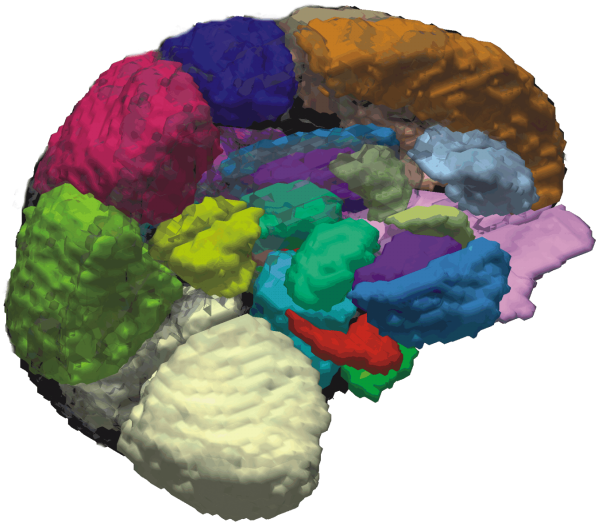
Annual Report 2005

Neurobiology Research Unit



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

www.nru.dk

Front page:
A 3D reconstruction of an automatic volume of interest brain template. Svarer et al., NeuroImage, 2005.

Preface

This annual report provides an overview of the scientific and organizational activities that took place at the Neurobiology Research Unit (NRU) in 2005.

Steen G. Hasselbalch, MD, was appointed as Associate Professor at the Faculty of Health Sciences to continue as part time scientist at the NRU and part time as consultant at the H:S Memory Disorder Clinic. A PhD thesis entitled 'Proprioception - an obstacle for motor control in conditions with a visuoproprioceptive conflict' was defended by MD Daniela Balslev. Daniela will continue to be associated to research projects in NRU and DRCMR at Hvidovre Hospital.

In September, Gitte Moos Knudsen signed a contract with the Lundbeck Foundation to establish a Neuroscience Center of Excellence where NRU is one amongst several other partners. The Lundbeck Foundation has - based on an international review process - decided to fund the establishment of the research center *Center for Integrated Molecular Brain Imaging* (Cimbi). The research in Cimbi focuses on the neural bases of personality dimensions that predispose individuals to affective and substance use disorders, with special emphasis on the serotonergic neurotransmitter system. Both PET and MRI are employed in studies of human subjects, and these are complemented with relevant studies using animal models. Advanced informatics techniques, new tracer compounds, and novel serotonergic challenge paradigms are also being developed within the center. The establishment of Cimbi was supported by the management of Rigshospitalet in different ways. Apart from co-financing the center, Rigshospitalet has also decided to allocate the entire building 92 for Cimbi/NRU activities. As these lines are written renovations of the old villa are undertaken to accommodate new Cimbi employees.

With the establishment of Cimbi we have decided that this NRU annual report will be the last of its kind. From now on, most NRU activities can be regarded as an integrated part of the combined Cimbi efforts, and an annual Cimbi report will be made available.

As in the previous annual reports, the NRU publications are described in separate sections within this report. We hope that you will enjoy reading the Year 2005 Annual Report!

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

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. With the establishment of Cimbi, the Director of Rigshospitalet has decided to allocate additional facilities for the center. That is, during 2006 the entire building 92 will be made available for Cimbi and NRU.

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

The NRU experimental laboratory resides in Building 93, Juliane Maries Vej 20, just opposite Building 92. The ground floor of Building 93 is shared with the 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. During 2006, NRU will take over the facilities from the Neuroimmunology Laboratory. The latter is now preparing to move to a larger laboratory location on the Rigshospitalet campus.

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

2. Objectives, Organization, and Staff

NRU has its main interest within neurotransmission brain research, with particular focus on neuroreceptor imaging. Traditionally, the research unit has also been involved with studies of cerebral blood flow and metabolism and functional brain mapping. As for the latter, most of these studies are now carried out at the Danish Research Centre for Magnetic Resonance (DRCMR), Hvidovre University Hospital. Finally, image analysis and tracer kinetics remain issues that receive high attention within the unit.
The research group is chaired by Professor Gitte Moos Knudsen. Professor Olaf B. Paulson, who since 1995 also has chaired the DRCMR at Hvidovre Hospital, Chief Engineer Claus Svarer, PhD, and Associate Professor Steen Hasselbalch are partners in the NRU steering group. The Chief Technologist is Gerda Thomsen.

In 2005 the research staff consisted of:

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

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

Junior Researchers:
Rasmus Lohals Larsen, Biologist
Michael Palner, Engineer
Jan Tønnesen, Biologist

Associated Researchers:
Lars Hageman Pinborg, MD

Students:
Bjarni Bödvarsson, engineer student
Ellen Christensen, medical student
Ruben Christensen, biology student
Carl Forsmark, engineer student
Louise Legaard, engineer student
Martin Mørkebjerg, engineer student
Rune Nielsen, psychology student
Morten Skøtt Thomsen, human biol.student
Helle Tolstrup, biology student
Anders Torp, physicist student
Sanne Wulff, medical student
Morten Ziebell, medical student

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

Research Assistants:
Haroon M. Arfan
Mads Haar
Allan Lyckegaard

Secretaries:
Pia Farup
Dorthe Givard

* shared with another research group

Guest Researchers:
Per Hartvig, Adj. Professor, Department of Analytical Pharmaceutical Chemistry, University of Uppsala, Sweden
Michael Pedersen, MD, PhD-student, Department of Epidemiology, Rigshospitalet
Maurizio Severino, MD, Neuroscience Department, 'Federico II', Naples, Italy

3. Collaborators in 2005

Copenhagen Brain Research Center, CBRC
www.cbrc.dk
CBRC consists of a multidisciplinary collaboration among institutes and departments in the Copenhagen area working with brain related research. These institutions include:

- Department of Medical Chemistry, The Danish University of Pharmaceutical Sciences
- H. Lundbeck A/S, Copenhagen
- Danish Research Center for Magnetic Resonance, Hvidovre Hospital
- The PET and Cyclotron Unit, Rigshospitalet
- Informatics and Mathematical Modelling, Technical University of Denmark
- Neurobiology Research Unit, Rigshospitalet
- Department of Psychology, Faculty of Humanities, University of Copenhagen

The center currently has 15 PhD-students engaged with supervisors from at least two different partners.

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

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

Development of New Radiotracers for the in-vivo Assessment of Biological Functions and Drug Interactions (COST).

Collaborators within COST, workgroup 1: Radioligands for Brain Receptors.

PET-centres in Orsay, Villigen-PSI, Jülich, Stockholm, London (Hammersmith), Turku, Kuopio, Uppsala, Brussels, Aarhus.

EU 6th Framework Program

DiMI - Diagnostic Molecular Imaging (LSHB-CT-2005-512146)

The goal of the Network of Excellence "Diagnostic Molecular Imaging" (DiMI) - Molecular Imaging for Diagnostic Purposes - is to integrate multidisciplinary research for the development of new probes and multimodal non-invasive imaging technology for early diagnosis, assessment of disease progression and treatment evaluation.

The general objectives of DiMI are to coordinate and efficiently integrate more than 50 research groups from various disciplines to study non-invasively gene expression and function in major diseases such as neurodegeneration, stroke, heart failure, atherosclerosis and autoimmune diseases.

For further information, please visit www.dimi-net.org.

NRU is training platform for image and data analyses for DiMI partners.

European Network of Excellence for Brain Imaging under the umbrella of the EANM

SPECT Centers from Italy, Germany, Belgium, Netherlands, Austria, Denmark, United Kingdom, France, and Spain.

Others

Department of Medical Biochemistry & Genetics (IMBG), University of Copenhagen
Erik Lykke Mortensen, Dept. of Health Psychology, Copenhagen University
Glaxo SmithKline Beecham, London, UK
H. Lundbeck A/S
Language Section, National Institutes of Health, Bethesda, Maryland, USA
Mannheim Central Mental Institute, University of Heidelberg
MAP Medical, Helsinki, Finland
NeuroSearch A/S
Philips Medical Systems

4. Doctoral and PhD Theses

Proprioception - an obstacle for motor control in conditions with a visuoproprioceptive conflict

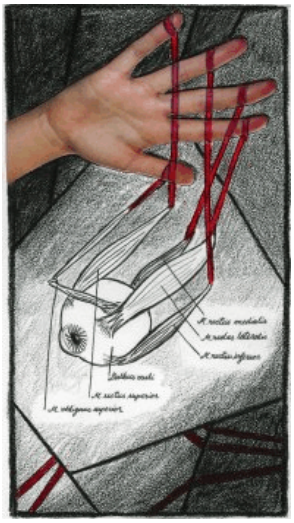
Daniela Balslev, MD, PhD

This PhD dissertation is an overview of the findings presented in three papers. The topic of these papers is the contribution of proprioception to motor control in conditions when vision and proprioception transmit incompatible information about the direction in which the hand has moved. Spatial misalignment of visual and proprioceptive spaces occurs for instance whenever a surgeon who performs a laparoscopic intervention adjusts the direction of view of the video camera.

The methods used in the experiments are: 1Hz-repetitive transcranial magnetic stimulation, functional magnetic resonance imaging and analysis of error rate/reaction time.

The results suggest that:

- Proprioception is an obstacle for trajectory control in conditions with a spatial conflict between vision and proprioception.
- Spatially incompatible proprioception slows down visual processing.
- Anterior parietal 1Hz-repetitive transcranial magnetic stimulation (rTMS) is an easy and safe method for acute proprioceptive deafferentation that can be applied to investigate the contribution of proprioception to motor control.



Spatial visual localization and proprioception normally fuse. In conditions with a visuoproprioceptive conflict proprioception may be an obstacle for motor control.

The thesis was accepted for evaluation at the Faculty of Health Sciences, Copenhagen University. The defence took place on September 12, 2005, at Rigshospitalet, Auditorium 93. The evaluators were Prof. Yves Rossetti, INSERM & Hôpital Henry Gabrielle, Lyon, France; Prof. Thomas Sinkjær, Center for Sensorimotor Interaction, Aalborg University; Prof. Jens Bo Nielsen, Department of Medical Physiology, Faculty of Health Sciences , University of Copenhagen. The PhD-project was completed with MD, PhD Ian Law and Professor, DMSc Olaf B. Paulson as supervisors.

