the relationship between these metrics.

Huntington's Disease (HD) is a mid-life onset autosomal dominant disorder that clinically is characterized by progressive involuntary choreiform movements, cognitive decline, and emotional disturbances. From onset of HD symptoms to death there is an average life span of 15 years. The benzodiazepine receptor (BZR) is expressed on virtually all cortical and striatal neurons and on their axon terminals. This means that mapping of the BZR reflects the amount of viable neural tissue. Seven patients, mildly to moderately affected by HD,

and seven age-matched controls were studied twice using [^{123}I]iomazenil-SPECT – one with and one without infusion of flumazenil (Pinborg et al, 2001a). Flumazenil IC50 was similar in the HD group as compared to the control group. This indicates that the BZR is functionally intact in HD. For the HD group a 31% reduction in the density of striatal BZRs was found. In HD, the density of striatal BZRs correlated significantly with functional capacity and chorea-symptoms. Those HD patients clinically least affected displayed striatal BZRs density within the range of the control group.

Dysfunction of the serotonergic system is implicated in several neuropsychiatric disorders. [^{18}F]altanserin and PET have previously been used in several studies for imaging of the $5HT_{2A}$ receptor. Previous methods for quantification of [^{18}F]altanserin binding have been limited by experimental complexity. Six healthy volunteers were studied using the bolus/infusion approach and a bolus worth 1.75 hours of infusion (Pinborg et al, 2001b). [^{18}F]altanserin steady-state in brain and plasma were attained within two hours allowing for easy quantification of binding parameters. This approach is particularly feasible in a clinical setting but may also be used to measure the effect of 5HT-enhancing challenges on [^{18}F]altanserin binding in a single baseline-challenge experiment. In five healthy subjects the baseline binding parameters of [^{18}F]altanserin were studied using the bolus/infusion approach (Adams et al). After approximately 3 hours 40-60 mg of citalopram was administrated orally. The inhibition of the serotonin reuptake by citalopram resulted in an average decrease in the cortical binding of the [^{18}F]altanserin by 13%. The exact mechanism by which the increase in synaptic serotonin translates into a decrease in cortical binding of [^{18}F]altanserin is not fully understood. In addition to simple competition between [^{18}F]altanserin and serotonin, agonist-induced membrane trafficking may produce similar results.

In a study of dopamine receptors, we have demonstrated the feasibility of SPECT and ^{123}IBZM and the steady-state method for assessment of in vivo measurements of drug affinities, in this case for the D2/D3 receptorligand haloperidol (Videbæk et al). We found a nice accordance between our Kd-values and those previously obtained in vitro supporting that this method can be used for the in vivo determination of ligand affinity.

Adams KH, Pinborg LH, Svarer C, Holm S, Knudsen GM. Imaging endogenous serotonin release in humans using PET and [^{18}F]altanserin. J Cereb Blood Flow Metab 2001;21, suppl.1:S541

Pinborg LH, Videbæk C, Hasselbalch SG, Sørensen SA, Wagner A, Paulson OB, Knudsen GM. Benzodiazepine receptor quantification in Huntington's disease with [^{123}I]iomazenil and SPECT. J Neurol Neurosurg Psychiatry 2001a;70:657-61

Pinborg LH, Adams KH, Svarer C, Holm S, Martiny L, Paulson OB, Knudsen GM. Quantification of $5HT_{2A}$ receptors in the human brain using [^{18}F]altanserin-PET and the bolus infusion approach. J Cereb Blood Flow Metab 2001b;21, suppl.1:S527

Videbæk C, Toska K, Friberg L, Holm S, Angelo HR, Knudsen GM. In vivo measurement of haloperidol affinity to dopamine D2/D3 receptors by [^{123}I]IBZM and single photon emission computed tomography. J Cereb Blood Flow Metab 2001;21, suppl.1:92-7

6. Publications

Peer-review Full-length Publications

Cerebral Blood Flow and Metabolism

Blinkenberg M, Rune K, Jensen CV, Ravnborg MH, Kyllingsbæk S, Holm S, Paulson OB, Sørensen PS. Reduceret cerebralt stofskifte korrelerer med MRI-forandringer og kognitiv dysfunktion hos patienter med dissemineret sklerose. Ugeskr Læg 2001;163:3788-92

