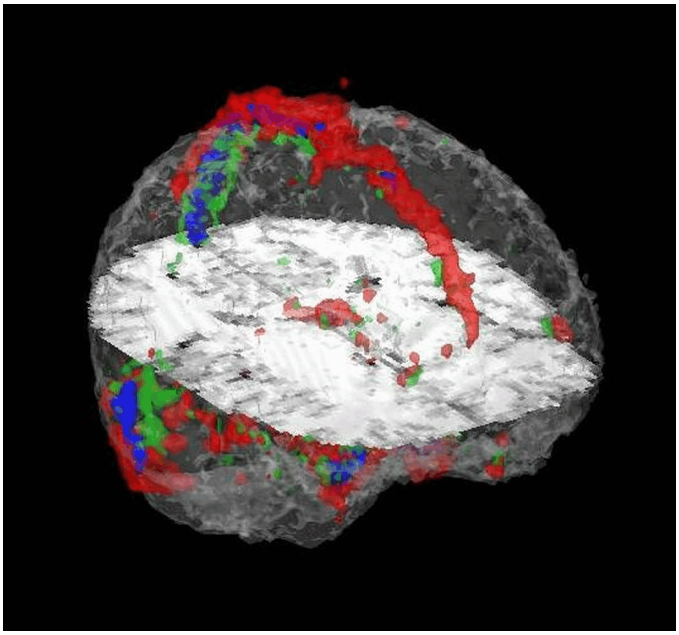
Annual Report 2004

Neurobiology Research Unit



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

www.nru.dk

Front page:
A 3D reconstruction of a hierarchical clustering. The central blue cluster matches well the spatial location of the cerebral venous vasculature. Liptrot et al., 2004.

Preface

This annual report provides an overview of the scientific activities that took place within the Neurobiology Research Unit (NRU) in 2004.

Two PhD-theses were defended in 2004: Karen Husted Adams defended her thesis on 5-HT_{2A} receptor binding measurements in a large healthy control group. Her thesis is the first of many theses to follow from NRU within the field of clinical molecular neuroimaging studies. Kristin Scheuer, MD, defended her thesis on patients with Hereditary Spastic Paraplegia (HSP). She studied cerebral affection in SPG4 linked HSP by employing functional and structural neuroimaging in combination with comprehensive neuropsychological testing.

In April, Professor Gitte M. Knudsen was appointed a tenure position as professor at the University of Copenhagen and in June, she replaced Olaf B. Paulson as chairman of NRU. This 'generation change' had been carefully planned over several years and consequently the transition went quite smoothly. Professor Olaf B. Paulson remains as professor at NRU and as chairman of the Danish Research Centre for Magnetic Resonance at Hvidovre University Hospital.

At the Neuroreceptor Mapping Meeting (NRM) that took place in Vancouver, Canada, this summer NRU was selected as a host of NRM in 2006. The preparations are already in full progress (for more information see also www.nrm06.org) and we look very much forward to welcome our colleagues to Copenhagen in July 2006.

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 2004 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.

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 next to Building 92. The ground floor of Building 93 is shared with the Neuroimmunology 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 PET research planning and developmental activities.

2. Objectives, Organization and Staff

NRU has its main interest within molecular imaging, 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, and Chief Engineer Claus Svarer, PhD, take part in chairing the research group. The Chief Technologist is Gerda Thomsen.

In 2004 the research staff consisted of:

Senior Researchers:
Susana Aznar, Biologist, PhD
Christian Gerlach, Psychologist, PhD*
Steen Hasselbalch, MD, DMSc (half time)
Gitte Moos Knudsen, Professor, MD, DMSc
Finn Årup Nielsen, Engineer, PhD
Olaf B. Paulson, Professor, MD, DMSc
Claus Svarer, Engineer, PhD

PhD-students:
Daniela Balslev, MD
David Erritzøe, MD
Vibe Gedsø Frøkjær, MD
Steven Haugbøl, MD
Esben Høgh-Rasmussen, Engineer
Viktorija Kostova, Human Biologist
Robin de Nijs, Physicist*
Kristin Scheuer, MD
Kåre Søndergaard, Chemist*

Junior Researchers:
Heidi Kristiansen, Biologist
Karine Madsen, MD
Birgitte Rahbek, Human Biologist
Thomas Rask, Engineer Student
Jan Tønnesen, Biologist

Associated Researchers:
Lars Hageman Pinborg, MD

Students:
Dorte Brask, medical student
Ellen Christensen, medical student
Ruben Christensen, biology student
Sofie Hansen, medical student
Kirsten Nielsen, medical student
Mikael Palner, engineer student
Anders Pryds, medical student*
Helle Tolstrup, biology student
Anders Torp, physicist student
Sanne Wulff, medical student
Morten Ziebell, medical student

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

Research Assistants:
Allan Frank
Mads Haar
Søren Hasbirk
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

3. Collaborators in 2004

Copenhagen Brain Research Center

www.cbrc.dk

When the center was inaugurated in April 2002 it was based on already existing collaboration between the involved partners. It 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 Centre 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 7 PhD-students engaged with supervisors from at least two different partners.

Other units at the Department of Neurology

The Memory Clinic

The Multiple Sclerosis Research Unit

Additional departments within Rigshospitalet

Department of Hepatology

Department of Infectious Diseases

Department of Neurosurgery

Department of Pediatrics

Department of Psychiatry

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

For more information, please visit www.mci.nru.dk

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

Electric Engineering Laboratories, University of Kent at Canterbury, United Kingdom

Inserm U320, Caen, France

National Council for Research (CNR), Centre for Nuclear Medicine, Napoli, Italy

PET Centre, Debrecen, Hungary

RASNA Imaging Systems, Firenze, 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.

Others

Behavioural Brain Sciences, School of Psychology, University of Birmingham, UK

Central Institute of Mental Health Mannheim, University of Heidelberg, Germany

Department of Biochemistry, National Institute of Mental Health Psychoactive Drug Screening Program, Cleveland, OH

Department of Medical Biochemistry & Genetics (IMBG), University of Copenhagen

Department of Pharmacology, Tours University Hospital, France

Glaxo SmithKline Beecham

Laboratory of Animal Sciences and Welfare, Department of Pharmacology and Pathobiology, The Royal Veterinary and Agricultural University, Copenhagen

Language Section, National Institutes of Health, Bethesda, Maryland, USA

Lundbeck A/S

MAP Medical, Helsinki, Finland

NeuroSearch A/S

Philips Medical Systems

4. Doctoral and PhD Theses

The in vivo brain distribution of serotonin 5-HT_{2A} receptors in healthy subjects and in patients with obsessive-compulsive disorder: A positron emission study with [^{18}F]-altanserin

Karen Husted Adams, cand.pharm, PhD

The serotonergic neurotransmitter system has an important pharmacological and physiological function in the central nervous system, and several psychiatric disorders including obsessive-compulsive disorder (OCD) may be associated with alterations in the cerebral concentration of serotonin (5-hydroxytryptamine, 5-HT) or 5-HT receptors.

This PhD thesis is based on research that focuses on in vivo imaging of the regional distribution of 5-HT_{2A} receptors. [^{18}F]-altanserin, a specific 5-HT_{2A} antagonist, and PET were used as well as magnetic resonance imaging (MRI). The thesis briefly covers the characteristics of [^{18}F]-altanserin, the experimental set-up typically used for [^{18}F]-altanserin PET, as well as quantification methods.

The distribution of 5-HT_{2A} receptors was examined in a large sample of 52 healthy subjects, aged between 21 and 79 years, and correlations between [^{18}F]-altanserin binding and physiological, demographic, and behavioural variables were made. The distribution volumes of specific [^{18}F]-altanserin binding (DV_3') were calculated for selected regions of interest.

The regional cerebral distribution of [^{18}F]-altanserin in the healthy subjects was in agreement with existing post-mortem human 5-HT_{2A} data. [^{18}F]-altanserin binding appears to be unaffected by gender, but correlations between regional DV_3' and age was observed, making age a factor to account for in clinical studies. A positive correlation between cerebellar binding and age was observed, and negative correlations between age and DV_3' were found in all cortical regions, except occipital cortex, corresponding to a decrease in DV_3' of approximately 6% per decade. In addition, correlations were found between body mass index (BMI) and DV_3' in several temporal and frontal cortices. Since the correlations were observed in very different and sparse regions, the finding should be corroborated in a separate data sample. Moreover, a positive correlation was found between neuroticism and DV_3' of [^{18}F]-altanserin in superior/medial frontal and orbito-frontal cortices, demonstrating a relationship between the 5-HT_{2A} receptor system and specific traits of personality.

In addition, the 5-HT_{2A} receptor distribution was investigated in 15 unmedicated OCD patients and also following successful treatment with selective serotonin reuptake inhibitors (SSRI) in 11 of the patients. In the OCD study a hypothesis was generated for specific regions of a fronto-subcortical brain circuit, known to be involved in the disease.

In patients with OCD an increased 5-HT_{2A} receptor binding was found bilaterally in the caudate nuclei when compared to a gender and age matched group of healthy subjects. The up-regulation in 5-HT_{2A} receptors might be compensatory for a relative lack of serotonin in the feedback loop between the thalamus and the orbito-frontal cortex, the caudate nuclei and the globus pallidus. Treatment with SSRI did however not alter the 5-HT_{2A} binding significantly in patients with OCD.