The thesis can be downloaded from:

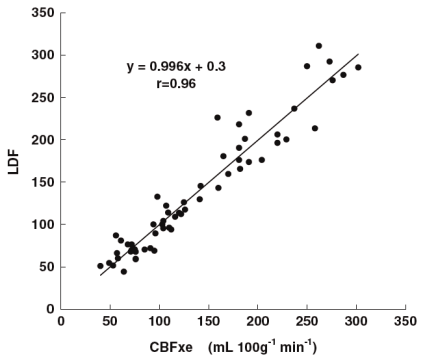
http://nru.dk/people/daniela/BalslevD2005Phd.pdf

5. Research Topics

5.1 Cerebral Blood Flow Autoregulation: Experimental Studies

Laser Doppler flowmetry is valid for measurements of cerebral autoregulation

Laser Doppler flowmetry (LDF) is a recent technique that is increasingly being used to monitor relative changes in cerebral blood flow whereas the intra-arterial ^{133}xenon injection technique is a well-established method for repeated absolute measurements of cerebral blood flow. The latter technique has been used for determination of cerebral blood flow autoregulation in a number of previous publications arising from the NRU laboratory. In this study we evaluated LDF for assessment of cerebral autoregulation and CO_2 reactivity with the ^{133}xenon injection technique as the gold standard. Simultaneous measurements of cerebral blood flow (CBF) were collected by LDF (CBF_{LDF}) and the ^{133}xenon method (CBF_{Xe}) while (1) cerebral autoregulation was challenged by controlled systemic haemorrhage, or (2) cerebral blood flow was varied by manipulating the arterial partial pressure of CO_2 ($P_{a,CO2}$). LDF slightly overestimated CBF under conditions of haemorrhagic shock and haemodilution caused by controlled haemorrhage. However, for pooled data, the autoregulation lower limit was similar when determined with the ^{133}xenon and the LDF techniques: 65 +/- 3.9 mmHg and 60 +/- 5.6 mmHg, respectively. Even for substantial changes in $P_{a,CO2}$, the two methods resulted in similar results. We conclude that even though LDF overestimated CBF during haemorrhagic shock caused by controlled haemorrhage, the lower limit autoregulation was correctly identified. The laser Doppler technique provides a reliable method for detection of a wide range of cerebral blood flow changes under CO_2 challenge. Haemodilution influences the two methods differently causing relative overestimation of blood flow by the laser Doppler technique compared to the ^{133}xenon method.

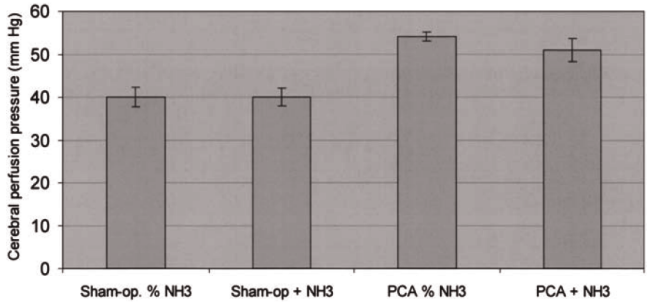


The correlation between CBF_{Xe} and CBF_{LDF} was found to be strong when varying $P_{a,CO2}$ between 25 and 70 mmHg. No significant difference could be demonstrated between the two groups (paired *t* test, $P > 0.05$). In total 66 data pairs were obtained from six rats. LDF values were given relative to xenon baeline measurements

Tønnesen J, Pryds A, Larsen EH, Paulson OB, Hauerberg J, Knudsen GM. Laser Doppler flowmetry is valid for measurement of cerebral blood flow autoregulation lower limit in rats. J Exp Physiol 2005;90:349-55.

Shunting of portal blood shifts lower limit of autoregulation to higher values

Portacaval shunting of blood, hyperammonemia, and impaired cerebral blood flow (CBF) autoregulation are assumed to be involved in the development of high intracranial pressure (ICP) in liver failure. In this study, we investigated CBF autoregulation in pentobarbital-sedated and mechanically ventilated rats after construction of a portacaval anastomosis or following sham operation. Half of the rats received either infusion of ammonia or saline for 3 hours. The lower limit of CBF autoregulation was preserved in all four groups of studied animals: sham-operated rats, sham rats receiving ammonia infusion, portacaval anastomosis-vehicle animals, and portacaval anastomosis-hyperammonemia animals. The lower limit of autoregulation was higher in portacaval anastomosis rats ($p = 0.01$) compared to the sham- operated rats. Hyperammonemia in portacaval anastomosis rats did not aggravate this. Portacaval anastomosis and hyperammonemia does not impair the lower limit of CBF autoregulation. However, shunting of portal blood to the systemic circulation shifts the lower limit of autoregulation to higher blood pressure values, making the brain more sensitive to episodes of arterial hypotension.



Lower limit of autoregulation in each group

Dethloff T, Knudsen GM, Hansen BA, Larsen FS. Effects of porta-systemic shunting and ammonia infusion on cerebral blood flow autoregulation in the rat. Neurocrit Care 2005;3(1):86-90.

Newborn rats have preserved CBF autoregulation

Perinatal brain injury has been associated with impaired CBF autoregulation. We investigated CBF autoregulation in Wistar 3 to 5-d old pups during normocapnia and hypercapnia. Hypotension was induced by hemorrhage and cerebral perfusion was monitored with LDF and near-infrared spectroscopy (NIRS). During normocapnia, the autoregulatory plateau was narrow. Resting systolic blood pressure was 39.2 mm Hg and CBF remained constant until blood pressure decreased below 36.0 mm Hg. Below the lower limit, CBF declined by a mean of 2.7% per mm Hg, and hemoglobin difference (HbD) and total hemoglobin (HbT) changed proportionally to CBF. After inhalation of carbon dioxide, CBF increased significantly by a mean of 17.7%. The CBF-CO_2 reactivity was estimated to 13.4% per kPa, $p=0.026$. Over the range of blood pressure 6-54 mm Hg, a

linear relationship between CBF and blood pressure was found during hypercapnia, indicating abolished pressure autoregulation. A linear correlation between CBF and HbD was found (r=0.80). CBF pressure autoregulation and reactivity to CO_2 operate in the newborn rat. This model may be useful for future investigations related to perinatal pathophysiology.

Pryds A, Tonnesen J, Knudsen GM, Greisen G. Cerebral autoregulation in a rat pup model. Pediatr Res. 2005;57:294-8.

5.2 Cerebral Blood Flow and Metabolism: Experimental Studies

Ketone body infusion increases CBF without any concomitant metabolic changes

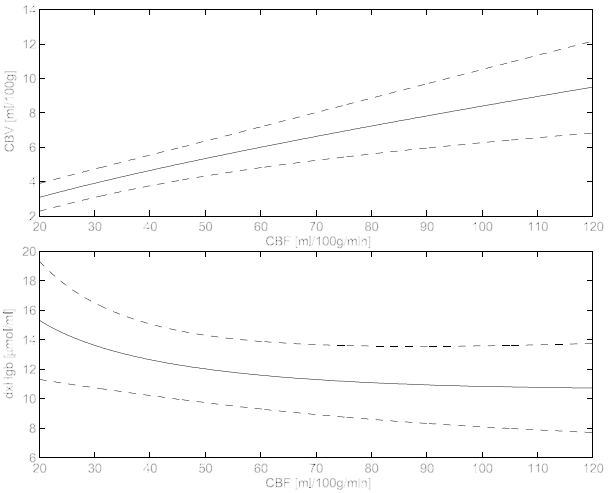
In the humans, acute increase in the concentration of ketone bodies by infusion of beta-hydroxybutyrate increases the cerebral blood flow (CBF) without affecting the overall cerebral metabolic activity. The mechanism mediating the effect of ketone bodies resetting the relation between CBF and cerebral metabolism is unknown. To study this phenomenon further, we measured global CBF and global cerebral metabolism with the Kety-Schmidt technique in the awake rat before and during infusion of ketone bodies. During acute hyperketonemia (average concentration of beta-hydroxybutyrate: 6 mmol/L), global CBF increased 65% and the cerebral metabolic rates for both oxygen and glucose remained constant. This resetting of the relation between CBF and cerebral metabolism could not be explained by alterations in blood pH or arterial CO_2 tension. Cerebral intracellular pH as measured by ^{31}P nuclear magnetic resonance spectroscopy revealed that brain pH also was unchanged during acute hyperketonemia. These observations indicate that the mechanism responsible for the increase in CBF operated through is a direct effect on the cerebral endothelium rather than via metabolic interactions.

Linde R, Hasselbalch SG, Topp S, Paulson OB, Madsen PL. Global cerebral blood flow and metabolism during acute hyperketonemia in the awake and anesthetized rat. J Cereb Blood Flow Metab, in press.

5.3 Cerebral Blood Flow and Metabolism: Clinical Studies

The relationship between cerebral blood flow and volume in humans

In this study we established the relationship between regional CBF and CBV at normal cerebral metabolic rates. Measurements of rCBF and rCBV were obtained using PET and ^{15}O-labelled water and carbon monoxide, respectively. At baseline conditions, the mean value of rCBF was 62 ± 18 ml 100 g^{-1} min^{-1}; hypercapnia lead to an average rCBF increase of 46% whereas hypocapnia was assoicated with a decrease of 29%. At baseline rCBV was 7.7 ml 100 g^{-1}, with 27% increase during hypercapnia and no significant decrease during hypocapnia. The presence of a uniform exponential relationship between $PaCO_2$ and rCBF as well as rCBV was found. The results of the study are applied to a numerical estimation of regional brain deoxy-haemoglobin content. Independently of the choice of model for the rCBV vs. rCBF relationship, a nonlinear deoxy-haemoglobin vs. rCBF relationship was predicted. Our findings have implications for the BOLD response in fMRI.