Estrup TM, Paulson OB, Strandgaard. No effect of angiotensin II AT_2 receptor antagonist PD123319 on cerebral blood flow autoregulation. JRAAS 2001;2:188-92

Gruhn N, Larsen FS, Boesgaard S, Knudsen GM, Mortensen SA, Thomsen G, Aldershvile J. Cerebral blood flow in patients with chronic heart failure before and after heart transplantation. Stroke 2001;32:2530-33

Hasselbalch SG, Holm S, Pedersen HS, Svarer C, Knudsen GM, Madsen PL, Paulson OB. The ^{18}F-fluorodeoxyglucose lumped constant determined in human brain from extraction fractions of ^{18}F-fluorodeoxyglucose and glucose. J Cereb Blood Flow Metab 2001;21:995-1002

Hasselbalch SG, Knudsen GM, Capaldo B, Postiglione A, Paulson OB. Blood-brain barrier transport and brain metabolism of glucose during acute hyperglycemia in humans. J Clin Endocrinol Metab 2001:86;1986-90

Høgh P, Knudsen GM, Kjaer KH, Jørgensen OS, Paulson OB, Waldemar G. SPECT and apolipoprotein E in Alzheimer's disease: Impact of the epsilon-4 allele on regional cerebral blood flow. J Geriatr Psychiatry Neurol 2001;14:42-51

Schreiber K, Sorensen PS, Koch-Henriksen N, Wagner A, Blinkenberg M, Svarer C, Petersen HC. Correlations of brain MRI parameters to disability in multiple sclerosis. Acta Neurol Scand 2001;104:24-30

Strauss GI, Møller K, Holm S, Sperling B, Knudsen GM, Larsen FS. Transcranial doppler sonography and internal jugular bulb saturation during hyperventilation in patients with fulminant hepatic failure. Liver Transpl 2001;7:352-8

Strauss GI, Knudsen GM, Kondrup , Møller K, Larsen FS. Cerebral metabolism of ammonia and amino acids in patients with fulminant hepatic failure. Gastroenterology 2001;121:1109-19

Strauss GI, Christiansen M, Møller K, Clemmesen JO, Larsen FS, Knudsen GM. S-100b and neuron-specific enolase as markers of cerebral dysfunction in patients with fulminant hepatic failure. Liver Transpl 2001;7:964-70

Strauss GI, Edvinsson L, Larsen FS, Møller K, Knudsen GM. Circulating levels of neuropeptides (CGRP, VIP, NPY) in patients with fulminant hepatic failure. Neuropeptides 2001;35:174-80

Sundgreen C, Larsen FS, Herzog TM, Knudsen GM, Boesgaard S, Aldershvile J. Autoregulation of cerebral blood flow in patients resuscitated from cardiac arrest. Stroke 2001;32:128-32

Brain Mapping

Law I, Jensen M, Holm S, Nickles RJ, Paulson OB. Using $^{10}CO_2$ for single subject characterization of the stimulus frequency dependence in visual cortex: A novel positron emission tomography tracer for human brain mapping. J Cereb Blood Flow Metab 2001;21:1003-12

Neuroreceptor Studies

Aznar S, Knudsen GM. Serotonin induces decrease of 5-HT_{1A} immunoreactivity in organotypic hippocampal cultures. NeuroReport 2001;12:3909-12

Elfving B, Bjørnholm B, Ebert B, Knudsen GM. Binding characteristics of selective serotonin reuptake inhibitors with relation to emission tomography studies. Synapse 2001;41:203-11

Pinborg LH, Videbæk C, Hasselbalch SG, Sørensen SA, Wagner A, Paulson OB, Knudsen GM. Benzodiazepine receptor quantification in Huntington's disease with [^{123}I]iomazenil and SPECT. J Neurol Neurosurg Psychiatry 2001;70:657-61

Videbæk C, Toska K, Friberg L, Holm S, Angelo HR, Knudsen GM. In vivo measurement of haloperidol affinity to dopamine D2/D3 receptors by [123I]IBZM and single photon emission computed tomography. J Cereb Blood Flow Metab 2001;21:92-7

Other

Bech-Azeddine R, Waldemar G, Knudsen GM, Høgh P, Bruhn P, Wildschiødtz G, Gjerris F, Paulson OB, Juhler M. Idiopatic normal-pressure hydrocephalus: evaluation and findings in a multidisciplinary memory clinic. Eur J Neurol 2001;8:601-11