In conclusion, [^{18}F]-altanserin PET was found to be a powerful tool for in vivo imaging of 5-HT_{2A} receptors. The large normative database of [^{18}F]-altanserin PET may serve as a resource to aid the design and interpretation of future clinical studies of the 5-HT_{2A} receptors. In addition, [^{18}F]-altanserin PET has shown that there are differences in the 5-HT_{2A} receptor distribution in patients with OCD as compared to healthy subjects, thereby adding to our understanding of OCD pathophysiology.

The thesis was accepted for evaluation at the Faculty of Health Sciences, Copenhagen University. The defence took place on April 2, 2004, at Rigshospitalet, Auditorium 93. The evaluators were Andreas Kjær, Copenhagen, Paul Grasby, London, and Rosamaria Moresco, Milan (all medical doctors). The PhD-project was completed with Professor, DMSc Gitte Moos Knudsen as supervisor.

Assessment of cerebral involvement in SPG4 linked hereditary spastic paraplegia

Kristin Husby Scheuer, cand.med., PhD

Hereditary Spastic Paraplegia (HSP) is a large group of inherited neurodegenerative disorders which all are characterised by slowly progressive spasticity and weakness of the lower limbs. About 40% are caused by mutations in the Spastic Paraplegia Gene 4 (SPG4), and although the protein product was identified in 1999, the underlying pathogenic mechanism is still unknown. Neuropathological investigations has exposed retrograde axonal degeneration in pyramidal tracts and dorsal columns of the spinal cord, however recent immunolabeling experiments and neuropsychological studies have suggested a more disseminated CNS involvement. Hence, the overall aim of the present thesis was to investigate the extent of cerebral affection in SPG4 linked HSP by employing functional and structural neuroimaging in combination with comprehensive neuropsychological testing. Two separate studies were undertaken: In the first study ^{15}O-labelled water PET was used to assess differences in regional cerebral blood flow (rCBF) between patients and normal controls. Furthermore, as a supplement to the rCBF study, structural brain imaging and neuropsychological testing were performed. The results from these analyses disclosed a relative decrease in rCBF in the left fronto-temporal cortex in the patient group as a whole, with the most pronounced changes taking place in the most disabled individuals. Neuropsychological impairments were very limited, however, and structural images were within the normal range.

The second study explored the extent of motor cortical reorganisation by comparing cerebral motor activation responses in patients to that in normal controls. Two different motor tasks were employed, separating motor performance of paraplegic and non-paraplegic limbs. In general, no major qualitative discrepancies were observed between patients and controls when comparing brain regions engaged during motor performance. Statistically significant differences, however, were identified in ankle activation response as patients had increased rCBF in the right and left primary motor sensory cortex, supplementary motor area and the right lateral premotor area.

In conclusion, the overall results from this thesis substantiate the hypothesis of cerebral involvement in SPG4 linked HSP. Cerebral pathology, however, may be very subtle since concurrent neuropsychological impairments and structural damage were negligible. Motor cortical functional reorganisation is likely to occur, but as differences in functional demands could not be ruled out, this question remains unresolved.

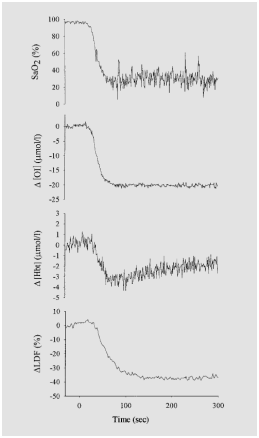
The thesis was accepted for evaluation at the Faculty of Health Sciences, Copenhagen University. The defence took place on September 28, 2004, at Rigshospitalet, Auditorium 93. The evaluators were Chief Physician, amanuensis II Chantal Tallaksen, Ullevål, Norway, Chief Physician, DMSc Steen Hasselbach, Rigshospitalet, and Chief Physician Lars Friberg, Bispebjerg Hospital. The PhD-project was completed with MD, PhD Ian Law and Professor, DMSc Olaf B. Paulson as supervisors.

5. Research Topics

5.1. Cerebral Blood Flow and Metabolism: Experimental Studies

Gitte Moos Knudsen, Professor, MD

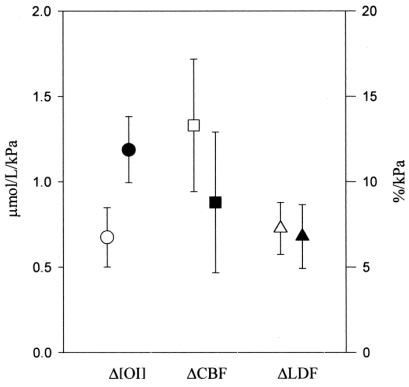
In collaboration with Department of Pediatrics, effects of oxygen exposure on cerebrovascular function was investigated in a newborn rat model established in the laboratory. Three to five-days-old rat pups were maintained on spontaneous breathing under light anesthesia for either 1 or 2 hours. Transcutaneous carbon dioxide tension and arterial oxygen saturation were monitored. Continuous infusion of doxapram limited respiratory acidosis. Cerebral blood flow (CBF) and volume (CBV) was monitored by near-infrared spectroscopy (NIRS) and laser-Doppler flowmetry (LDF); the values remained stable throughout the study at values of 36.3±3.1 ml/100 g/min and 6.0±0.3 ml/100 g, respectively. Cerebrovascular responses, as monitored by LDF and NIRS, to hypoxic and hypercapnic gas mixtures were consistent.



Representative changes in SaO_2, [OI], [Hbt] and LDF during 5 min of exposure to hypoxia (FiO_2 0.08), starting at time = 0. Note that the noise level of SaO_2 is lower at normoxemia compared to hypoxemia (hypoxic responses were calculated from mean values over 30 s)

Fumagalli M, Mosca F, Knudsen GM, Greisen G. A newborn rat model for the study of cerebral hemodynamics by near-infrared spectroscopy and laser-Doppler flowmetry in the immature brain. Biol Neonate 2004;85:112-20.

In a subsequent study we investigated the effects of oxygen on CBF in newborn rats. We hypothetized that hyperoxic exposure limits cerebral vasodilation in response to an increase in carbon dioxide tension (PCO_2). To investigate residual cerebrovascular effects of transient hyperoxia, we monitored the rats with LDF and NIRS. Twenty-four 3- to 5-days-old rats were randomized to either exposure to room air or 100% oxygen for 30 min. After 15 min of stabilization in normoxia, 8% CO_2 was given for 5 min. The oxygenation index [(HbO_2 - Hb)/2] increased similarly in the two groups, by about 0.9 micro mol/L/kPa. No significant differences in CO_2 responses were observed between the two groups: mean CBF-CO_2 reactivity as measured by NIRS was in the order of 10% in both groups. Cortical perfusion as monitored by LDF increased by about 7%/kPa in both the normoxia and hyperoxia groups. We conclude that in newborn rats the CBF-CO_2 reactivity remains intact even after 30 min of oxygen exposure.



Changes in [OI] (Δ [OI] µmol/LkPa, *circles*), CBF (ΔCBF %/kPa, *squares*) and LDF (ΔLDF %/kPa, *triangles*) in the normoxia (*open symbols)* and hyperoxia groups (*closed symbols*) during 8% CO_2 inhalation (○, *n* = 12; ●, *n* = 12; □, *n* = 10; ■, *n* = 9;△, *n* = 10; ▲, *n* = 6). Values are mean ± SE. No statistically significant differences were found between the two groups for any of the parameters.

Fumagalli M, Mosca F, Knudsen GM, Greisen G. Transient hyperoxia and residual cerebrovascular effects in the newborn rat. Pediatr Res 2004;55:380-4.

5.2. Cerebral Blood Flow and Metabolism: Clinical Studies

Gitte Moos Knudsen, MD, Professor

The modulation of CBF, CBV and glucose consumption (CMRglc) by physiological and pathophysiological alterations are pertinent and relevant also in the light of our interpretation of the fMRI signal. For small changes in arterial pCO_2, e.g., CBF changes approx. by 30% and CBV by 15% per kPa change in arterial pCO_2. Quantification of regional CMRglc using positron emission tomography and [^{18}F]-fluorodeoxyglucose (PET-FDG) requires knowledge of the correction factor between FDG and glucose net clearances, the lumped constant (LC). Recent reevaluations have convincingly demonstrated that the correct value of LC is higher than the usually applied value, in the order of 0.8 instead of 0.5. In starvation, the human brain derives an increasing amount of its energy demand from ketone bodies as their blood level increase during fasting. This adaptative shift in fuel consumption also occurs with acute hyperketonemia. Hyperinsulinemia does not alter the overall CMRglc but it alters the brain glucose distribution which has consequences for the estimation of CMRglc by PET-FDG. Finally, in acute or chronic hyperglycemia there is no substantial evidence for changes in blood-brain barrier glucose transport capacity or CMRglc, whereas LC changes. The assessment of the implications of normal physiological variations underscores the caution with which findings in various pathophysiological conditions are interpreted.

Knudsen GM, Rostrup E, Hasselbalch SG. Quantitative PET for assessment of cerebral blood flow and glucose consumption under varying physiological conditions. Int Congress Series 2004;1265:189-200.