Estimated rCBV (ml 100 g^{-1}, upper panel) and deoxy-haemoglobin (tissue content, µmol ml^{-1}, lower panel) vs. rCBF (ml 100 g^{-1} min^{-1}) based on the power function model of the rCBV-rCBF relationship. The solid lines show the mean curves of nine subjects, and dotted lines show ±2 times the standard error of the mean. As seen in the figure, the rCBV-rCBF relationship is near-linear, whereas the deoxy-haemoglobin was found to be nonlinear regardless of the model used for rCBV-rCBF relationship.

Rostrup E, Knudsen GM, Law I, Holm S, Larsson HBW, Paulson OB. The relationship between cerebral blood flow and volume in humans. Neuroimage 2005;24:1-11.

Lack of insight in own memory dysfunction is associated with CBF reduction in the right inferior frontal lobe

Lack of insight of cognitive and functional deficits (anosognosia) is a striking symptom among many neurological patients and in Alzheimer's disease (AD) impaired awareness is a common symptom, even in the earliest stages. Although influential theories have suggested that the prefrontal cortex (and frontal connectivity) plays an important role in anosognosia, many studies have failed to establish a correlation between frontal dysfunction and anosognosia.

In the present study, anosognosia was correlated to behavioural symptoms, performance on frontal cognitive (executive) tests, and frontal cortex regional cerebral blood flow (rCBF) in patients with mild Alzheimer's disease (AD, n=36) and 'amnestic mild cognitive impairment' (MCI, representing prodromal AD, n=30). Patients were recruited from a prospective Memory Clinic cohort. Anosognosia was assessed using a categorical scale and discrepancy scores between patients' and relatives' reports on a 20-item Memory Questionnaire (MQ). Tc99m-HMPAO SPECT was obtained in an unselected sample of 55 of the 66 patients, and rCBF was analysed in six cortical frontal regions.

Insight was equally impaired in AD and MCI patients. A significant correlation was found between impaired awareness and dementia severity (MMSE). Discrepancy-scores on the MQ were significantly correlated to scores on FBI (Frontal Behavioural Inventory) and to rCBF in the right inferior frontal gyrus, but not to executive function. The groups classified by the categorical ratings 'full', 'shallow' and 'no' awareness were not characterized by differences in behavioural symptoms, executive performance or frontal

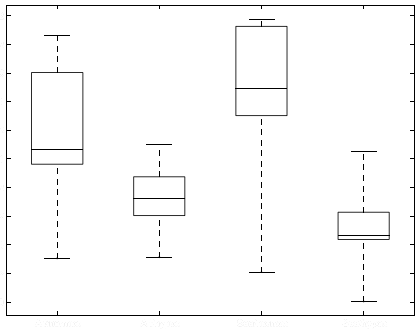
rCBF. It was concluded that impaired awareness was associated with behavioural symptoms and may reflect functional impairment in the right inferior frontal cortex.

Vogel A, Hasselbalch SG, Gade A, Ziebell M, Waldemar G. Cognitive and functional neuroimaging correlates for anosognosia in Mild Cognitive Impairment and Alzheimer's disease. Int J Geriatr Psychiatry 2005;20:238-46.

5.4 Functional Brain Activation

Hypoxia diminishes the BOLD response

Acute normobaric or longstanding hypobaric hypoxia induce pronounced physiological changes potentially leading to impairment of cerebral function. We investigated the effect of hypoxia both on the cerebral activation response and on structural changes as measured by diffusion weighted imaging. Eleven healthy sea-level residents were studied after 5 weeks of adaptation to high altitude conditions at Chacaltaya, Bolivia (5260 m). The subjects were studied immediately after return to sea-level in hypoxic and normoxic conditions, and the examinations repeated 6 months later after re-adaptation to sea-level conditions. The BOLD response was severely reduced during acute hypoxia both in the altitude and sea-level adapted states (50% reduction during an average S_aO_2 of 75%). On average, the BOLD response magnitude was 23% lower in altitude than sea-level adaptation in the normoxic condition, but in the hypoxic condition, no significant differences were found. A small but statistically significant decrease in the apparent diffusion coefficient (ADC) was seen in some brain regions during acute hypoxia, whereas ADC was slightly elevated in high altitude as compared to sea-level adaptation. It is concluded that hypoxia significantly diminishes the BOLD response, and the mechanisms underlying this finding may involve both CBF increase and of the deoxyhemoglobin level. Furthermore, altitude adaptation may influence both the magnitude of the activation-related response, as well as micro-structural features.

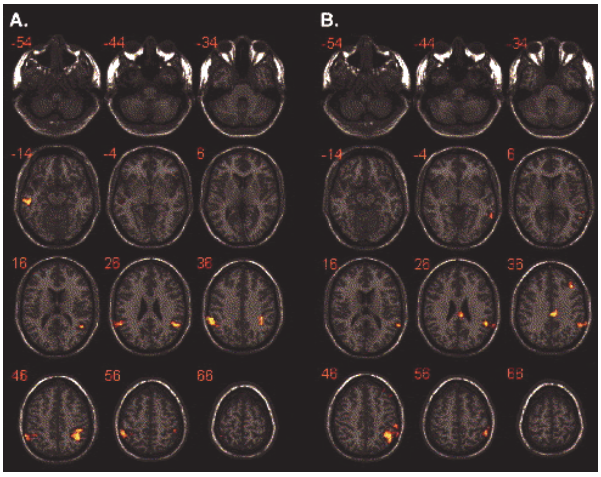


Magnitude of BOLD response (see text for ROI definition) during conditions of altitude adaptation (Alt), and sea-level adaptation (Sea), as well as normoxia and hypoxia. Box and whiskers show the median, the interquartile and full range of the data.

Rostrup E, Larsson HBW, Born AP, Knudsen GM, Paulson OB. Changes in BOLD and ADC weighted imaging in acute hypoxia during sea-level and altitude adapted states. Neuroimage 2005;28:947-55.

Similar brain networks for recognition of visual feedback during active and passive movement

The ability to recognize feedback from own movement as opposed to the movement of someone else is important for motor control and social interaction. The neural processes involved in feedback recognition are incompletely understood. Two competing hypotheses have been proposed: the stimulus is compared with either (a) the proprioceptive feedback or with (b) the motor command (efferent copy) and if they match, then the external stimulus is identified as feedback. Hypothesis (a) predicts that the neural mechanisms or brain areas involved in distinguishing self from other during passive and active movement are similar, whereas hypothesis (b) predicts that they are different. In this fMRI study, healthy subjects saw visual cursor movement that was either synchronous or asynchronous with their active or passive finger movements. The aim was to identify the brain areas where the neural activity depended on whether the visual stimulus was feedback from own movement and to contrast the functional activation maps for active and passive movement. We found activity increases in the right temporoparietal cortex in the condition with asynchronous relative to synchronous visual feedback from both active and passive movements. However, no statistically significant difference was found between these sets of activated areas when the active and passive movement conditions were compared. With a posterior probability of 0.95, no brain voxel had a contrast effect above 0.11% of the whole-brain mean signal. These results do not support the hypothesis that recognition of visual feedback during active and passive movement relies on different brain areas.

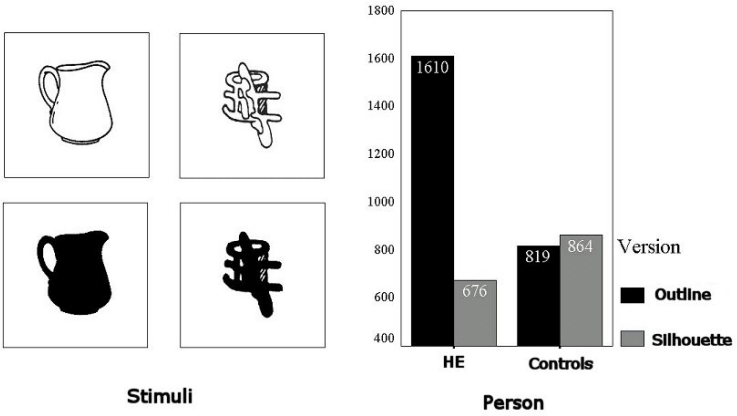


Clusters of voxels showing significant activity increase in the asynchronous compared with the synchronous condition. (A) Active conditions (Aa–As). (B) Passive conditions (Pa–Ps). The statistical parametric maps are thresholded at cluster-level $P < 0.001$, corrected (voxel-$P < 0.001$, uncorrected, extent threshold = 0) and superposed on single-subject anatomical template for the purpose of anatomical localization. The figure shows the vertical coordinate of the brain slice in the MNI space (red numbers). The left side of the brain is shown to the left.

Balslev D, Nielsen FÅ, Lund TE, Law I, Paulson OB. Similar brain networks for detecting visuo-motor and visuo-proprioceptive synchrony. Neuroimage, in press.

Visual perception of shape configuration and category-specificity

When we recognize objects, we do it by creating a visual representation based on the information that is available on our retinas. This visual representation can then be matched with visual representations stored in our visual long-term memory. The ease with which we achieve this belies the complexity of the operations that allow us to do so. How does the visual system decide which pieces of information belong together (represent the same object)?, how are local details coded with respect to the global outlay?, and so on. While we cannot answer any of these questions satisfactorily today, we are beginning to solve the puzzle. In 2005 we have reported two studies which shed some light on these issues. In the first study (Gerlach, Marstrand, Habekost, and Gade, 2005) we present an in-depth case study of the patient HE who was left with a remarkably selective impairment in visual shape integration following an infarct in the right occipito-temporal region. To illustrate the problems experienced by HE one can take a look at the figures presented below.



Left panel: Examples of the stimuli used. The subjects' task was to decide whether the drawings depicted real objects or non-objects. Right panel. The mean reaction times (in milliseconds) to outline drawings and silhouette drawings for HE and two control subjects. As can be seen, HE is slower than the normal subjects to recognize outline drawings but faster to recognize silhouette drawings.

Usually, normal subjects finds it easier to recognize outline drawings of objects than silhouette versions of the same drawings. As can be seen, the reverse is true for HE. HE is faster at recognizing silhouettes and actually faster than the normal control subjects. The reason for this is that HE, due to HE's shape integration deficit, gets confused when there are many local details in the visual display (as is the case for outline drawings compared with silhouettes). HE is probably the most pure case yet reported with a shape integration deficit and the pureness of HE's impairment has allowed us examine many interesting questions regarding the operations that underlie shape integration. One of the more controversial questions we have addressed is whether shape integration is important for the recognition of single objects at all? We prove this to be the case.