Gerlach C. Structural similarity causes different category-effects depending on task characteristics. Neuropsychologia 2001;39:895-900

Textbooks and Reviews

Strandgaard S, Paulson OB. Management of hypertension with cerebrovascular disease. In: Anand MP, Billimoria AR, eds. Hypertension. An International Monograph 2001. India: IJCP Group; 2001. p. 271-3

Other (Abstracts Excluded)

Hansen ES, Knudsen GM. Tvangstanker. Helse 2001;3:14-15

Knudsen GM, Hansen ES. Tourettes syndrom. Helse 2001;3:16-17

Nørgaard K, Lind, AM, Thomsen G, Poulsen A-M, Hansen B. Bioanalytikere og laboranter på Rigshospitalet. Laboratoriebeskrivelser og udviklingsaktiviteter. Rigshospitalets symposium for bioanalytikere og laboranter; 2001. p. 1-112

Paulson OB, Bolwig TG. David H. Ingvar. 3. februar 1924-27. September 2000. Ugeskr Læger 2001;163:1293

Paulson OB, Schousboe A. Alternativ behandling - godt eller ondt? Magasin for Alzheimers og andre demenssygdomme 2001;2:14-6

Pinborg LH, Knudsen GM. Kan man måle hjernens egen frisætning af neurotransmitter? Ugeskr Laeger 2001;163:4596-7

7. Other Activities

7.1. Congress Participation

The staff of NRU has participated in 20 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

A book has been published from the Brain99 og BrainPET99 Symposia, which were organized by NRU in the Bella Center in June 1999: Gjedde A, Hansen SB, Knudsen GM, Paulson OB, eds. Physiological imaging of the brain with PET. San Diego: Academic Press 2001.

The research unit organized a Symposium at the European Winter Brain Research Conference, Arc 1800, March 2001.

7.3 Pre- and Postgraduate Teaching

In 2001 the research group organized the following courses:

Functional Imaging Techniques II: Tracer Kinetics in Nuclear Medicine and Magnetic Resonance Imaging, December 3-7, 2001 (Gitte Moos Knudsen, Henrik Larsson, Egill Rostrup, and Claus Svarer).

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 14, 2001 NRU organized a one day symposium which was announced to the public.

Pregraduate Supervision:

OSVAL1: Medical student Hans Gustav Thyregod: Cerebral blood flow and metabolism at high altitude adaptation. Supervisor: Gitte Moos Knudsen.

OSVAL1: Medical student Christian Skovgaard Nielsen: Lactate consumption of the working brain. Supervisor: Gitte Moos Knudsen.

OSVAL 2: Medical student Kristin Thygesen: The activation pattern during REM sleep dreaming. Supervisor: Ian Law.

Graduate thesis student Heidi Kristiansen: An experimental study of the 5-HT_{2A} receptor system in obsessive-compulsive disorder. Supervisor: Gitte Moos Knudsen and Susana Aznar.

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.

Cell biology project for Human Biology student Henrik Hassendam: Neuronal stem cells. Supervisor: Gitte Moos Knudsen.

Cell biology project for Human Biology student Birgitte Rahbek: The involvement of abnormal protein aggregates in neuronal degeneration. Supervisor: 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 Scientific-Ethics Committee for Copenhagen and Frederiksberg County (Gitte Moos Knudsen)

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)

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

Board Member of the World Federation of Neurology, Research Group on Dementia (Olaf B. Paulson)

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

Evaluation:

Member of the European Commission 5. Framework Programme expert panel 2001, Brussels (Olaf B. Paulson)

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

Evaluator of one Ph.D.-thesis (Olaf B. Paulson)

Evaluator of one Ph.D.-thesis and one Doctoral thesis (Gitte Moos Knudsen)

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

Evaluator for two positions as Associate Professors and for one Research Professor position at the University of Copenhagen (Gitte Moos Knudsen)

Evaluator for a position as Professor of neurology at Helsinki University (Olaf B. Paulson)

Evaluator for a position as Professor of neurology at Karolinska Institute (Olaf B. Paulson)

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

Awards:

Olaf B. Paulson: Niels A. Lassen Award 2000 (awarded on late Niels A. Lassen's 75 years birthday December 7th 2001).