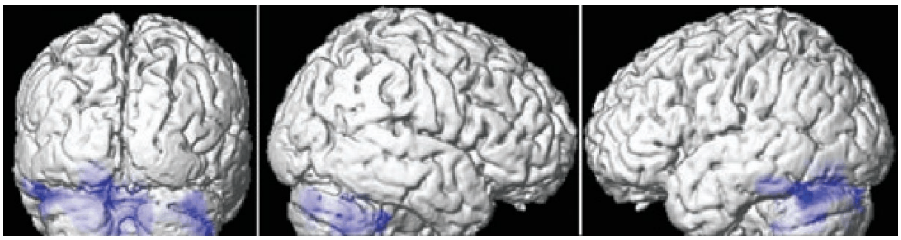
In patients with severe bacterial meningitis, norepinephrine is often infused to increase mean arterial pressure (MAP). The associated increase in CBF may either be caused by an impaired CBF autoregulation or by an increased cerebral glucose metabolism, mediated through a central effect of norepinephrine. We studied the effect of norepinephrine and propofol on CBF and oxidative metabolism in seven patients with severe pneumococcal meningitis and in 7 healthy subjects. While norepinephrine was infused intravenously global CBF was measured by the Kety-Schmidt technique; cerebral oxidative metabolism and net flux of norepinephrine and epinephrine were calculated from measured arterial-to-jugular venous concentration differences. During norepinephrine infusion, median MAP increased from 79 to 99 mm Hg in patients, and from 87 to 123 mm Hg in controls. Whereas CBF remained unchanged in the controls, it increased from 51 to 59 mL/100g/min in the patients. The cerebral metabolic rate of oxygen ($CMRO_2$) decreased in patients and remained unchanged in controls. No cerebral net flux of norepinephrine or epinephrine was found at any time in the 2 groups. We conclude that in patients with severe bacterial meningitis, norepinephrine increases both MAP and CBF but not $CMRO_2$, indicating impaired autoregulation. Propofol reduces CBF relatively less than cerebral metabolism, suggesting a resetting of the CBF-$CMRO_2$ relationship.

Møller K, Qvist T, Tofteng F, Sahl C, Sønderkær S, Dethloff T, Knudsen GM, Larsen FS. Cerebral blood flow and metabolism during infusion of norepinephrine and propofol in patients with bacterial meningitis. Stroke 2004;35:1333-9.

Olaf B. Paulson, MD, Professor

Complex forms of hereditary spastic paraplegia (HSP) are rare and usually transmitted in an autosomal recessive pattern. A family of four generations with autosomal dominant hereditary spastic paraplegia (AD-HSP) and a complex phenotype with variably expressed co-existing ataxia, dysarthria, unipolar depression, epilepsy, migraine, and cognitive impairment was investigated. Genetic linkage analysis and sequencing of the SPG4 gene were performed and electrophysiologic investigations were carried out in six individuals and cerebral blood flow measurement by positron emission tomography in one patient. The disease was linked to a novel mutation of the SPG4 locus on chromosome 2p as previously reported for pure HSP. Electrophysiologic investigation showed increased central conduction time at somatosensory evoked potentials in two affected individuals with the SPG4 mutation. Moreover, in one patient relatively decreased regional cerebral blood flow in most of the cerebellum was found.

We conclude that considerable overlap between cerebellar ataxia and spastic paraplegia could be demonstrated, emphasizing the marked clinical heterogeneity of HSP associated with spastin mutations.



Cluster of significantly relatively decreased cerebral blood flow overlaid on a surface rendering of the structural MRI image warped into the stereotactic space of Talairach and Tournoux (1988). The image is thresholded at $P < 0.05$ uncorrected ($T > 2.02$).

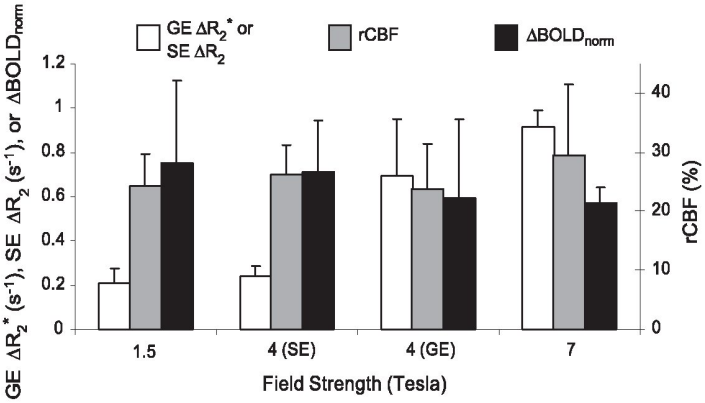
Nielsen JE, Johnsen B, Koefoed P, Scheuer KH, Grønbech-Jensen M, Law I, Krabbe K, Nørremølle A, Eiberg H, Søndergård H, Dam M, Rehfeld JF, Krarup C, Paulson OB, Hasholt L, Sørensen SA. Hereditary spastic paraplegia with cerebellar ataxia: a complex phenotype associated with a new SPG4 gene mutation. Eur J Neurol 2004;11:817-24.

5.3. Brain Mapping

Olaf B. Paulson, MD, Professor

The blood oxygenation level-dependent (BOLD) functional magnetic resonance imaging (fMRI) signal response to neurostimulation is influenced by many factors that are unrelated to the stimulus. These factors include physiological ones such as blood volume and instrument dependent ones: pulse sequences and magnetic field strength. These factors render it difficult to quantify the BOLD response correctly and thus to compare it both in between subjects and different scanners. In order to improve quantification of the

BOLD signal a study was undertaken where the BOLD response to functional activation using finger tapping was compared to the BOLD response induced by vasodilation and flow increase during hypercapnia. The MR investigations were performed at the Danish Research Centre for Magnetic Resonance at Hvidovre Hospital and at collaborating departments in USA. The data suggests that this hypercapnic normalization approach can improve the spatial specificity and interpretation of BOLD signal allowing comparison of BOLD signals across subjects, field strengths and pulse sequences.

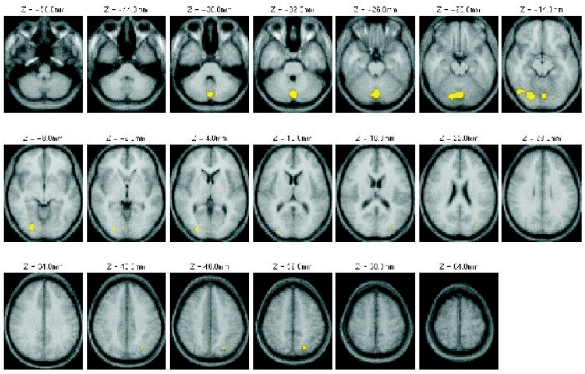


A comparison of ΔR_2^* , ΔR_2, rCBF, and $\Delta BOLD_{norm}$ averaged over all subjects at each magnetic field strength at 1.5, 4, and 7 tesla. Error bars represent one standard deviation. The mean rCBF did not significantly differ across field strength nor did the mean $\Delta BOLD_{norm}$.

Cohen ER, Rostrup E Sidaros K Lund TE, PaulsonOB, Ugurbil K, Kim S-G. Hypercapnic normalization of BOLD fMRI: comparison across field strengths and pulse sequences. Neuroimage 2004;23:613-24.

Brain mapping, functional activation of visual marking

Search for a colour-form conjunction target can be facilitated by presenting one set of distractors prior to a second set of distractors and the target. The time course of the preview benefit was investigated in two settings. It was demonstrated that the benefit has a relative short time course, old items need to precede a new set by 600 ms or more in order to be fully filtered from search. In the other setting the neural locus for this filtering effect over time was investigated using PET of ^{15}O-labelled water. Regions of the parieto-occipital cortex are selectively activated in the preview search condition relative to a detection baseline. These regions also increase in activation as a preview interval increases and search becomes easier, consisting with them modulating the parallel filtering of distractors from targets in spatial search.



Areas of significant increased activation in both the conjunction and preview search condition relative to each respective detection baseline.

Humphreys GW, Kylingsbæk S, Watson DG, Olivers CNL, Law I, Paulson OB. Parieto-occipital areas involved in efficient filtering in search: A time course analysis of visual marking using behavioural and functional imaging procedures. Q J Exp Psychol A 2004;57:610-35.

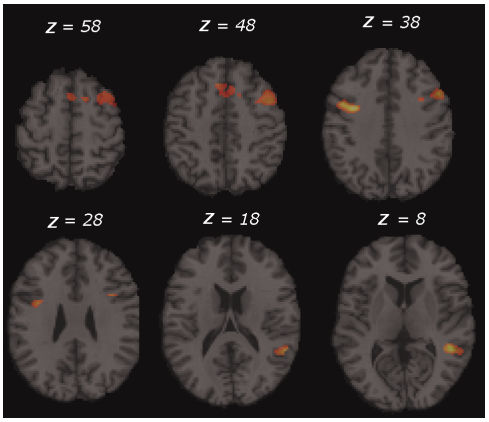
Daniela Balslev, MD, PhD-student

When performing visually guided actions under conditions of perturbed visual feedback, e.g. in a mirror or a video camera, there is a spatial conflict between visual and proprioceptive information. Recent studies have shown that subjects without proprioception avoid this conflict and show a performance benefit. In this study we tested whether deafferentation induced by repetitive transcranial magnetic stimulation (rTMS) can improve mirror tracing skills in normal subjects. Hand trajectory error during novel mirror drawing was compared across two groups of subjects that received either 1 Hz-rTMS over the somatosensory cortex contralateral to the hand or sham stimulation. Mirror tracing was more accurate after rTMS than after sham stimulation. Using a position-matching task we confirmed that rTMS reduced proprioceptive acuity and that this reduction was largest when the coil was placed at an anterior parietal site. It is thus possible, with rTMS, to enhance motor performance in tasks involving a visuo-proprioceptive conflict, presumably by reducing the excitability of somatosensory cortical areas that contribute to the sense of hand position.