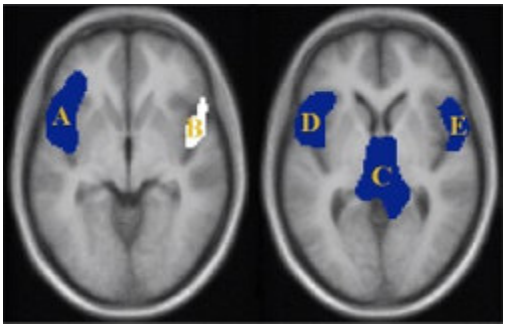
This also helps explain why we in our second study (Gerlach, Law, and Paulson, in press), which is based on functional imaging, have not been able to find areas more activated during recognition of outline drawings compared with fragmented versions of the same drawings, even though fragmented drawings were more difficult to recognize: the

explanation being that both recognition of outline drawings and fragmented drawings require that shape integration take place. We did, however, find that subjects took longer to identify fragmented drawings of artefacts (tables, chairs etc.) than fragmented drawings of natural objects (animals, plants etc.) whereas the reverse effect was found for outline drawings. This interaction between category (artefacts vs. natural objects) and stimulus type (outlines vs. fragmented forms) is actually what we predicted based on our refined account of category-specific processing that we published last year (Gerlach, Law, and Paulson, Neuropsychologia 2004;42:1543-53).

Gerlach C, Law I, and Paulson OB. Shape configuration and category-specificity. Neuropsychologia, in press.
Gerlach C, Marstrand L, Habekost T, and Gade A. A case of impaired shape integration: Implications for models of visual object processing. Visual Cognition 2005;12:1409-43.

Subtle supraspinal degeneration is present in hereditary spastic paraplegia gene 4

The spastic gait gene 4 (SPG4) linked Hereditary Spastic Paraplegia (SPG4 HSP) is a rare neurodegenerative disorder mainly characterised by slowly progressive spasticity and weakness of the lower limbs. So far treatment regiments merely consist of alleviating measures, and as age at onset and severity of symptoms are highly variable, patients are left with uncertain prognoses of expected rate of progression and end stage disability level. Neuropathologically, degenerative changes mainly reside in the ascending and descending tracts of the spinal cord, however in some cases, cerebral neuronal degeneration and cognitive deficits have been reported. The present study was therefore undertaken to ascertain the extent of cerebral involvement in SPG4 linked HSP by measurements of rCBF during rest using the ^{15}O-labelled water bolus technique, and by neuropsychological assessment.



Significantly (blue) (A,C,D,E), and sub-significantly (white) (B) relatively reduced rCBF. Left panel: all patients ($T > 2.44$ and $k > 490$ voxels). Right panel: the highly disabled patients only ($T > 2.60$ and $k < 2900$ voxels). PET clusters are projected on to an average T1-weighted MRI image of all 36 subjects.

Eighteen SPG4 patients and 18 matched control subjects were studied. Relative differences in rCBF were explored with SPM 99, and neuropsychological assessment was performed using the RH Basic Battery. Results showed, that compared to healthy controls, SPG4 patients had a significantly decreased rCBF in the left fronto-temporal cortex ($P < 0.05$), and in the most disabled individuals even more comprehensive changes were

observed. In contrast, neuropsychological deficits were limited to impaired recognition memory for faces. In conclusion, these results substantiates the hypothesis of subtle supraspinal degeneration in SPG4 HSP, however, major manifest cognitive deficits was not confirmed.

Scheuer KH, Nielsen JE, Krabbe K, Simonsen C, Koefoed P, Sørensen SA, Gade A, Paulson OB, Law I. Reduced regional cerebral blood flow in SPG4-linked hereditary spastic paraplegia. J Neurol Sci. 2005 Aug 15;235(1-2):23-32.

In succession of the previous PET study, we continued by exploring functional motor cortical reorganisation in SPG4 linked hereditary spastic paraplegia by investigating the motor cortical activation response during movements of the clinically affected (lower) and unaffected (upper) limb. Thirteen patients and 13 controls were included. They all underwent ^{15}O-labelled water positron emission tomography during 1) right ankle flexion-extension, 2) right shoulder flexion-extension and 3) rest. Within group comparisons of movement versus rest (simple main effects) and between groups comparisons of movement versus rest (group - behavioural state interaction) were performed using a random effects approach and statistical parametric mapping (SPM99). Results showed that patterns of motor activation generally were comparable between both groups during both tasks. Still, statistically significant differences were found in the ankle movement response as where patients showed significantly larger increase in regional cerebral blood flow in the right and left primary motor cortices, the supplementary motor areas, and the right premotor cortex compared to controls. This result could indicate some degree of functional motor cortical reorganisation in the patient group, however as no significant differences were recognised in the motor response of the unaffected limb, differences in functional demands should also be considered.

Scheuer KH, Nielsen JE, Krabbe K, Paulson OB, Law I. Motor Activation in SPG4-linked hereditary spastic paraplegia. J Neurol Sci., in press.

Multi-slice echo-planar spectroscopic MR imaging in multiple sclerosis

MR spectroscopy (MRS) provides information about neuronal loss or dysfunction by measuring decreases in N-acetyl aspartate (NAA), a metabolite widely believed to be a marker of neuronal viability. In multiple sclerosis (MS), whole-brain NAA has been suggested as a marker of disease progression and treatment efficacy in treatment trials, and the ability to measure NAA loss in specific brain regions early in the evolution of this disease may have prognostic value. Multi-slice echo-planar spectroscopic imaging is presented as a promising alternative to singlevoxel or nonlocalized spectroscopy for obtaining global metabolite estimates in MS. In the same session, measurements of metabolites in specific brain areas chosen after image acquisition (e.g., normal-appearing white matter, gray matter, and lesions) can be obtained. The reproducibility of the technique makes it a promising tool for future longitudinal spectroscopic studies of MS.

Mathiesen HK, Tscherning T, Sorensen PS, Larsson HBW, Rostrup E, Paulson OB, Hanson LG. Multi-slice echo-planar spectroscopic MR imaging provides both global and local metabolite measures in multiple sclerosis. Magn Reson Med 2005;53:750-9.

Brain volumes assessed with in vivo MR imaging compares well to volumes determined stereologically

The object of the present study was to compare stereological estimates of brain volumes obtained in vivo by magnetic resonance imaging (MRI) to corresponding volumes from physical sections in vitro. The volumes of different brain compartments were obtained from MR images by two observers and from physical sections using the Cavalieri estimator in combination with point counting. Paired t tests revealed no significant differences between the two methods for any of the five compartments considered, except for the basal gray compartment. A statistical highly significant difference of 11–41% was observed between observers for volume estimates of all compartments considered. The study demonstrates that quantitative MRI is susceptible to observer dependent interpretation of images.

Jelsing J, Rostrup E, Markenroth K, Paulson OB, Gundersen HJG, Hemmingsen R, Pakkenberg B. Assessment of in vivo MR imaging compared to physical sections in vitro - A quantitative study of brain volumes using stereology. NeuroImage 2005;26:57-65.

Decline in intelligence is associated with progression in white matter hyperintensity volume

From a Danish cohort of 698 people born in 1914, 26 were investigated in order to quantify the time course of white matter hyperintensities (WMH) and assess the association between progression and cognitive decline in non-demented octogenarians. The investigation included neuropsychological assessment (Wechsler adult intelligence scale) initiated at age 50 and cerebral magnetic resonance imaging (MRI) at the 80 and 85 year. WMH volumes were quantified and partial correlations were calculated between WMH volume change and decline in WAIS scores from 80 to 85. Progression in WMH volume ranged from 0 ml to 20.7 ml, providing a median increase of 2.6 ml (range 0.1 to 20.7, p,0.001) and, with a mean time interval between scans of 3.8 years, a rate of progression was calculated to 0.63 (0 to 6.8) ml/year. Increase in WMH volume was correlated with a simultaneous decline in verbal IQ ($r=20.65$, $p=0.001$), while baseline WMH was associated with subsequent decline in performance subtests (digit symbol, $r=20.57$, $p=0.02$). In conclusions the association between WMH and decline in essential cognitive abilities even in well preserved elderly people suggests that WMH should be regarded as a risk factor for cognitive impairment and dementia.

Garde E, Mortensen EL, Rostrup E, Paulson OB. Decline in intelligence is associated with progression in white matter hyperintensity volume. J Neurol Neurosurg Psychiatry 2005;76:1289-91.

5.5 Cerebral Neuroreceptors: Radiosynthesis and Experimental Studies

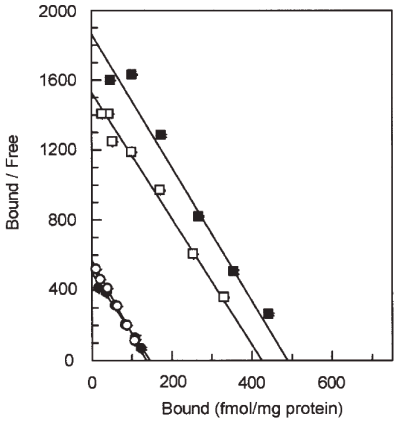
Development of D2 agonists for PET imaging

Development of D2 agonist PET tracers are of particular interest since it will allow for reliable in vivo imaging of endogenous dopamine release. From codeine, four different 2-aryl substituted apomorphines were synthesised in 6 steps each. Oxidation of codeine with IBX followed by acid catalysed rearrangement gave morphothebaine, which was selectively triflylated at the 2-position and subsequently O-acetylated at the 11-position. The resulting triflate was coupled in a Suzuki-Miyaura type reaction with a series of 4-substituted arylboronic esters which, after deprotection, gave the desired 2-aryl apomorphines. The analogues were tested for affinity towards a range of dopaminergic, serotonergic and adrenergic receptors. 2-(4-Hydroxyphenyl)-apomorphine exhibited high affinity for the dopamine D2 receptor. Subsequent radiolabeling will be done to test the compounds suitability as PET-ligand for the D2-receptor site.