Karin Stahr: Brain Imaging Council Awards, Society of Nuclear Medicine, First Place (poster): Evaluation of a metabolite assay - Quantification of ^{18}F-altanserin in human plasma.

Gerda Thomsen: Brain Imaging Council Awards, Society of Nuclear Medicine, Third Place (oral presentation): SPECT-^{123}I-β-CIT as a diagnostic tool with Parkinson's disease/Parkinson plus syndrome.

8. SPECT-Laboratory

Due to the exchange of the old SPECT-scanner with a new one, for the SPECT-laboratory 2001 has been a busy year, yet not very productive scientifically. Most commercially-available SPECT scanners today do not have optimal facilities for brain research. This necessitated us to take the difficult decision to leave out the Xenon-option for our new camera. We believe, however, that the choice of Marconi's (now Philip's) three-headed IRIX-scanner was the best compromise, for the time being. The renovation of the SPECT-facilities to ensure up-to-date laboratories that can be approved by modern standards has taken a substantial amount of time, consideration, and finances. We are happy that the new scanner is still hosted at the Dept. Neurology, since the close physical association between the patients and the scanner is needed in order to assure the important collaboration between the clinically working neurologists and the research facilities. The many decisions to be made regarding the rebuilding have kept our technologists occupied more than full-time. The old scanner, which dates back to the late 1970's, can soon be found at the Copenhagen Museum of Medical History along with a HMPAO brain image obtained the very last day before it was taken apart. In spite of its advanced age, the old scanner still contributed to the publication of four scientific papers in 2001.

The newly installed SPECT scanner at the Department of Neurology

9. Prospects

2002 will also see a number of installations and expansion. In the first week of January, the new SPECT-scanner will be delivered. A substantial amount of work needs to be done to improve the data analysis and presentation for use in both a clinical context as well as for research projects. The PET-unit at Rigshospitalet has planned a substantial expansion of their radiochemistry facilities, to be conducted in the Spring of 2002. This has been a fundamental requirement to match 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 this context, neuroscience in Copenhagen has in 2001 been greatly reinforced with the establishment of the Graduate School of Neuroscience at the Copenhagen University. This school is anticipated to become an important aid to attract young investigators along with foreign senior research associates to our area.

In the coming year we also expect that some of our recently developed data analysis tools (methods for precise co-registration of functional and structural images, methods that automate the process of extracting region-of-interest data from 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 2002, complete their term at NRU. In January, Charlotte Videbæk, MD, will defend her Doctoral thesis entitled “Single Photon Emission Computer Tomography for Neuroreceptor Studies: Methodological Considerations”. Another two Doctoral theses and a Ph.D.-thesis will be submitted during 2002.

In 2001, a strategy plan for evaluation of research conducted at Rigshospitalet was performed by Rigshospitalet’s management and Rigshospitalet’s Research Council. Among several research groups, NRU has been selected as one of two centres to undergo a thorough site-visit by foreign referees. It is anticipated that this site-visit will help us to identify strengths and weaknesses in the research unit. We have great expectations for this site-visit, which is scheduled for the Spring/Summer 2002.

Finally, we are looking forward to reinforce our collaboration both with previous and new international collaborators and with research colleagues at the Danish Technical University, the Royal Danish School of Pharmacy, the MR-department at Hvidovre Hospital, the Department of Psychology at the University of Copenhagen as well as with the neuroscience industry.

10. Acknowledgements

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

Substantial support has been given from:

Danish Medical Research Council

Danish Research Agency

The Health Insurance Foundation

The Lundbeck Foundation

The 1991 Pharmacy Foundation

Toyota-Fonden

Other public and private funds:

Bioanalytikernes Udviklings- og Forskningsfond

Danish Research Council for the Humanities

IMK Almene Fond

Kræftens Bekæmpelse

Lægeforeningens Forskningsfond

NeuroSearch

Novo Nordisk Fond/Fabrikant Vilhelm Pedersen og hustrus Mindelegat

Rigshospitalets Jubilæumsfond

Savværksejer Jeppe Juhl og hustru Ovita Juhls Mindelegat

University of Copenhagen, Faculty of Health Sciences

International research funding:

EU Biomed 2 Project

EU 5th Framework program

The Human Brain Project

11. Dansk resumé

2001 har for Neurobiologisk Forskningsenhed på flere måder været et år, hvor der er sket udvidelser. Flere nye samarbejdsprojekter er påbegyndt, såvel nationalt som internationalt, og der er også blevet mulighed for en udskiftning af forskningsenhedens godt 20 år gamle SPECT-skanner.