Balslev D, Christensen LOD, Lee J-H, Law I, Paulson OB, Miall RC. Enhanced accuracy in novel mirror drawing after repetitive transcranial magnetic stimulation-induced proprioceptive deafferentation. J Neurosci 2004;24:9698-9702.

The conflict between vision and proprioception has been proposed to explain why healthy subjects perform worse than proprioceptively deafferented patients in conditions with optical displacement, e.g. novel mirror drawing. It is not known which brain processes depend upon the successful integration of visual and proprioceptive information and are therefore impaired when these modalities disagree. With fMRI in healthy subjects we compared brain activity across two conditions with similar visual and proprioceptive stimulation and similar task demands that only differed by the congruence of movement

showed by the two modalities. Subjects felt the passive movement of the right index finger on a rectangular field and watched a cursor moving on a computer screen. Cursor and finger locations either mapped onto each other (congruent condition) or did not (incongruent condition). Monitoring incongruent compared with congruent movement activated the premotor area bilaterally and the right temporoparietal junction (see figure). These brain areas have previously been associated with shifts in the attended location in the visual space. These findings suggest an interaction between vision and proprioception in orienting to spatial locations.



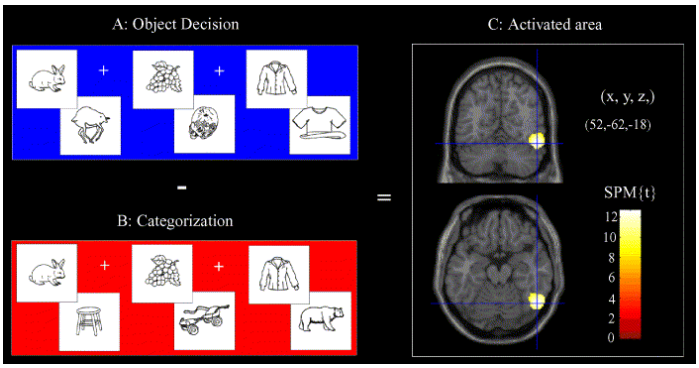
Brain areas with higher activity in the incongruent compared with the congruent condition. The congruent condition was subtracted from the incongruent condition and the result is showed as a parametric map of the t-statistic. The map is thresholded at a corrected p-value < 0.001 at the cluster level (random-effects analysis). For the purpose of anatomical localization, the map is superposed on a single-subject T1-weighted image coregistered to the MNI template. The z-value for each transversal slice is the stereotactic coordinate in vertical direction in the MNI space. The left side of the brain is shown to the left .

Balslev D, Nielsen FÅ, Paulson OB, Law I. Right temporoparietal cortex activation during visuo-proprioceptive conflict. Cereb Cortex Advance Access; 2005, in press.

Christian Gerlach, cand.psych, PhD

We have continued our investigation of category-specific effects in visual object recognition by means of PET. In patients, category-specific recognition effects show up as impairments in visual recognition limited to specific categories of objects, for example natural objects such as animals, vegetables etc. Category-specific effects, however, are not limited to patients but can be demonstrated in normal subjects also, as we have shown previously. One working hypothesis has been that category-effects in the recognition of natural objects reflect that natural overlap more in shape than artefacts and therefore become harder to recognize visually than artefacts. On this account one might expect that rCBF should be higher in areas important for visual object recognition during recognition of natural objects compared with artefacts. Contrary to this hypothesis we found that rCBF was higher in such areas during processing of artefacts compared with natural objects. Despite this surprising finding, we still find that the recognition of natural objects is slower and more error-prone than the recognition of artefacts. To account for these findings we have proposed a new model of category-specificity. This model is capable of explaining a wide range of category-effects found with both normal subjects and patients across different types of tasks and helps reconcile findings that have been considered incompatible

hitherto. The model is presented in the article which also provides a selective review of studies addressing category-specificity. The model is sufficiently articulated to yield testable predictions concerning category-effects as a function of different parameter relating to task requirements. We are currently investigating some of these hypotheses in new studies.



(A) Examples of the stimuli used in the three object decision tasks. (B) Examples of the stimuli used in the three categorization tasks. (C) Two cross-sections showing the activation difference between the object decision tasks and the categorization tasks. The activated area is projected onto a template anatomical MRI scan in coregistration with the Talairach atlas. The image was thresholded at P<0.05 corrected for multiple comparisons.

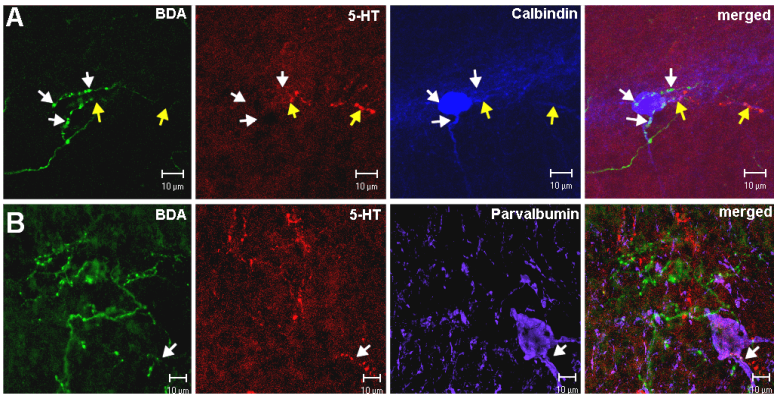
Gerlach C, Law, Paulson OB. Structural similarity and category-specificity: a refined account. Neuropsychologia 2004;42:1543-53.

5.4. Cerebral Neuroreceptors: Radiosynthesis and Experimental Studies

Susana Aznar, Biologist, PhD

In our laboratory we conduct experimental neuroreceptor 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. We make primarily use of in vivo experimental studies where we apply neuronal tracing and double and triple immunostaining techniques.

We have found and described a non-serotonergic projection from the raphe nucleus to 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 may be involved.



Non-serotonergic median raphe fibers projecting on calbindin-containing interneurons in hippocampus: Confocal images of median raphe BDA-labeled fibers in hippocampus. In A, triple labeling for serotonin shows a calbindin-positive cell in stratum dentate gyrus making multiple contacts with a non-serotonergic BDA-labeled fiber (white arrows) and a serotonin positive fiber (yellow arrows). In B, the white arrow points to a serotonin-positive BDA-labeled fiber contacting a parvalbumin-positive cell in CA3. Scale bar = 10 µm.

Aznar S, Qian Z-X, Knudsen GM. Non-serotonergic Dorsal and Median Raphe projection onto parvalbumin- and calbindin-containing neurons in hippocampus and septum. Neuroscience 2004;124 (3):573-81.

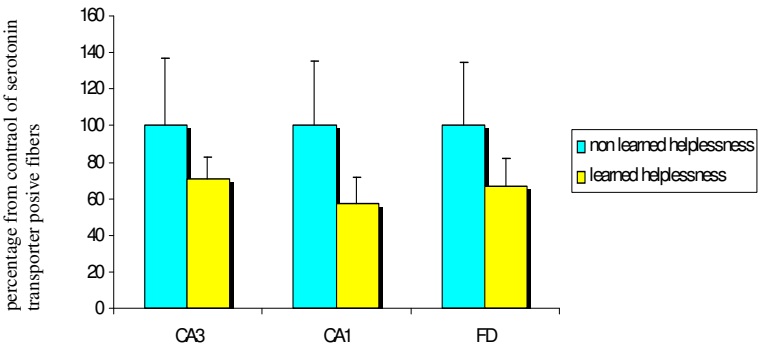
In another line of study we investigated how the serotonergic and the cholinergic systems interact with each other. This is relevant for understanding how the serotonergic system is affected in Alzheimer's diease where the cholinergic system is severely affected. We have found that the α7 nicotinic receptors, which are very important in relation to Alzheimer's disease, are present in serotonin neurons projecting to hippocampal and septal areas.

Aznar S, Kostova V, Christiansen SH, Knudsen GM. The a-7 nicotinic receptor subunit is present on serotonin neurons projecting to hippocampus and septum. Synapse 2005, In press.

In an organotypic culture model we have investigated the effect of MDMA (ecstasy) on neuronal cell death and its effect on 5-HT_{2A} serotonin receptor levels. We found no toxic effect of MDMA in this in vitro model, and no change of 5-HT_{2A} receptor levels in the deafferentiated hippocampus after exposure to MDMA.

Sveen ML, Knudsen GM, Aznar S. No effect of MDMA (ecstasy) on cell death and 5-HT_{2A} receptor density in organotypic rat hippocampal cultures. Neuroscience Letters 2004;362:6-9.

We have also investigated whether differences in the serotonergic system could be of importance for the predisposition for depression. By use of an inbred rat model for depression, the learned helplessness rat, and with the help of stereological techniques we have quantified the number of serotonin and serotonin transporter positive fibers. Although no difference in serotonin fiber density was found, it seems there is a difference in the serotonin transporter protein.



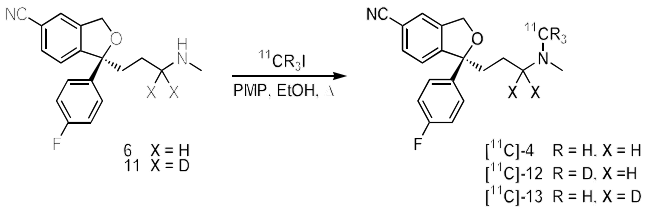
Rats with a predisposition to depression have less fibers positive for the serotonin transporter.