Søndergaard K, Kristensen JL, Palner M, Gillings N, Knudsen GM, Roth BL, Begtrup M. Synthesis and binding studies of 2-arylapomorphines. Org Biomol Chem 2005;3(22):4077-81.

Altanserin and MDL possess similar $5HT_{2A}$ binding characteristics

For the study of the 5-HT_{2A} receptors in the living human brain with PET, two selective radiotracers are currently in use: ^{18}F-altanserin and ^{11}C-MDL 100907. It is, however, currently unknown to what extent data obtained with either tracer are directly comparable. The aim of this study was to compare binding characteristics of these two radiotracers in rat brain with respect to affinity (K_d, receptor binding density (B_{max}), binding potential (BP), and nonspecific binding. Further, binding kinetics, sensitivity towards competition with the endogenous transmitter serotonin, and the competitive/noncompetitive interaction between the two radioligands as evaluated. In addition, the selectivity of ^{18}F-altanserin for the 5-HT_{2A} receptor was assessed. The K_d value of ^{18}F-altanserin and ^{3}H-MDL 100907 was in the order of 0.3 nM. B_{max} in frontal cortex was 523 and 527 fmol/mg protein, respectively. The binding of ^{18}F-altanserin was not influenced by blocking either the 5-$HT_{2B/2C}$ or the α_1-adrenergic receptors. Both ligands displayed similar association and dissociation constants. Both radioligands were displaced by 5-HT at very high concentrations; the K_i value of 5-HT ranging between 650 and 3,300 nM. This indicates that binding of both radioligands in PET studies is not directly influenced by changes in endogenous 5-HT. Overall, the binding of ^{18}F-altanserin and ^{3}H-MDL 100907 to the 5-HT_{2A} receptor was very comparable, showing selective high affinity binding in the subnanomolar range.

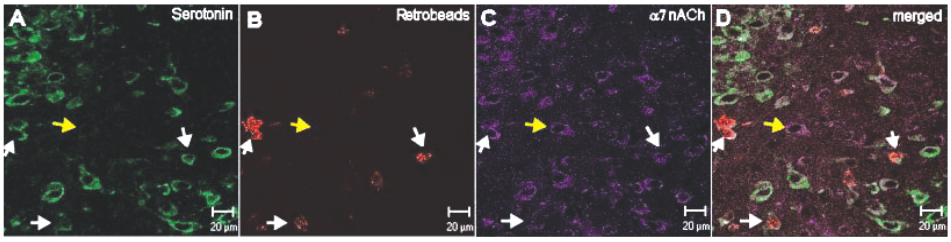


Scatchard transformation of saturation binding data for [^{18}F]altanserin (closed) and [3H]MDL 100907 (open) in cerebrum (circle) and frontal cortex (square) at 37˚C. Each point represents the mean of at least three independent experiments

Kristiansen H, Elfving B, Plenge P, Pinborg LH, Gillings N, Knudsen GM. Binding characteristics of the 5-HT2A receptor antagonists altanserin and MDL100907. Synapse 2005 Dec 15;58(4):249-57.

Serotonin neurons projecting to hippocampus and septum contain the α7 subunit

Studying the different levels of interaction between the serotonergic and other neurotransmitter systems is of great relevance for better understanding how the serotonergic system is involved in diseases where other neurotransmitter systems are the primarily systems affected, such as in Alzheimer's disease, characterized by dysfunction in the cholinergic system. Specially the alpha-7 nicotinic acetylcholine receptor has been in focus in relation to Alzheimer's disease, since the betaamyloid peptide, one of the hallmarks of the neuropathology behind this disease, binds with high affinity to this receptor. We have shown that the alpha-7 receptors are located onto serotonergic neurons projecting to hippocampus, one of the main areas involved in memory processing and regions early affected in Alzheimer's disease (Aznar et al. 2005).



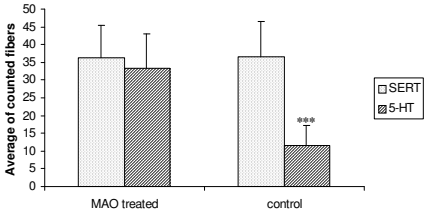
Serotonin-positive (A) Retrobeads-filled (B) dorsal raphe neurons projecting to medial septum are immunopositive for the α7 nicotinic receptor subunit (C), as shown in D (white arrows). Colocalization between serotonin and α7 receptor are observed in A and C (white arrows). The yellow arrow points to a non-serotonergic α7-positive neuron. Scale bars = 20 µm

Aznar S, Kostova V, Christiansen SH, Knudsen GM. Serotonin neurons projecting to hippocampus and septum contain the α7 subunit. Synapse 2005;55:196-200.

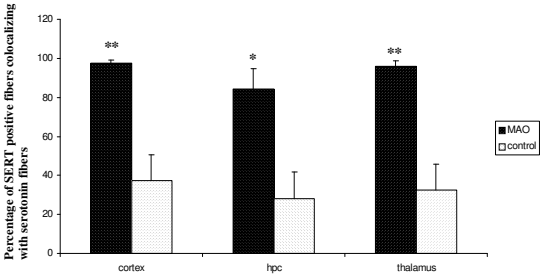
Immunodetection of the serotonin transporter

We investigated whether immunodetection for serotonin is a valid marker for intact serotonergic fibers. This was done by studying the degree of colocalization between serotonin and serotonin transporter immunopositivity in animals, where serotonin degradation was blocked by monoaminase inhibitors, and in untreated animals. The results showed that immunodetection of serotonin positive fibers is very dependent on serotonin levels present in the fibers, and that serotonin immunodetection is rather a marker for serotonin content and turnover rate than of intact serotonergic fibers (Nielsen et al. , in press).

We also investigated genetic differences in the serotonergic system in two inbred rat models of depression: congenital learned helplessness rats and the Flinders Sensitive Line rats. With the help of stereological techniques we looked for differences in number and density of serotonin and serotonin transporter positive fibers. An age related faster decline of serotonin positive fibers was found in the Flinders Sensitive Line rats as compared with the Flinders Resistant Line, the first one being characterized as being more vulnerable to depression. This work was done in collaboration with the Laboratory of Neuropsychiatry, Rigshospitalet (Husum et al. 2005).



Average of number of counted serotonin and SERT positive fibers for all regions in MAO treated and control rats. There is no difference in total number of SERT positive fibers in MAO-inhibitor treated vs. nontreated rats. By contrast, a significant difference ($P < 2.2 \times 10^{-10}$) was found in the number of serotonin positive fibers, indicating the presence of a higher number of serotonin positive fibers after MAO-inbibitor treatment. Error bars represent SEM.



Colocalization between SERT and serotonin positive fibers in cortex, hippocampus, and thalamus of MAO-inbibitor treated and untreated rats. The percentage of SERT positive fibers colocalizing with serotonin positive fibers was significantly higher, reaching almost 100%, in cortex ($P < 0.01$), hippocampus ($P < 0.05$), and thalamus ($P < 0.01$) in MAO-inhibitor treated rats when compared with untreated control rats. Error bars represent SEM.

Nielsen K, Brask D, Knudsen GM, Aznar S. Immunodetection of the serotonin transporter protein is a more valid marker for serotonergic fibers than serotonin. Synapse, in press.

Husum H, Aznar S, Høyer-Hansen S, Hald Larsen M, Mikkelsen J, Math A, Wortwein G. Exacerbated aging-related loss of neurogenesisi NPY-positive cells and 5-HT-immunoreactive fibers in the hippocampus of the Flinders-Sensitive Line ""depressed"" rat. Implications to the pathophysiology of depression in adult and aged individual. S Program No. 92.15. 2005 Abstract Viewer/Itinerary Planner. Washington, DC: Society for Neuroscience, 2005. Online.

Serotonin depletion results in a decrease of the neuronal activation caused by Rivastigmine

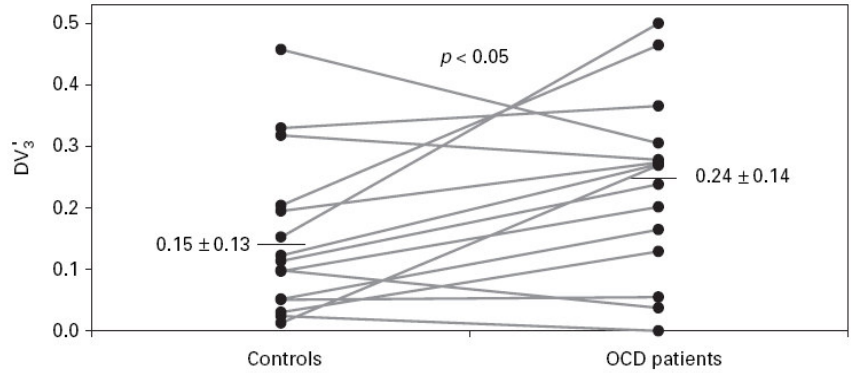
From a functional level we have investigated how serotonin depletion affects cholinergic mediated neuronal activation. We hypothesized that regulation of serotonin release in the hippocampus, and thereby hippocampal activity, is partly mediated through activation of alpha-7 nicotinic acetylcholine receptors located on serotonergic terminals. In that case, depletion of serotonin would substantially affect hippocampal neuronal activation. We confirmed that serotonin depletion specifically affects hippocampal neuronal activation resulting through a general increase in cholinergic tone (Kornum et al. 2006).

Kornum BR, Weikop P, Møller A, Rønn LCB, Knudsen GM, Aznar S. Serotonin depletion results in a decrease of the neuronal activation caused by Rivastigmine in the rat hippocampus. Brain Research, in press.

