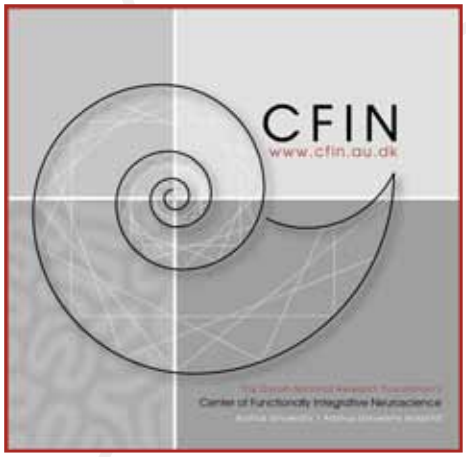

The Danish National Research Foundation's
Center of Functionally Integrative Neuroscience

ANNUAL REPORT 2006

cognition
PET
statistics
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physics
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music
neuroanatomy

Introduction - 2006 in words

by Leif Østergaard

In 2006 The Danish National Research Foundations Center of Functionally Integrative Neuroscience (CFIN) entered its second funding period. With the hard work of founding CFIN scientists, PhD projects initiated during the first funding cycle have now fostered exciting results and promising young talent, just as CFIN cross-disciplinary research profile has attracted prominent scientists and grants to develop exciting neuroscience.

In early 2006, an application from Andreas Roepstorff to The Danish National Research Foundation led to the granting of one of five Niels Bohr Guest Professorships to CFIN. This guest professorship has made it possible to attract two unique researchers to the University of Aarhus – Chris Frith, professor of neuropsychology at Welcome Department of Imaging Neuroscience in London and Uta Frith, professor from the Institute of Cognitive Neuroscience & Dept. Psychology, University College London. The Frith's are famous for their groundbreaking work on the use of theoretical models of cognition and consciousness, advanced brain scanning techniques, and clinical examinations to understand what happens when people communicate. At the University of Aarhus they will be affiliated with both the Faculty of Humanities and the Faculty of Health at CFIN.

In 2006, CFIN received a major grant from EU for over 3 million Euros for the research project I-Know (Integrating Information from Molecule to Man: Knowledge Discovery Accelerates Drug Development and Personalized Treatment in Acute Stroke). In cooperation with leading European research groups and two software companies from Aarhus, this project aims to develop advanced technology to help diagnostics and treatment of stroke. With the grant, results from basic neuroscience within CFIN is brought into the clinical management of patients, hopefully leading to better treatment for stroke patients worldwide – and new, cutting-edge neuroscience.
Read more at: http://www.i-know-stroke.eu

In 2006, Arne Møller, M.D. took over the coordination of the CFIN neurotransmission research, from February 2007 in an Associate Professor position. Arne Møller has a strong academic and industrial background in experimental neurotransmission research. Meanwhile, prof. Doris Doudet, a neurobiologist from University of British Columbia in Vancouver, joined CFIN in October 2006, initially in a visiting professor position. The strong scientific profiles of Arne Møller and Doris Doudet, has led to the initiation of exciting integrative neurotransmission research, and the acquisition of additional funding through the impressive grantsmanship of Arne Møller and Jakob Linnet, PhD, who coordinate pathological gambling research.

CFINs postgraduate teaching and research school SFINX (Graduate School of Functionally Integrative Neuroscientific Experimentation) was started in January 2006. Head of the PET-center at Aarhus Hospital and coordinator of neuroenergetics research, Professor Albert Gjedde, coordinates the new research school which offers courses, workshops and seminars within the neuroscientific area.
Read more at: http://www.cfin.au.dk/SFINX.

In January 2006, CFIN hosted the symposium Brain Storm 2006, a celebration of Albert Gjedde's 60th birthday and the inauguration of SFINX. The symposium brought a long list of esteemed and internationally recognized researchers within neuroscience to Aarhus. The symposium was very well attended.
Read more at: http://www.cfin.au.dk/brainstorm

In 2006, CFIN continued to work on establishing pre-graduate cross-disciplinary teaching at the University of Aarhus. In 2005, CFIN coordinated courses and teaching from all five faculties at the university and introduced a course catalogue called NEUROVIDEN 2005/2006. This catalog offered teaching in neuroimaging, cognition, brain research and similar topics. In 2006/2007 the course catalogue has become web-based.
Read more at: http://www.cfin.au.dk/neuroviden-06-07

In April 2006, CFIN and The Royal Academy of Music hosted the first international music and brain research conference Music in the Brain. The conference was successful, bringing highly esteemed researchers to Denmark. The conference marked the formation of a cross-disciplinary, international research network examining the connection between music and brain. This cooperation has its roots in a fruitful research cooperation between CFIN, The Royal Academy of Music and University of Aarhus.
Read more at: http://www.musicinthebrain.dk

CFIN is continuing to grow. By fall 2006, with the help of Aarhus University Hospital, additional office space was acquired at Peter Sabroes Gade 14A. However CFIN researchers look forward to 'being together again'. In a visionary project, aiming to bring cutting edge neuroscience, patient management, and industrial innovation, Region Midtjylland and University of Aarhus will build the Danish Neuroscience Center (DNC). The new counsel for Region Midtjylland approved this project on December 16th, 2006. The 6000 m2 DNC building will be completed by 2008/2009, and will house CFIN on two floors.

The Annual Report provides an overview of main CFIN research areas, highlighting events and research projects finalized during 2006. We wish to acknowledge the support that made this work possible.