Aznar S, Møller A, Knudsen GM, Henn FA, Vollmayr B. Looking for differences in serotonin innervation and serotonin transporter in hippocampus of a rat model of learned helplessness. Program No. 570.8. 2004 Abstract Viewer/Itinerary Planner. Washington, DC: Society for Neuroscience, 2004. Online.

Jacob Madsen, Chemist, PhD

S-[*N*-Methyl-d_3-^{11}C]citalopram was synthesized by reaction between gas phase produced [^{11}C]methyl iodide-d_3 and *S*-desmethylcitalopram. *S*-[*N*-Methyl-^{11}C]citalopram-d_2 (the two deuterium atoms were placed in the side chain α to the nitrogen atom) was synthesized in a reaction between [^{11}C]methyl iodide and deuterium labelled *S*-desmethylcitalopram as precursor. The deuterium labelled precursor was synthesized in 10 steps from escitalopram. *S*-[*N*-Methyl-d_3-^{11}C]citalopram and *S*-[*N*-methyl-^{11}C]citalopram-d_2 were synthesized to investigate a potential deuterium isotope effect in the metabolism of the radioligands.

Compared to ^{11}C-labelled escitalopram the deuterium labelling of these compounds did not have any effect on the regional brain distribution observed in ex vivo rat studies.



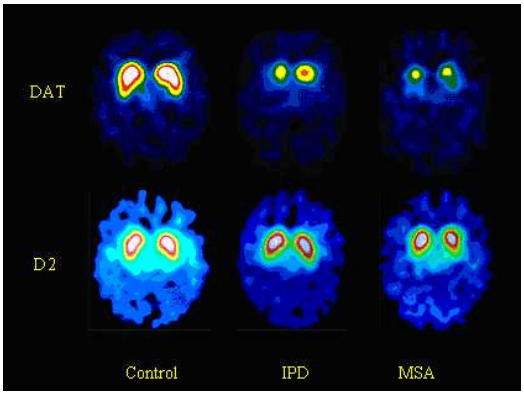
Scheme. Radiosynthesis of *S*-[*N*-methyl-^{11}C]citalopram (**[^{11}C]-4**), *S*-[*N*-methyl-d_3-^{11}C]citalopram (**[^{11}C]-12**), and *S*-[*N*-methyl-^{11}C]citalopram-α,α-d_2 (**[^{11}C]-13**).

Madsen J, Elfving B, Andersen K, Martiny L, Knudsen GM. Gas phase production of [11C]methyl iodide-d3. Synthesis and biological evaluation of S-[N-methyl-11C]citalopram and deuterated analogues. J Label Compd Radiopharm 2004;47:335-48

5.5. Cerebral Neuroreceptors: Clinical Studies

Gitte Moos Knudsen, MD, Professor and Lars H. Pinborg, MD

The aim of this study was to ascertain whether combined presynaptic and postsynaptic dopaminergic SPECT scanning is useful for differentiation between patients with idiopathic Parkinson's disease (IPD), patients with multiple system atrophy of the striatonigral type (MSA) and healthy subjects. For that purpose, SPECT measurements of the dopamine transporter (DAT) were done with [^{123}I]-beta-CIT, while for determination of the dopamine D2-like receptors (D2), [^{123}I]-epidepride was used. Clinical evaluation and SPECT scans were carried out in 14 patients with IPD, eight patients with MSA and 11 healthy age-matched control subjects. We found that putaminal DAT binding was reduced to 32% of control values in IPD and to 19% of control values in MSA. Significantly higher striatal asymmetry in DAT binding was found in MSA than in controls, but IPD patients had significantly higher asymmetry than MSA patients. Striatal D2 binding did not differ significantly between patients and healthy controls but the ratio between caudate DAT and D2 binding was significantly higher in patients with IPD than in those with MSA, even when disease severity was taken into account. We conclude that patients with reduced striatal [^{123}I]-beta-CIT binding and a side-to-side difference greater than 15% are likely to suffer from IPD. Patients with reduced striatal [^{123}I]-beta-CIT binding and a side-to-side difference of between 5% and 15% are more likely to have MSA. [^{123}I]-epidepride SPECT measurements may add further diagnostic information, since the ratio between DAT and D2 receptor binding is significantly higher in IPD than in MSA.



Representative examples of DAT and D_2 binding in IPD, MSA and healthy controls. The images are scaled to enable comparison between the R_v values

Knudsen GM, Karlsborg M, Thomsen G, Regeur L, Krabbe K, Nygaard T, Videbaek C, Werdelin L. Imaging of dopamine transporters and D(2) receptors in patients with Parkinson's disease and multiple system atrophy. Eur J Nucl Med Mol Imaging 2004;31:1631-1638.

Lars Hageman Pinborg, MD

In collaboration with the PET and Cyclotron Unit at Rigshospitalet, NRU has since 2000 conducted more than 150 [^{18}F]altanserin-PET studies in neuropsychiatric patients and healthy controls. [^{18}F]altanserin is a PET-tracer with high selectivity for the 5-HT$_{2A}$ receptor compared to other monoamine receptors. The vast majority of these studies have been conducted using a bolus/infusion approach developed at NRU. Compared to administration of [^{18}F]altanserin as a single bolus, administration of [^{18}F]altanserin as a combination of an initial bolus injection followed by a constant infusion offers advantages in terms of both experimental and analytical simplicity. In addition, the bolus/infusion approach allows for monitoring of the effect of pharmacological challenges during a single scan session. For quantification of [^{18}F]altanserin binding to the 5-HT$_{2A}$ receptor, the bolus/infusion approach is particularly well suited, since it allows for simple correction for labeled metabolites of [^{18}F]altanserin passing the blood-brain-barrier. For this purpose cerebellum was used to represent free and non-specifically bound [^{18}F]altanserin and its metabolites.

In a separate human study, we tested the effect of acute changes in the extracellular concentration of 5-HT upon [^{18}F]altanserin binding to the 5-HT$_{2A}$ receptor. One hour after [^{18}F]altanserin steady-state was attained in brain and plasma, the selective serotonin reuptake inhibitor, citalopram was administered to all subjects as a constant infusion for 20 minutes. To reduce 5-HT$_{1A}$ mediated autoinhibiton of cortical 5-HT release four of the seven subjects were pretreated with the partial 5-HT$_{1A}$ agonist pindolol for three days at an increasing oral dose (25 mg on the day of the PET scanning). Despite a pronounced increase in plasma prolactin and two subjects reporting hot flushes compatible with an 5-HT induced adverse effect, cortical [^{18}F]altanserin binding was insensitive to the citalopram challenge, even after pindolol pre-treatment.

Pinborg LH, Adams KH, Hasselbalch SG, Holm S, Yndgaard S, Svarer C, Knudsen GM. It is not possible to measure acute fluctuations of 5HT using [18F]altanserin-PET and citalopram. J Cereb Blood Flow Metab 2004;24:1037-45.

Finally, we reported the initial results from our [^{18}F]altanserin-PET database of 5-HT$_{2A}$ re ceptor studies in healthy volunteers. Fifty-two healthy subjects aged between 21 and 79 years were included. The relation between binding parameters and a number of methodological and demographic variables was studied to aid the design and interpretation of clinical studies of the 5-HT$_{2A}$ receptors. Whereas [^{18}F]-altanserin binding was not influenced by gender, ageing effects must be taken into account when designing clinical studies. A significant decrease in 5-HT$_{2A}$ receptors was found with age (6% decrease in [^{18}F]altanserin binding per decade) and in addition, a confounder in terms of an apparent increase in cerebellar non-specific binding and/or increase in 5-HT$_{2A}$ receptor density is present. Finally, correlations between BMI and [^{18}F]altanserin binding in several frontal and temporal cortex regions were demonstrated.

Cover photo on Neuroimage 2004, volume 21, Number 3: 5-HT_{2A}-receptor binding in the human brain as visualized by ^{18}F-altanserin, demonstrating a high number of receptors in temporal and occipital cortex, and virtually absent amount in cerebellum. The image is overlaid a structural and surface-rendered MR-image.

Adams KH, Pinborg LH, Hasselbalch S, Svarer C, Holm S, Knudsen GM. A database of [18F]-altanserin binding to 5-HT_{2A} receptors in normal volunteers: normative data and relationship to physiological, and demographic variables Neuroimage 2004;21:1105-13.

5.6. Methods for Brain Data Analysis

Esben Høgh-Rasmussen, MSc; PhD-student, Finn Årup Nielsen, PhD, MSc, Robin de Nijs, PDEng, MSc, and Claus Svarer, PhD, MSc.

The data analysis section is currently involved in the optimization of a Marconi/Philips SPECT scanner for clinical and research purposes. In 2004 we continued to develop in-house made reconstruction software. The software enables reconstruction from exported raw projection images and includes uniform attenuation correction. In addition, it enables to subtract images from different energy windows. The latter part is included for correcting SPECT scans for scatter from high energy photons coming from e.g. the ^{123}I isotope. The reconstruction code is capable of handling multiple frame (dynamic) data. *(Robin de Nijs)*

A PhD project focuses on improving the quality of functional SPECT and PET scans using structural information derived from MR scans in the reconstruction process. The limited spatial resolution and high noise levels in SPECT and PET scans are often limiting for the quality of the scans. In 2004, NRU released a Matlab toolbox to the public, BBTools [can be downloaded from http://nru.dk/software/bbtools], to handle certain large-scale problems in linear algebra. This forms an essential part of a framework to deliver improved images, especially for statistical analysis of dynamic scans and group studies. *(Esben Høgh-Rasmussen)*

In an ongoing EU-supported project (NCI-MCI EU 5th framework program) we have developed a standardized and automatized way of defining volumes of interests in brain images. This approach is based on high resolution structural MR images. The objective and

standardized volumes of interest will be used for extraction of data from SPECT and PET studies. *(Claus Svarer)*

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, in press.