5.6 Cerebral Neuroreceptors: Clinical Studies

Frontal lobe function and 5-HT_{2A} receptor binding in patients with obsessive-compulsive disorder

Obsessive-compulsive disorder (OCD) is a devastating psychiatric disorder where the patients experience various obsessions. It is likely that patients with OCD have alterations in their cerebral serotonergic (5-HT) receptor system, and previous neuroimaging studies of OCD patients have shown abnormalities in several fronto-subcortical regions. We investigated 15 OCD patients and 17 control subjects and tested frontal lobe functions [Wisconsin Card Sorting Test (WCST) and tests of fluency], a smell identification test and one computerized test: the Intra/Extra Dimension test. The Intra/Extra Dimension test showed a significant difference between the two groups in reversal of response. The test of Figural fluency showed a significant difference between the two groups in numbers of produced figures. In addition, we investigated cerebral 5-HT_{2A} receptor binding by[^{18}F]altanserin PET and MRI. Eleven of the patients were rescanned with PET after receiving treatment with a selective serotonin reuptake inhibitor (SSRI). The distribution volumes of specific tracer binding (BP_1) were calculated for 12 brain regions and significantly higher values were recorded in the caudate nuclei in OCD patients (BP_1: 0.24 ± 0.14) compared to the healthy control group (BP_1: 0.15 ± 0.13). This difference between groups was not present after treatment with SSRIs. There was no correlation between the severity of OCD symptoms and 5-HT_{2A} receptor binding. The up-regulation in 5-HT_{2A} receptors might be compensatory for a lack of serotonin in the feedback loop between the thalamus and orbito-frontal cortex, the caudate nuclei, and the globus pallidus.

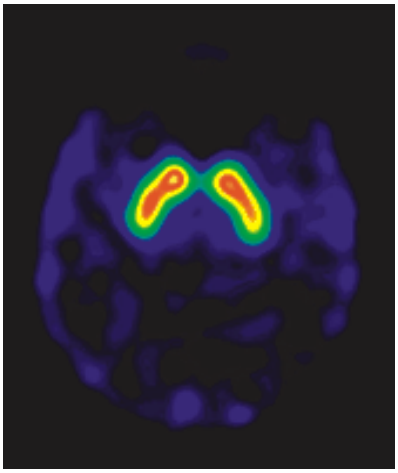


Distribution volume (DV_3') for the caudate nuclei in controls and untreated OCD patients (n=15). The mean DV_3' value for the controls is 0.15±0.13 (S.D.) and the mean DV_3' value for the OCD patients is 0.24±0.14 (S.D:). p<0.05 indicates that the DV_3' for the caudate nuclei is significantly higher than in OCD patients when compared to healthy volunteers.

Fenger MM, Gade A, Adams KH, Hansen ES, Bolwig TG, Knudsen GM. Cognitive deficits in obsessive-compulsive disorder on tests of frontal lobe functions. Nord J Psychiatry 2005;59:39-44.
Adams KH, Hansen ES, Pinborg LH, Hasselbalch SG, Svarer C, Holm S, Bolwig TG, Knudsen GM. Patients with obsessive-compulsive disorder have increased 5-HT2A receptor binding in the caudate nuclei. Int J Neuropsychopharmacol 2005;8:391-401

Quantification of dopamine transporters with ^{123}I-PE2I SPECT after bolus and bolus/infusion

An accurate and precise method for quantification of in vivo brain dopamine transporter binding with ^{123}I-PE2I and SPECT was examined in healthy subjects that were studied twice. In the first experiment, dynamic SPECT data and arterial plasma input curves obtained after ^{123}I-PE2I bolus injection were assessed using Logan, kinetic, transient equilibrium, and peak equilibrium analyses. Accurate and precise determination of binding potentials was achieved using Logan analysis and kinetic analysis, with a total study time of 90 min. In the second experiment, ^{123}I-PE2I was administrated as a combined bolus and constant infusion with the bolus being equivalent to 2.7 h of constant infusion. Steady state was attained in brain and plasma within 2 h, and time-activity curves remained constant for another 2 h. Even when an average bolus-to-infusion ratio was used, the striatal BP_1 and BP_2 values calculated with kinetic analysis (BP1 = 21.1 ± 1.1; BP_2 = 4.1 ± 0.4) did not significantly differ from those calculated with bolus/infusion analysis (BP_1 = 21.0 ± 1.2; BP_2 = 4.3 ± 0.3). We find that the bolus/infusion approach allows accurate and precise quantification of ^{123}I-PE2I binding to dopamine transporter and the approach has been implemented in our clinical setting.



123I-PE2I SPECT image obtained from 2 to 3 h after tracer injection in healthy subject

Pinborg LH, Ziebell M, Frokjaer VG, de Nijs R, Svarer C, Haugbol S, Yndgaard S, Knudsen GM. Quantification of 123I-PE2I binding to dopamine transporter with SPECT after bolus and bolus/infusion. J Nucl Med 2005;46:1119-27.

5.7 Methods for Brain Data Analysis

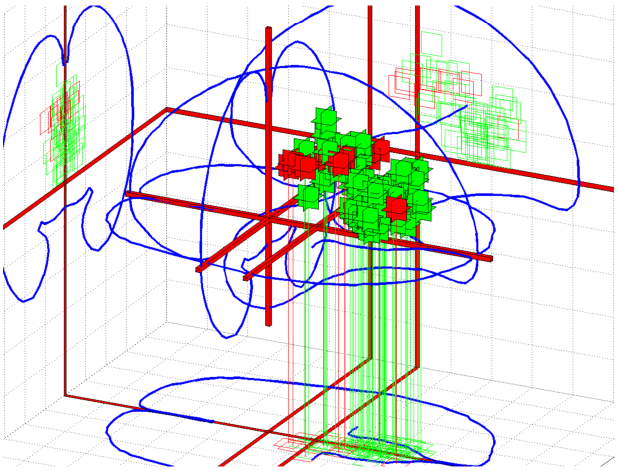
The data analysis section is involved in projects regarding optimization of the use of a Marconi/Philips SPECT scanner for clinical and research purposes. With our in house developed reconstruction code it is possible to reconstruct from the scanner exported raw projection images, apply uniform attenuation correction and subtract images from different energy windows. The reconstruction code is capable of handling multiple frame (dynamic) data. In 2005 a method was developed to correct a third energy window, a so-called scatter or Compton window, below the imaging window for high energy. In this way it is possible to apply the well-known dual energy window scatter correction for isotopes with high energy photons. The dual energy window scatter correction is preferable for low count dynamic SPECT-studies to the more noise sensitive triple energy window scatter correction, which does not need high energy correction.

A tool for subtracting SPECT images has been developed. Before subtraction the images need to be appropriately scaled to each other. The scaling is performed by the published z-map method or alternatively by an iterative method. With this tool ictal and interictal images can be subtracted after alignment for easier identification of epileptic foci.

Resolution and noise often limit the utility of PET and SPECT. Improving these imaging techniques is an ongoing effort at NRU. At the most fundamental level, NRU has developed a reconstruction technique that is applicable to all SPECT and PET scans. The method allows advanced scanner models (including e.g. attenuation and beam divergence) and incorporation of anatomical information derived from MR scans. At the same time it

maintains similarity with the well-known method FBP (Filtered Back-Projection) available on all current scanners.
The reconstruction is based on BBTools, a Matlab toolbox designed to handle certain large-scale problems in linear algebra. The first version was made public in 2004, and in 2005 it matured to the point where the parameters of a 2D SPECT-reconstruction can be specified, reconstructed, displayed, and reviewed in real-time on commodity computers. The package can be freely downloaded http://nru.dk/software/bbtools.
Within the EU 5th framework program an automatic method for delineating volumes of interests (VOI's) at functional SPECT and PET scans using structural MR images has been developed at NRU and implemented in several European centres. This method will now be extended and tested for clinical use in order to automatically apply VOI's and extract regional values from SPECT scans using functional scans only.
Neuroinformatics techniques are used for extraction information about neuroreceptor studies. In this work, the Brede Database and the Brede Toolbox will be further extended (http://hendrix.imm.dtu.dk/services/jerne/brede/) for subsequent use in neuroimaging meta-analyses.
This year NRU joined a Network of Excellence Program within EU's 6th framework program, DiMI (http://dimi-net.org). NRU will be responsible for the so-called TTP7 (Training Platform 7: Image analysis and Kinetic Modeling). The first PhD course "Basic Kinetic Modeling" will be given in February 2006 and a second one is scheduled for July 2006 where a faculty of international experts will be teaching.

Mining the posterior cingulate: segregation between memory and pain components
Neuroscience information increases at rapid rate making it more difficult for the neuroscientist to keep track of recent advances and to get an overview of present knowledge. A project aimed at developing computer-based methods for data mining neuroscience information. These methods were aimed at a specific brain structure, the posterior cingulate gyrus, and a specific subfield of neuroscience, neuroimaging: Scientific abstracts about posterior cingulate gyrus and neuroimaging were downloaded from the American web-service Entrez-PubMed. Features from the texts were extracted and the abstracts were automatically classified into groups based on these features using a multivariate analysis technique known as non-negative matrix factorization. This grouping showed that memory, Alzheimer's Disease and pain were often occurring topics in scientific studies where the posterior cingulate gyrus was involved. Subsequently, the full scientific articles associated with the most representative abstracts in each group were examined. If the full text mentioned 3-dimensional coordinates reported with respect to a standard brain space then these were extracted. Such coordinates would typically represents focal brain activation. Statistical tests were made on the coordinates with the coordinates grouped according to the classification of the abstracts. The test showed that memory and pain coordinates tended to be separately distribution within the posterior cingulate gyrus.



Three-dimensional visualization of local brain-changes in the posterior cingulate area plotted as colored glyphs. The glyphs are extracted from scientific articles stored in a neuroscience database, and coloring of the glyph is based on the group they belong to, after grouping of the scientific articles with multivariate analysis.

Nielsen FA, Balslev D, Hansen LK. Mining the posterior cingulate: segregation between memory and pain components. Neuroimage 2005;27(3):520-32.