Nationalt er der startet et samarbejde med NeuroSearch omkring kvantificering af kolokalisation af forskellige receptorer og hjernecelletyper. Af internationale samarbejdsprojekter er der netop etableret aftale om samarbejde med det finske firma MAP Medical samt en anden aftale med forskergrupper i Taiwan, begge vedrørende undersøgelser af nye SPECT-ligander til visualisering af hjernens receptorsystemer. Yderligere er et projekt vedrørende patienter med 'mild cognitive impairment', støttet af EUs 5. rammeprogram, blevet startet i løbet af foråret. Her deltager PET- og SPECT-centre fra Sverige, Holland og Italien i en 'concerted action', der har til formål at undersøge patienter med hukommelsesforstyrrelser for mulige forstyrrelser i forskellige receptorsystemer.

Nedtagningen af den godt 20 år gamle SPECT-skanner, som har medvirket til produktionen af over 150 publikationer og 7 doktordisputatser var betimelig og samtidig lidt vedmodig. Professor Niels A. Lassen var blandt pionererne på dette område, og det var ikke mindst takket være hans indsats, at denne skanner, der som een af de første dedikerede hjerneskannere i verden, blev et vigtigt instrument i hjerneforskning. Nu venter den gamle skanner, der lige til den sidste dag producerede kliniske skanninger, på at blive overført til Medicinsk-Historisk Museum. En omfattende modernisering af SPECT-skannerrummet på neurologisk afdeling er afsluttet, og den nye skanner forventes nu installeret først i det nye år. Dette har kun været muliggjort pga. en generøs donation fra Forskningsstyrelsen og Toyota-Fonden. Vi har store forventninger til, at den ny skanner vil kunne medvirke til megen og væsentlig hjerneforskning inden for de kommende år. Også i PET-enheden under klinisk-fysiologisk og nuklearmedicinsk afdeling har året været præget af installationen af den ny PET-CT skanner, som kunne indvies midt i december. Udvidelsen er et velkomment bidrag til forskningsmulighederne, også for NRU. Alt i alt har de to ombygninger imidlertid betydet, at flere projekter har ligget stille i op til seks måneder. Vi forventer dog, at forsinkelserne kan indhentes i løbet af det kommende år.

Igen i år har mange fonde bidraget til, at forskningsaktiviteterne har kunnet 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 2001, skal særligt fremhæves Forskningsstyrelsens og NeuroSearch innovations post doc-stipendium til Ph.D. Susana Aznar samt Rigshospitalets tildeling af en klinisk assistent-stilling til cand.med. Daniela Balslev. Statens Sundhedsvidenskabelige

Forskningsråd har desuden bevilget en 3-årig rammebevilling til neuroreceptorforskning. Det er desuden særligt glædeligt, at en stigende antal specialestuderende inden for bla. humanbiologi har fundet interesse i at gennemføre deres afsluttende speciale i NRU's laboratorier. Et vellykket rekrutteringsmøde, der i september afholdtes for læge-studerende, medførte endvidere, at forskergruppen også på denne måde kunne bidrage til forskerrekruttering blandt de unge kommende læger.

Publiceringsmæssigt har NRU siden 1997 haft en støt stigende produktion. I år er det særligt en række tidligere projekter inden for hjernens blodcirkulation og stofskifte, der har kunne afsluttes. Dette har bl.a. drejet sig om undersøgelser af patienter med dissemineret sklerose, Alzheimers sygdom, Huntingtons sygdom samt lever- eller hjertesvigt. Der er også et stigende antal publikationer inden for hjernens receptor-systemer, herunder de første fra forskningsgruppens eksperimentelle laboratorium.

Vi ser nu frem mod et nyt år. Også 2002 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 samarbejdspartnerne til NRU, og da de trange forhold i radiokemilaboratoriet reelt har været begrænsende for udviklingsmulighederne. Vi kan endvidere se frem til at en (måske flere?) af NRU's mangeårige medarbejdere vil forsvare disputatsafhandling.

NRU staff December 2001