Finally, in 2004 neuroinformatics techniques for extracting and storing information about neuroreceptor studies in a web-enabled database were introduced. This includes development of computerized methods for meta-analytic clustering of experiments and defining taxonomies for brain anatomy and neuroreceptors. The Brede Database (http://hendrix.imm.dtu.dk/services/jerne/brede/brede.html) is a collection of human brain mapping studies. It contains the abstract as well as stereotaxic coordinates for foci of brain activations from published scientific articles. The database allows for meta-analysis with a high degree of automation. We have constructed an algorithm that mines for association between words in the abstract and brain activations, i.e., detect when words and brain activation co-occur. The spatial distribution of brain activation in standardized stereotaxic space was modelled with kernel density estimators. When combined with indicators for occurrences of words in abstracts, a joint probability results. The local maxima in this joint probability are the associations of most interests, and these can be reported in a sorted list, resulting in an overview of the most important facts in the database. The results show that this automated information extraction is well aligned with general neuroscientific knowledge. *(Finn Årup Nielsen)*

Nielsen FÅ, Hansen LK, Balslev D. Mining for associations between text and brain activation in a functional neuroimaging database. Neuroinformatics 2004;2:369-80.

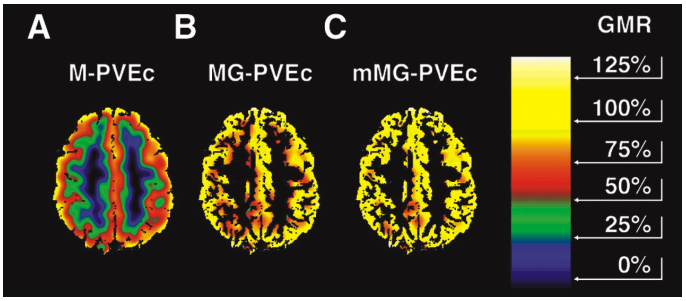
In a multi-author review software for integrated analysis of brain PET studies and co-registered segmented MRI is presented and discussed. The software has been developed as a part of an EU 5th framework program. Four alternative methods for partial volume effect correction (PVEc) was tested with the accuracy and precision of the methods being measured in four simulated [^{18}F]-FDG PET studies with increasing degrees of 'atrophy'.

The ROIs were transferred onto the PET studies in native patient space, and corresponding values were corrected according to the four PVEc techniques under investigation. To evaluate the outcome of the different PVEc techniques, the software was applied to the four simulated [^{18}F]-FDG PET studies. Increasingly larger experimental errors were introduced, including errors in co-registration (0- to 6-pixel misregistration), segmentation (-13.7% to 14.1% gray matter [GM] volume change) and resolution estimate errors (-16.9% to 26.8% full-width-at-half-maximum mismatch).

Even in the absence of segmentation and co-registration errors, uncorrected PET values showed a -37.6% GM underestimation and 91.7% white matter [WM] overestimation. Voxel-based correction only for the loss of GM activity as a result of spill-out onto extraparenchymal tissues left a residual underestimation of GM values (-21.2%).

Application of the method that took into account both spill-in and spill-out effects between any possible pair of ROIs (R-PVEc) and of the voxel-based method that corrects also for the WM activity derived from R-PVEC (mMG-PVEc) provided an accuracy above 96%. The coefficient of variation of the GM ROIs, a measure of the imprecision of the GM concentration estimates, was 8.5% for uncorrected PET data and decreased with PVEc, reaching 6.0% for mMG-PVEc. Co-registration errors appeared to be the major determinant of the imprecision.

Coupling of automated ROI delineation and PVEc provides a tool for integrated analysis of brain PET/MRI data, which allows a recovery of true GM ROI values, with a high degree of accuracy when R-PVEc or mMG-PVEc is used. Among the 4 tested PVEc methods, R-PVEc showed the greatest accuracy and is suitable when corrected images are not specifically needed. Otherwise, if corrected images are desired, the mMG-PVEc method appears to be the most adequate, showing a similar accuracy.



PET image corrected for PVE according to Meltzer PVE correction (A), Müeller-Gartner PVE correction (B), and modified Müeller-Gartner PVE correction (C) under optimal conditions.

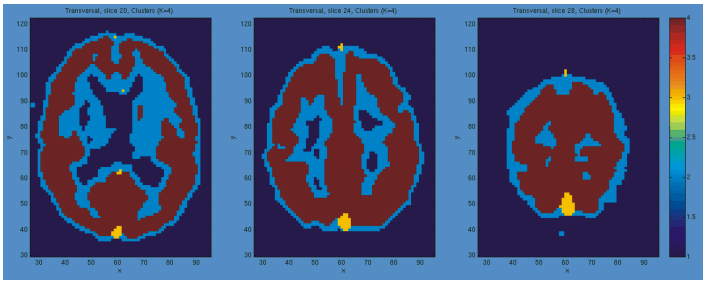
Quarantelli M, Berkouk K, Prinster A, Landeau B, Svarer C, Balkay L, Alfano B, Brunetti A, Baron JC, Salvatore M. Integrated Software for the Analysis of Brain PET/SPECT Studies with Partial-Volume-Effect Correction. J Nucl Med 2004;45:192-201.

In PET, quantification of brain tracer uptake, metabolism or binding requires knowledge of the cerebral input function. Traditionally, this is achieved with blood sampling, either arterial or venous. Both are invasive, and the former, although it gives the better results, is more risk-prone, and so the latter is often used, albeit with inferior results. Other, non-invasive, methods have been developed, but these usually suffer from lack of robustness, or quantification errors. Instead, we developed a noninvasive alternative via the use of a blood vessel time– activity curve (TAC) extracted directly from the PET scans by cluster analysis.

Five healthy subjects were injected with the $5HT_{2A}$-receptor ligand [^{18}F]-altanserin and blood samples were subsequently taken from the radial artery and cubital vein. Eight regions-of-interest (ROI) TACs were extracted from the PET data set. Hierarchical K-means cluster analysis was performed on the PET time series to extract a cerebral vasculature ROI. The number of clusters was varied from K = 1 to 10 for the second of the

two-stage method. Determination of the correct number of clusters was performed by the 'within-variance' measure and by 3D visual inspection of the homogeneity of the determined clusters.

An example of the extracted cluster can be seen in yellow in the adjacent figure. The mean time-response of this cluster was then taken as the input-curve for the Logan plot analysis. It was compared with the arterial and venous blood samples, and additionally with one of the currently used alternatives to arterial blood sampling, the Simplified Reference Tissue Model (SRTM), and Logan analysis with cerebellar TAC as an input.



Axial image slices from a K-means (K = 5) clustering of the voxels. Each color indicates a cluster. The yellow cluster is the identified vascular cluster.

There was a good agreement ($P < 0.05$) between the values of Distribution Volume (DV) obtained from the K-means-clustered input function and those from the arterial blood samples. This work acts as a proof-of-principle that the use of cluster analysis on a PET data set could obviate the requirement for arterial cannulation when determining the input function for kinetic modelling of ligand binding, and that this may be a superior approach as compared to the other noninvasive alternatives.

Cover photo on Neuroimage 2004, Volume 21, Number 2: A 3D reconstruction of a hierarchical clustering. Note how well the central blue cluster matches the spatial location of the sagittal sinus.

Liptrot M, Adams KH, Martiny L, Pinborg LH, Lonsdale MN, Olsen NV, Holm S, Svarer C, Knudsen GM: Cluster analysis in kinetic modelling of the brain: a non-invasive alternative to arterial sampling. NeuroImage 2004;21:483-493.

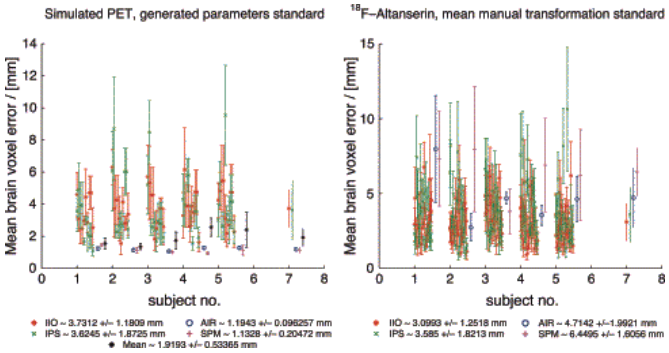
In this study the accuracy and reproducibility of two fully automatic and two manual methods for co-registration of structural T1-weighted MR images and functional images with localized binding is accessed and compared.

Four co-registration methods were tested:

- Interactive Point Selection, IPS (semi-automatic method implemented at NRU).
- Interactive Image Overlay, IIO (manual method implemented at NRU).
- Automatic Image Registration, Air 5.0.
- Statistical Parametric Mapping, SPM 99.

In total, five sets of corresponding, simulated [^{18}F]-FDG PET images, [^{18}F]-altanserin receptor PET images, and T1 MR images were co-registered using all four methods. A panel of seven users tested the two manual methods implemented at NRU to assess the inter- and intra-user variability and reproducibility of each method.