The development and evaluation of an observer independent approach for automatic generation of volume-of-interest (VOI) brain templates in emission tomography studies of the brain has been developed. A VOI probability map is created on the basis of a database of several subjects' MR-images where VOIs have been manually delineated. The figure below illustrates the principles of the method.
High-resolution structural MR-images and 5-HT_{2A} receptor binding PET-images (in terms of ^{18}F-altanserin binding) from 10 healthy volunteers and 10 patients with mild cognitive impairment were included for the analysis. A template including 35 VOIs was manually delineated on the subjects' MR images. Through a warping algorithm template VOI sets defined from each individual were transferred to the other subjects MR-images and the voxel overlap was compared to the VOI set specifically drawn for that particular individual. Comparisons were also made for the VOI templates 5-HT_{2A} receptor binding values. It was shown that when the generated VOI set is based on more than one template VOI set, delineation of VOIs is more reproducible as compared to transfer of a single set of template VOIs as well as manual delineation of the VOI set. The approach was also shown to work equally well in individuals with pronounced cerebral atrophy. Probability-map-based automatic delineation of VOIs is a fast, objective, reproducible, and safe way to assess regional brain values from PET or SPECT scans. In addition, the method applies well in elderly subjects, even in the presence of pronounced cerebral atrophy.

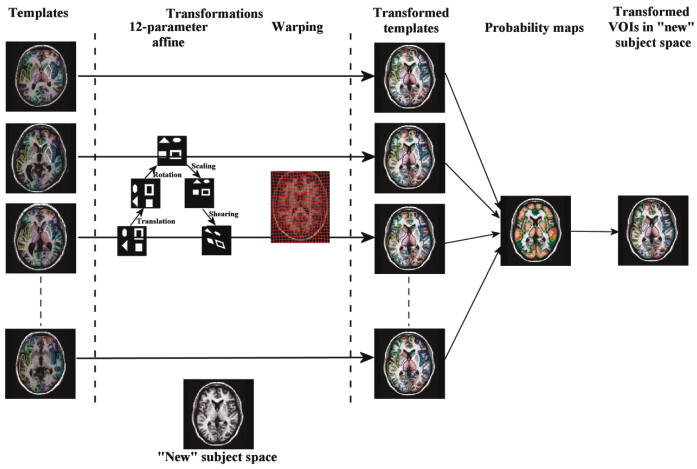


Illustration of the automatic method for delineation of volumes of interest in the space for a “new” subject. Structural images are used for estimation of the transformations and the resulting transformation parameters are subsequently used to transform VOI’s to the “new” subjects functional image.

Svarer C, Madsen K, Hasselbalch SG, Pinborg LH, Haugbol S, Frokjaer VG, Holm S, Paulson OB, Knudsen GM. MR-based automatic delineation of volumes of interest in human brain PET images using probability maps. Neuroimage 2005;24(4):969-79.

6. Publications

Peer-review Full-length Publications

Cerebral Blood Flow and Metabolism

Dethloff T, Knudsen GM, Hansen BA, Larsen FS. Effects of porta-systemic shunting and ammonia infusion on cerebral blood flow autoregulation in the rat. Neurocrit Care 2005;3(1):86-90.

Pryds A, Tonnesen J, Knudsen GM, Greisen G. Cerebral autoregulation in a rat pup model. Pediatr Res. 2005;57:294-8.

Rostrup E, Knudsen GM, Law I, Holm S, Larsson HB, Paulson OB. The relationship between cerebral blood flow and volume in humans. Neuroimage 2005;24:1-11

Rostrup E, Larsson HBW, Born AP, Knudsen GM, Paulson OB. Changes in BOLD and ADC weighted imaging in acute hypoxia during sea-level and altitude adapted states. Neuroimage 2005;28:947-55.

Tønnesen J, Pryds A, Larsen EH, Paulson OB, Hauerberg J, Knudsen GM. Laser Doppler flowmetry is valid for measurement of cerebral blood flow autoregulation lower limit in rats. J Exp Physiol 2005;90:349-55.

Vogel A, Hasselbalch SG, Gade A, Ziebell M, Waldemar G. Cognitive and functional neuroimaging correlates for anosognosia in Mild Cognitive Impairment and Alzheimer's disease. Int J Geriatr Psychiatry 2005;20:238-46.

Brain Mapping

Balslev D, Nielsen FÅ, Paulson OB, Law I. Right temporoparietal cortex activation during visuo-proprioceptive conflict. Cereb Cortex 2005;15:166-9.

Garde E, Lykke Mortensen E, Rostrup E, Paulson OB. Decline in intelligence is associated with progression in white matter hyperintensity volume. J Neurol Neurosurg Psychiatry 2005;76:1289-91.

Gerlach C, Marstrand L, Habekost T, Gade A. A case of impaired shape integration: Implications for models of visual object processing. Visual Cognition 2005;12(8):1409-43.

Jelsing J, Rostrup E, Markenroth K, Paulson OB, Gundersen HJG, Hemmingsen R, Pakkenberg B. Assessment of in vivo MR imaging compared to physical sections in vitro - A quantitative study of brain volumes using stereology. NeuroImage 2005;26:57-65.

Mathiesen HK, Tscherning T, Sorensen PS, Larsson HBW, Rostrup E, Paulson OB, Hanson LG. Multi-slice echo-planar spectroscopic MR imaging provides both global and local metabolite measures in multiple sclerosis. Magn Reson Med 2005;53:750-9.

Nielsen FÅ, Balslev D, Hansen LK. Mining the posterior cingulate: Segregation between memory and pain components. Neuroimage 2005;27:520-32.

Scheuer KH, Nielsen JE, Krabbe K, Simonsen C, Koefoed P, Sorensen SA, Gade A, Paulson OB, Law I. Reduced regional cerebral blood flow in SPG4-linked hereditary spastic paraplegia. J Neurol Sci 2005;15;235:23-32.

Neuroreceptor Studies

Adams KH, Hansen ES, Pinborg LH, Hasselbalch SG, Svarer C, Holm S, Bolwig TG, Knudsen GM. Patients with obsessive-compulsive disorder have increased 5-HT2A receptor binding in the caudate nuclei. Int J Neuropsychopharmacol 2005;8:391-401

Aznar S, Kostova V, Christiansen SH, Knudsen GM. Alpha7 nicotinic receptor subunit is present on serotonin neurons projecting to hippocampus and septum. Synapse 2005;55(3):196-200

Fenger MM, Gade A, Adams KH, Hansen ES, Bolwig TG, Knudsen GM. Cognitive deficits in obsessive-compulsive disorder on tests of frontal lobe functions. Nord J Psychiatry 2005;59:39-44.

Haugbol SR, Ebert B, Ulrichsen J. Upregulation of glutamate receptor subtypes during alcohol withdrawal in rats. Alcohol Alcohol 2005 Mar-Apr;40(2):89-95

Kristiansen H, Elfving B, Plenge P, Pinborg LH, Gillings N, Knudsen GM. Binding characteristics of the 5-HT2A receptor antagonists altanserin and MDL100907. Synapse 2005 Dec 15;58(4):249-57.

Pinborg LH, Ziebell M, Frokjaer VG, de Nijs R, Svarer C, Haugbol S, Yndgaard S, Knudsen GM. Quantification of 123I-PE2I binding to dopamine transporter with SPECT after bolus and bolus/infusion. J Nucl Med 2005;46:1119-27.

Svarer C, Madsen K, Hasselbalch SG, Pinborg LH, Haugbøl S, Frøkjær VG, Holm S, Paulson OB, Knudsen GM. MR-based automatic delineation of volumes of interest in human brain PET-images using probability maps. NeuroImage 2005;24:969-79

Søndergaard K, Kristensen JL, Palner M, Gillings N, Knudsen GM, Roth BL, Begtrup M. Synthesis and binding studies of 2-arylapomorphines. Org Biomol Chem 2005;3(22):4077-81.

Textbooks and Reviews

Knudsen GM, Paulson OB, Petersen P. Neurologiske sygdomme. I: Hansen NE, Haunsø S, de Muckadell OBS, eds. Medicinsk Kompendiums Lommebog, 3. udgave. København: Nyt Nordisk Forlag Arnold Busck A/S, 2005:526-68

7. Other Activities

7.1 Congress Participation

The staff of NRU has participated in 21 international and national meetings and congresses related to their research fields. Staff members have participated as evaluators of abstracts and as chairmen at scientific sessions.

7.2 Congress Organizing

Gitte Moos Knudsen: Organizer of Symposium at the Annual Congress of the European Association of Nuclear Medicine: 'Mild Cognitive Impairment', October 2005.

7.3 Pre- and Postgraduate Teaching

PhD-course: 'Kinetics and Modelling with particular emphasis on imaging', February 28-March 4, 2005.
PhD-course under the auspices of Graduate School of Neuroscience, University of Copenhagen: 'Multimodal Brain Imaging', October 25-26, 2005.
NRU organizes every other week seminars open to the public within the areas of NRU research interests. The meetings are announced on the homepage http://nru.dk/meetings/FIG.
On December 16, 2005, 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 Jenny Hansen. Sociala komplikationer vid Tourette's syndrom. (Supervisor: Steven Haugbøl)
OSVAL 1: Medical Student Truels Ingebrigtsen. Teknikker til billeddannelse, EEG og juvenil myoklon epilepsi. (Supervisor: Lars Pinborg)
OSVAL 1: Medical Student Rie Harboe Nielsen. Hjernens funktionelle aktivering ved BOLD-fMRI (Supervisor: Olaf B. Paulson)
OSVAL 1: Medical Student Anna-Maria Sofia Lantz: Fødselsdepression og graviditet. (Supervisor: Vibe Frøkjær)
OSVAL 2: Medical Student Anna-Kirstine Bojsen-Møller. The association between frontal and limbic 5-HT_{2A}–receptor binding and neuroticism in healthy twins with genetic predisposition to depressive disorder (Supervisor: Vibe Frøkjær)
OSVAL 2: Medical Student Dorte Nymark Brask. Immunhistokemisk visualisering af serotonintransporteren og serotonin (Supervisor: Gitte Moos Knudsen)
Master thesis engineering: Mikael Palner. Evaluation of new potential Positron Emission Tomography tracers for the dopamine D2 receptor (Supervisors: Gitte Moos Knudsen and Susanne Jacobsen, DTU)

Cell Biology Project II: Barbara Lykke Lind. Effects of glutamate activated astrocytes on neurons and endothelial cells (Supervisor: Gitte Moos Knudsen)
Cell Biology Project II: Mette Hauge Lauritzen. Drug delivery to the brain - Problems and possibilities (Supervisor: Gitte Moos Knudsen)
Cell Biology Project II: Celia Kjærby Hansen. Nicotinic acetylcholine receptors in CNS (Supervisor: Gitte Moos Knudsen and Susana Aznar)
Pregraduate research student: Medical Student Morten Ziebell. SPECT-skanning og degenerative hjernelidelser (Supervisors: Gitte Moos Knudsen and Lars Pinborg)
Pregraduate research student: Medical Student Ellen G. Christensen. Does cholinergic lesion of the medial septum lead to changes in the serotonergic system in the hippocampus? (Supervisors: Gitte Moos Knudsen and Susana Aznar)
Pregraduate research student: Medical Student Sanne Wulff. HMPAO-SPECT and arterial spin labelling as diagnostic tools in the clinic (Supervisor: Steen G. Hasselbalch)
Engineer project: Engineer Student Carl Forsmark. Analysis of cerebral functionality - Comparison of MR and PET data with psychological mapping (Supervisors: Claus Svarer and Lars Kai Hansen, IMM, DTU).