It is concluded that for functional images with distributed binding all over the brain, such as [^{18}F]-FDG images, the automatic methods are preferable, while for images with localized binding, such as [^{18}F]-altanserin 5-HT$_{2A}$ neuroreceptor images where there is no binding in cerebellum, it is essential to use methods that handle these special problems, like the proposed manual methods.



Results of co-registration using the different approaches. Left panel: simulated [^{18}F]-FDG PET image. Right panel: real [^{18}F] altanserin PET image. The left panel shows that in this ideal case with distributed gray matter binding in all brain regions the automatic methods perform much better than the manual methods, whereas manual methods are preferable in case of more localized binding in the PET images.

Willendrup P, Pinborg LH, Hasselbalch SG, Adams KH, Stahr K, Knudsen GM, Svarer C: Assessment of the precision in co-registration of structural MR-images and PET-images with localized binding. Int Congress Series 2004;1265:275-80.

6. Publications

Peer-review Full-length Publications

Cerebral Blood Flow and Metabolism

Fumagalli M, Mosca F, Knudsen GM, Greisen G. Transient hyperoxia and residual cerebrovascular effects in the newborn rat. Pediatr Res 2004;55(3):380-4

Fumagalli M, Mosca F, Knudsen GM, Greisen G. A newborn rat model for the study of cerebral hemodynamics by near-infrared spectroscopy and laser-Doppler flowmetry in the immature brain. Biol Neonate 2004;85(2):112-20

Møller K, Qvist T, Tofteng F, Sahl C, Sønderkær S, Dethloff T, Knudsen GM, Larsen FS. Cerebral blood flow and metabolism during infusion of norepinephrine and propofol in patients with bacterial meningitis. Stroke 2004;35:1333-9

Brain Activation Studies

Balslev D, Christensen LOD, Lee J-H, Law I, Paulson OB, Miall RC. Enhanced accuracy in novel mirror drawing after repetitive transcranial magnetic stimulation-induced proprioceptive deafferentation. J Neurosci 2004;24:9698-9702

Cohen ER, Rostrup E Sidaros K Lund TE, PaulsonOB, Ugurbil K, Kim S-G. Hypercapnic normalization of BOLD fMRI: comparison across field strengths and pulse sequences. Neuroimage 2004;23:613-24

Gerlach C, Law, Paulson OB. Structural similarity and category-specificity: a refined account. Neuropsychol 2004;42:1543-53

Humphreys GW, Kylingsbæk S, Watson DG, Olivers CNL, Law I, Paulson OB. Parieto-occipital areas involved in efficient filtering in search: A time course analysis of visual marking using behavioural and functional imaging procedures. Q J Exp Psychol A 2004;57:610-35

Nielsen FÅ, Hansen LK, Balslev D. Mining for associations between text and brain activation in a functional neuroimaging database. Neuroinformatics 2004;2:369-80

Neuroreceptor Studies

Adams KH, Pinborg LH, Svarer C, Hasselbalch SG, Holm S, Mortensen EL, Haugbøl S, Madsen K, Frokjaer V, Martiny L, Paulson OB, Knudsen GM: A database of [18F]-altanserin binding to 5-HT_{2A} receptors in normal volunteers: normative data and relationship to physiological, and demographic variables. NeuroImage 2004;21:1105-13

Aznar S, Qian ZX, Knudsen GM. Non-serotonergic dorsal and median raphe projection on parvalbumin- and calbindin-containing neurons in hippocampus and septum. Neuroscience 2004;124(3):573-81

Knudsen GM, Karlsborg M, Thomsen G, Regeur L, Krabbe K, Nygaard T, Videbaek C, Werdelin L. Imaging of dopamine transporters and D2 receptors in patients with Parkinson´s disease and multiple system atrophy. Eur J Nucl Med Mol Imaging. 2004;31:1631-8

Madsen J, Elfving B, Andersen K, Martiny L, Knudsen GM. Gas phase production of [11C]methyl iodide-d3. Synthesis and biological evaluation of S-[N-methyl-11C]citalopram and deuterated analogues. J Label Compd Radiopharm 2004;47:335-48

Pinborg LH, Adams KH, Yndgaard S, Hasselbalch SG, Holm S, Kristiansen H, Paulson OB. Knudsen GM. [^{18}F]altanserin binding to human 5HT2A receptors is unaltered after citalopram and pindolol challenge. J Cereb Blood Flow Metab 2004;24:1037-45

Sveen ML, Knudsen GM, Aznar S. No effect of MDMA (ecstasy) on cell death and 5-HT(2A) receptor density in organotypic rat hippocampal cultures. Neurosci Lett. 2004;362:6-9

Other

Liptrot M, Adams KH, Martiny L, Pinborg LH, Lonsdale MN, Olsen NV, Holm S, Svarer C, Knudsen GM. Cluster analysis in kinetic modelling of the brain: a non-invasive alternative to arterial sampling. NeuroImage 2004;21:483-93

Nielsen JE, Johnsen B, Koefoed P, Scheuer KH, Grønbech-Jensen M, Law I, Krabbe K, Nørremølle A, Eiberg H, Søndergård H, Dam M, Rehfeld JF, Krarup C, Paulson OB, Hasholt L, Sørensen SA. Hereditary spastic paraplegia with cerebellar ataxia: a complex phenotype associated with a new SPG4 gene mutation. Eur J Neurol 2004;11:817-24

Quarantelli M, Berkouk K, Prinster A, Landeau B, Svarer C, Balkay L, Alfano B, Brunetti A, Baron JC, Salvatore M. Integrated Software for the Analysis of Brain PET/SPECT Studies with Partial-Volume-Effect Correction. J Nucl Med 2004;45:192-201

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7. Other Activities

7.1. Congress Participation

The staff of NRU has participated in 34 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 was a member of the organizing committee of the 34th Scandinavian Neurology Congress and organized the session: 'Neuroimaging clinical relevance and perspectives'.

Gitte Moos Knudsen was a program committee member of the European Association of Nuclear Medicine Congress, Helsinki, September 2004.

Olaf B. Paulson was a member of the Programme Committee for the Federation of European Neuroscience Society's annual meeting in Lisbon in 2004.

Olaf B. Paulson was Chairman of the local organizing committee of ESMRMB's annual meeting in Copenhagen September in 2004.

7.3. Pre- and Postgraduate Teaching

PhD-course: Functional Imaging Techniques II: Tracer kinetics in nuclear medicine and magnetic resonance imaging, March 1-5, 2004.

SPM and Co. Workshop - Workshop on the technical issues of neuroimage analysis. November 2-3, 2004.

Teaching course: Functional neuroimaging: PET and fMRI for studies of the functional activation of the brain. Methodological and physiological considerations at the 14th Meeting of the European Neurological Society, June 2004.

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 18, 2004, NRU organized an open-to-the-public one day symposium where scientists from NRU presented their most recent data.

Pregraduate Supervision:

Master thesis biology. Jan Tønnesen: Validation of laser Doppler flowmetry against the intraarterial 133-xenon injection method for measurement of cerebral blood flow in rats (supervisor: Gitte Moos Knudsen).

Master thesis biology. Heidi Kristiansen: Binding characteristics of the serotonin$_{2A}$

receptor antagonists [^{18}F]-altanserin and [^{3}H]MDL 100907 (supervisor: Gitte Moos Knudsen).

OSVAL2. Medical student Karine Madsen: Quantitation of regional cerebral blood flow in Brain SPECT (supervisor: Gitte Moos Knudsen).

OSVAL 2. Sarah Stenum Poulsen: Langt QT syndrom hos synkopepatienter i neurologisk regi (supervisor: Gitte Moos Knudsen).

OSVAL 2. Sofie Høyer-Hansen: Serotonergic projections and synapses in the hippocampus in a genetic rat model of depression (supervisors: Susana Aznar and Gitte Moos Knudsen).

OSVAL 2. Shanu F. Rømer: Billeddannende spektroskopi til måling af metabolitratioer i grå substans blandt 18 patienter med relapsing-remitting multipel sklerose (supervisors: Henrik Mathiesen, MR Dept., Hvidovre and Olaf B. Paulson).

OSVAL 1. Matias Vested: Hjernen og dens autoregulation ved hypertension (supervisor: Olaf B. Paulson).

OSVAL 1. Tanja Korfitsen: Motorisk indlæring belyst ved funktionel billeddannelse (supervisor: Daniela Balslev).

Cell Biology Project I. Cecilie Löe Licht: Evaluation of different approaches for 5-HT depletion in the rat brain (supervisor: Gitte Moos Knudsen).

Cell Biology Project II. Cecilie Löe Licht: Receptor splice variants in the serotonin system (supervisor: Gitte Moos Knudsen).

Cell Biology Project II. Morten Skøtt Thomsen: Hippocampal plasticity and cellular resilience in depression (supervisor: Gitte Moos Knudsen).

Cell Biology Project II. Sandra Vergo: Regulation of intraneuronal dopamine homeostasis (supervisor: Gitte Moos Knudsen).

Engineer Project ('forspeciale'). Mikael Palner: Evaluation of new PET ligands by quantitative autoradiography (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 Health Science Faculty Research Council, Copenhagen University (Gitte Moos Knudsen)

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

Member of the committee for implementation of clinical neuroscience and psychiatry in the new curriculum for the physician education at the University of Copenhagen (Olaf B. Paulson)

Member of the board of directors of the Ludvig and Sara Elsass' Foundation (Olaf. B. Paulson)

Member of the board of directors of the Jørgen Wendelboe-Jørgensen and Laura Wendelboe-Jørgensens' Foundation (Olaf B. Paulson)

Member of the board of directors of the Niels A. Lassen Foundation (Olaf B. Paulson)

Member of the advisory committee for the 'Fondsbørsvekselerer Henry Hansen og Hustru Karla Hansen, født Westergaards Foundation' (Olaf B. Paulson)

International Committees:

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

Member of the Executive Board of the European Society for Magnetic Resonance in Medicine and Biology (ESMRMB) 2003-04 (Olaf B. Paulson)

Evaluation:

Evaluator of doctoral thesis: Helle Iversen (Gitte Moos Knudsen)

Evaluator of PhD thesis: Carsten Reidies Bjarkam (Gitte Moos Knudsen)

Evaluator of PhD-thesis: Steffen Birk (Gitte Moos Knudsen)

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

Reviewer (member of basic science session) on the Swedish 'Brain Power', (Gitte Moos Knudsen)

Reviewer (chairman of the methodology session) on the Swedish 'Brain Power' project (Olaf B. Paulson)

Member of mid-time review committee PhD-project: Zsolt Cselényi (Claus Svarer)

Member of mid-time review committee PhD-project: Judit Sovago (Claus Svarer)

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

Olaf B. Paulson received the Mogens Fog Prize of Honour 2004, donated by the 'Fonden for Neurologisk Forskning'.

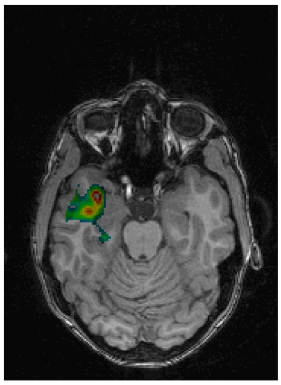
From the left:
Per Soelberg Sørensen representing the Foundation and Olaf B. Paulson

Claus Svarer: Best poster and poster presentation at the 'International Workshop on Quantification in Biomedical Imaging with PET and fMRI', Osaka, Japan, January 26-27, 2004.

From the left:
Congress Chairman Hidehiro Iida, Osaka, Japan and Claus Svarer

8. SPECT Laboratory

A total of 368 scans, of which 326 were conducted for diagnostic purposes, have been performed in 2004. Further a new clinical procedure has been implemented: Software for subtraction of interictal and ictal SPECT images as a clinical tool in the presurgical work-up.



Subtraction image of interictal/ictal [^{99m}Tc]-SHMPAO SPECT superimposed on a MR scan

The dopamine transporter ligand [^{123}I]-PE2I is now fully implemented as a tool for diagnostic work-up of parkinsonistic patients.

Research projects carried out in 2004

- Database of healthy controls with and without transmission scan correction completed
- 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
- Cerebral blood flow changes in a patient cohort from the Memory Clinic
- High energy photon correction for [^{123}I] in SPECT-studies
- The clinical application of arterial spin labelling in dementia evaluation
- Implementation of system for correcting SPECT acquisitions for head movements during scanning using a Polaris Accedo System
- Tracer evaluation in pig studies

9. Prospects

In 2005, there will continue to be new tasks and challenges for NRU. We anticipate that several new PET radiotracers for the serotonergic and GABA-ergic transmitter systems will be introduced at the PET Unit at Rigshospitalet. In addition, Rigshospitalet will in 2005 inaugurate another PET/CT scanner which is likely to better accommodate the increasing needs for clinical FDG PET scans. The scanner has kindly been donated by the John and Birthe Meyer Foundation.

The Faculty of Health Sciences of Copenhagen University has enabled the creation of two new initiatives to be established within the Faculty. Firstly, the NeuroCluster which is a consortium of Faculty employed neuroscientists has been created. The NeuroCluster currently encompasses about fifty neuroscientist groups dealing with the basic or clinical neuroscience research. The mission of the NeuroCluster is to strengthen the Faculty's neurobiological research and teaching by promoting collaborative cross-disciplinary research and pre- and postgraduate education within the neuroscience field. We look very much forward to strengthen the collaboration with our Copenhagen colleagues.

Secondly, the Faculty has decided to establish a cluster dealing with molecular imaging, this will involve that the Faculty establishes optical imaging and small animal PET facilities as a core facility for Faculty employees.

Also, on the international arena, we expect that the collaboration will be further strengthened. The EU funded concerted action 'Neuroreceptor Imaging in Mild Cognitive Impairment' has been granted an extension until March 2006. This will allow us to better complete the milestones and deliverables laid out from the beginning. In 2005, a network of excellence project funded by the sixth framework program will be initiated. The project 'Diagnostic molecular imaging (DiMI)' is led from the Institute of Neurology in Cologne, Germany. This is a huge network of molecular imaging scientists consisting of approximately fifty different European Centres and private companies. Important issues to be dealt with in this program include development of new radiotracers for brain imaging, neurodegenerative and neuroinflammatory disorders.

With these new prospects we look forward to a strengthen collaboration, both nationally and internationally, during 2005.

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Ludvig og Sara Elsass Fond
M.L. Jørgensen og Gunnar Hansens Fond
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The Lundbeck Foundation
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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. Et kort resumé gives nedenfor.

To PhD-studier er blevet afsluttet ved afhandlinger: Farmaceut Karen Husted Adams, der har været tilknyttet NRU siden 1998 og blandt andet har været udstationeret ved Hammersmith Hospital i London, forsvarede sin afhandling om 5-HT_{2A} receptorbinding målt med PET. Hendes studier omfattede dels rapportering af resultater af en stor database af raske forsøgspersoner, der har fået foretaget 5-HT_{2A} receptorbindingmålinger. Denne database vil give udgangspunkt for fremtidige detaljerede analyser. Hun har endvidere i samarbejde med Psykiatrisk Klinik (professor Tom G. Bolwig og afdelingslæge Elsebet Steno Hansen) gennemført en undersøgelse af patienter med obsessiv-kompulsiv sygdom og kunne her påvise specifikke forandringer i 5-HT_{2A} receptorbindingen. Endvidere forsvarede læge Kristin Scheuer sin PhD-afhandling omhandlende patienter med en nedarvet sygdom i centralnervesystemet, der især viser sig ved spasticitet i benene. Hendes studier omfattede såvel funktionelle som strukturelle billeddannende undersøgelser, der blev sammenholdt med fundene ved omfattende neuropsykologisk testning.

Hovedinteressen i NRU's forskningsaktiviteter er molekylær billeddannelse, specielt med fokus på undersøgelse af hjernens receptorforhold. Dette forskningsfelt har fået stigende betydning igennem de senere år og spænder over cellekulturer, dyreeksperimenter og kliniske undersøgelser. Det mere traditionalle arbejde ved forskningsenheden med udforskning af hjernens blodcirkulation og stofskifte samt funktionel kortlægning af hjernen fortsætter også, om end i noget mindre omfang end tidligere. Inden for det sidstnævnte forskningsfelt om hjernens funktionelle aktivering har funktionelle magnetiske resonansundersøgelser, fMRI, vundet indpas og efterhånden helt erstattet undersøgelser med PET til måling af ændringer af blodcirkulationen. Sidstnævnte undersøgelser udføres derfor nu på MR-afdelingen på Hvidovre Hospital, med hvem NRU har et tæt samarbejde. NRU's forskning om datanaalyse og tracerkinetiske modeller ved receptorundersøgelser er et felt, som har fået stigende interesse gennem de senere år, og NRU har her flere eksterne samarbejdspartnere.

I april 2004 blev forskningsprofessor Gitte Moos Knudsen ansat i en tidsubegrænset stilling som professor ved det Sundhedsvidenskabelige Fakultet ved Københavns Universitet. I juni 2004 overtog Gitte Moos Knudsen herefter den formelle ledelse af NRU efter professor Olaf B. Paulson. Dette generationsskifte har været omhyggeligt planlagt over en årrække og har følgelig ikke medført drastiske ændringer. Professor Olaf B. Paulson forbliver som professor ved Neurobiologisk Forskningsenhed og som chef for Dansk Forskningscenter for Magnetisk Resonans på Hvidovre Universitetshospital.

2005 forventer vi bliver et spændende og udfordrende år. Københavns Universitets

Sundhedsvidenskabelige Fakultet har besluttet at etablere et 'Neuro-cluster', det vil sige en sammenslutning af fakultetsansatte forskere, som består af omkring 50 neurovidenskabeligt arbejdende forskergrupper. Ligeledes vil der blive etableret et Center for Molekylær Billeddannelse, som en 'core facilitet' for fakultetets ansatte. I løbet af 2005 vil NRU desuden have en nøgleposition i et af EU's 6. rammeprogram finansieret 'Network of Excellence', hvori der indgår omkring 50 europæiske forskningsmiljøer. De vigtigste hovedtemaer for NRU bliver udvikling af nye radiomærkede sporstoffer til hjerneundersøgelser samt studier af patienter med tidlig Alzheimers sygdom, Parkinsons sygdom og betændelsestilstande i hjernen.

Ved NeuroReceptor Mapping mødet i Vancouver i Canada i sommeren 2004 blev det besluttet at udpege NRU som vært ved det næste møde, som skal afholdes i 2006. Vi er allerede i fuld gang med at arrangere dette og ser frem til at kunne byde vores internationale kolleger velkommen til København i juli 2006.

Slutteligt vil vi gerne benytte anledningen til at takke de mange fondsydere, der har støttet NRU's forskning. Uden denne støtte ville store og væsentlige dele af NRU's forskning ikke kunne gennemføres.

NRU staff September 2004