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 NeuroCluster, Health Science Faculty, Copenhagen University (Gitte Moos Knudsen)

International Committees:
Secretary of the International Society for Cerebral Blood Flow and Metabolism (Gitte Moos Knudsen)
International scientific advisor for Brain Imaging Centre West, Jülich, Germany (Gitte Moos Knudsen)

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

Evaluation:
Evaluator of PhD thesis: Jane Skjøth-Rasmussen, University of Southern Denmark: Cerebral metabolites, proteins and cerebral blood flow in patients with subarachnoid hemorrhage, delayed ischemic neurological deficits and infarction of the brain (Gitte Moos Knudsen)
Evaluator of Doctoral Thesis: Jussi Hirvonen, Turku University, Finland: Brain dopamine receptors and genetic risk for schizophrenia. A twin study using positron emission tomography (Gitte Moos Knudsen)
Chairman of the evaluation committee for Doctoral Thesis: Mads Dalsgaard, University of Copenhagen: Fuelling cerebral activity in exercising man (Gitte Moos Knudsen)
Evaluator of Doctoral Thesis: Judit Sóvágó, Karolinska Institute, Sweden: Methodological Advances in the Examination of the Dopamine System in Brain (Gitte Moos Knudsen)
Evaluator of PhD thesis: Jim Luther, Technical University of Denmark: Advanced neural network engine control (Claus Svarer)
Member of the Editorial Board of the Journal of Cerebral Blood Flow and Metabolism (Gitte Moos Knudsen)
Expert Evaluator at the Norwegian Research Council and at EU, Brussels (Gitte Moos Knudsen)
External examiner at the Technical University of Denmark (Claus Svarer)
Finally, staff members of NRU regularly conduct peer-reviews for several international journals and at international congresses.

7.5 Awards

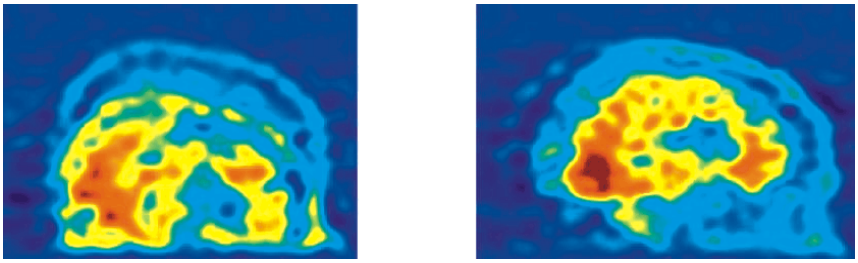
Chief Technologist Gerda Thomsen was elected as 'Technologist of the Year' by the symposium organizers at the Annual Technologist Symposium at Rigshospitalet.

From left: Center Technologist Karin Nørgaard and Gerda Thomsen. Photo: Sine Fiig

8. SPECT Laboratory

A total of 375 clinical scans have been performed in 2005, fifty of these with the dopamine transporter ligand ^{123}I-PE2I, the remaining with ^{99m}Tc-SHMPAO.

Two physics students, Anders Torp and Louise Legaard have been attached to the SPECT laboratory for the conduction of their master thesis. Anders Torp has worked with the Polaris System for correction of head movements while scanning (see figure below).



A method where head movements during SPET scanning is measured and used for correction of sinograms before reconstruction of the images has been developed. Left: movement during scanning (two skulls). Right: the image has been reconstructed from a corrected sinogram.

Research projects carried out in 2005

- Reproducibility of ^{123}I-PE2I binding to dopamine transporter with SPECT following bolus/infusion
- ^{123}I-PE2I SPECT as a diagnostic tool in clinically uncertain parkinsonian syndromes
- Investigations of the serotonin transporter with ^{123}I-ADAM
- High energy photon correction for I-123 in SPECT-studies
- The clinical application of arterial spin labelling in dementia evaluation
- Implementation of a system for correcting SPECT acquisitions for head movements during scanning using a Polaris Accedo System
- The time delay from injection to data acquisition using ^{99m}Tc-SHMPAO SPECT
- Validation of FAN beam collimator

9. Prospects

With this last annual report, we are preparing for entering into the Center for Integrated Molecular Brain Imaging (Cimbi). At the same time, NRU staff with the expert assistance from the PET & Cyklotron Unit was heavily engaged with the organization of the 6th Neuroreceptor Mapping Meeting to be held at Rigshospitalet in 2006, July 6-8.
The research in Cimbi focuses on the neural bases of personality dimensions that predispose individuals to affective and substance use disorders, with special emphasis on the serotonergic neurotransmitter system. Both PET and MRI are employed in studies of human subjects, and these are complemented with relevant studies using animal models. Advanced informatics techniques, new tracer compounds, and novel serotonergic challenge paradigms are also being developed within the center.
Cimbi consists of a number of core institutions in Copenhagen and a number of associated national and international laboratories. The core institutions are different departments at the Copenhagen University Hospitals, The Technical University of Denmark and the Danish University of Pharmaceutical Studies. These include:

- Neurobiology Research Unit (NRU), Copenhagen University Hospital, Rigshospitalet
- Danish Research Centre for Magnetic Resonance (DRCMR) , Copenhagen University Hospital, Hvidovre
- PET and Cyclotron Unit, Copenhagen University Hospital, Rigshospitalet
- Informatics and Mathematical Modelling, Technical University of Denmark
- Department of Medicinal Chemistry, Danish University of Pharmaceutical Sciences

More information can be found at www.cimbi.org.

As these lines are written, the new Lundbeck Foundation Research Center Cimbi has been inaugurated. In the last part of 2005, the senior staff has been busy preparing for the opening of the new center, including planning for the expansion of the staff in the NRU villa. Seven postdoc positions were posted in Nature resulting in many applications from Denmark and (mostly) abroad. The Cimbi Center Manager, Karam Sidaros, was already employed in November to prepare for the opening.

10. Acknowledgements

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

Bioanalytikernes Uddannelses- og Forskningsfond
Danish Medical Research Council
Danish Research Agency
H:S - Copenhagen Hospital Corporation
Ludvig og Sara Elsass Fond
Rigshospitalets Jubilæumsfond
Savværksejer Jeppe Juhl og hustru Ovita Juhls Mindelegat
Scandinavian Society for Laboratory Animal Science
Speciallæge i neurology Jørgen Wendelboe-Jørgensen og Laura Wendelboe-Jørgensens Fond
The Health Insurance Foundation
The Lundbeck Foundation
The Research Council of Rigshospitalet
University of Copenhagen, Faculty of Health Sciences
Villum Kann Rasmussen Fonden

International research funding:
EU 5th Framework program
EU 6th Framework program

NRU staff September 2005

11. Dansk Resumé

Vi håber, at du har haft fornøjelse af at læse denne årsrapport fra Neurobiologisk Forskningsenhed (NRU), og at rapporten har givet et godt indtryk af forskningsenhedens aktiviteter.

År 2005 var på mange måder et begivenhedsrigt år for NRU. Forskergruppen indtrådte sammen med mere end 50 øvrige europæiske forskningscentre i det af EU's 6. rammeprogram finansierede Network of Excellence, Diagnostic Molecular Imaging (DiMI). Derudover blev NRU i foråret styrket ved, at overlæge, dr. med. Steen G. Hasselbalch blev tilknyttet som lektor. Dette indebar en betydelig styrkelse af supervision af bl.a. PhD-studerende ved forskningsenheden.
NRU og flere af enhedens samarbejdende forskergrupper indsendte januar 2005 en interessetilkendegivelse til Lundbeckfonden om at oprette et center for integreret molekylær billeddannelse af hjernen. Fonden udvalgte 6 ud af de 26 modtagne interessetilkendegivelser og gav disse ansøgere mulighed for at indsende en egentlig ansøgning, som blev fremsendt i april. I juni meddelte fonden, at et internationalt ekspertpanel havde indstillet, at fonden skulle oprette Cimbi, Center for Integrated Molecular Brain Imaging, med hovedsæde ved Rigshospitalet, ved tildeling af 40 mio kr. over 5 år.
Gitte Moos Knudsen tiltrådte i maj det kliniske professorat ved neurologisk klinik ved Rigshospitalet, men traf senere på året beslutning om at vende tilbage til professoratet i klinisk neurobiologi for fuldt at varetage ledelsen af Cimbi.
Efteråret har været præget af aktiviteterne til forberedelse af det nye center, herunder ansættelser af post docs samt ombygninger. Rigshospitalets ledelse har valgt at støtte Cimbi, bl.a. ved at tildele de ekstra arealer, som centret vil kræve. Der vil fremover ikke blive udgivet flere årsrapporter fra NRU, idet forskningsenhedens aktiviteter fremover naturligt vil blive beskrevet i årsrapporterne for Cimbi.

Til sidst vil vi gerne benytte anledningen til at takke de mange fondsydere, der har støttet NRU's forskning ikke bare i 2005, men gennem mange år. Uden denne støtte ville store og væsentlige dele af NRU's forskning ikke kunne gennemføres.