Leif Østergaard
CFIN director

NEUROENERGETICS

by Albert Gjedde

Progress in 2006

In 2006, the activity in the field of neuroenergetics at the Center of Functionally Integrative Neuroscience has been devoted to the critical test of the convential claim that changes of blood flow to the brain serve the needs of brain energy metabolism that is coupled tightly to the changes of brain function. Comparisons carried out by multiple groups of researchers at CFIN engaged in different projects involving young and elderly subjects at steady-state and during changes of brain function caused by voluntary and involuntary finger movement, exhaustive exercise, bicycle motion, and smoking, as well as without or with evidence of hypertension, white matter lesions, stroke, hepatic encephalopathy, Alzheimer's disease, and Parkinson's disease.

From the comparisons, the researchers calculated oxygen-glucose indices and oxygen extraction fractions to evaluate the relative changes. The researchers investigating oxidative metabolism in the human brain include the PhD-students Mahmoud Askanian, Christopher Bailey, Per Borghammer, Peter Iversen, Ericka Peterson, and groups of collaborators in Copenhagen (headed by Professor Niels H. Secher at Rigshospitalet and Professor Martin Lauritzen at Glostrup Hospital) and New Haven, CT (headed by Associate Professor Fahmeed Hyder at Yale School of Medicine), where Christopher Bailey is completing a major part of his PhD-work.

Several conclusions were reached in the course of this effort. First, it is an exciting new finding that the oxygen tension in the vicinity of mitochondria declines during functional activation, such that brain tissue generally hovers on the brink of insufficient oxygen supply because of the special relationship between oxygen binding to hemoglobin in arterial blood and the diffusion of oxygen from brain microvessels to mitochondria. The diffusion is driven almost entirely by the average partial pressure of oxygen in brain capillaries. The effective oxygen tension in brain tissue therefore is the result of a balance between the consumption of oxygen, driven by the tension, and the diffusion of oxygen from the circulation, which is inhibited or counteracted by this tension.

Second, the efforts have confirmed that the oxygen-glucose index declines immediately following a change of functional activity, most likely because of greater activation of astrocytes than of neurons during the first phase of an activation. This finding suggests a degree of delegation of brain work between a receiving unit consisting of the presynaptic terminals of afferent neurons, the postsynaptic dendrites of efferent neurons, the foot-processes of astrocytes, and the microvessels, and a discharging unit consisting of the cell bodies and axons of the efferent neurons, and the cell bodies and axons of the inhibitory interneurons. It is possible that the activity of the receiving unit is reflected in changes of glutamatergic neurotransmission, blood flow, and glucose consumption, while the activity of the discharging unit is reflected in changes of GABAergic neurotransmission and oxygen consumption.

Third, it is evident from the work on different types of activation of the awake human brain that the blood flow changes are much more substantial than the oxygen consumption changes and that increases of blood flow in some brain regions are matched by decreases in other places, as predicted many years ago by Niels A. Lassen and his co-workers using SPECT imaging of inhaled xenon-133. The default mode of brain operation results in a state of energy metabolism that is reflected in a stable oxygen extraction fraction of about 40%, and it is this extraction fraction that rises and falls in response to blood flow changes, not the absolute energy metabolic rate itself.

Fourth, it is clear that we have no good clue to the function served by the blood flow fluctuations when energy metabolism remains unaffected. An excellent example of this mystery is the well-known fact that changes of CO2 during hyper- or hypoventilation lead to great changes of blood flow that have little or no influence on brain function and oxygen consumption. But it also means that it is not reasonable always to interpret changes of blood flow as changes of brain function.

The summary above yields the prediction that low oxygen tension in brain over longer periods of time can initiate a process of degeneration (apoptosis) which eliminates mitochondria and subsequently causes cell death. It is not easy to measure oxygen tensions in live brain tissue, but several direct and indirect methods have become available in recent years. One indirect approach is to calculate the tissue oxygen tension from the oxygen extraction fraction and the oxygen consumption rate on the assumption of certain basic facts about brain tissue (that may themselves be less than certain). Work with Associate Professor Arne Møller shows that non-ionizing radiation as emitted by cellular telephones may raise oxygen metabolism in medial temporal lobe without a concomitant increase of blood flow, thus raising oxygen extraction and potentially lowering mitochondrial oxygen tensions.

In the future, the work of neuroenergetics at CFIN is focused on the critical testing of the specific hypothesis that the tension of oxygen at the sites where the oxygen is consumed (i.e., the mitochondria) is poised just above a critical threshold associated with fatigue in the short run and degeneration in the long run. The relations among blood flow, oxygen consumption, oxygen extractions and oxygen tension are about to be measured during activations of brain tissue in young and aged individuals. Preliminary work on more and less strenuous exercise by healthy young volunteers suggests that fatigue and sleepiness sets in when oxygen tensions are low and perhaps are designed to prevent further reductions in brain, even when sources of energy are still available in the muscles.

Next page:
Brain surface images of cerebral blood flow (CBF)
Above: CBF during normal breathing of atmospheric air
Below: CBF during inhalation of carbogen (5% CO2 og 95% O2)
Courtesy Mahmoud Ashkanian

Neuroenergetics Publications 2006

Gjedde A. Blood-brain transfer and metabolism of oxygen. In: Blood-Brain Barriers: From Ontogeny to Artificial Interfaces. Dermietzel RS, Spray DC, Nedergaard M, eds. 2006. Hoboken: John Wiley & Sons, Ltd., volume 2, chapter 22, pp. 523-549.

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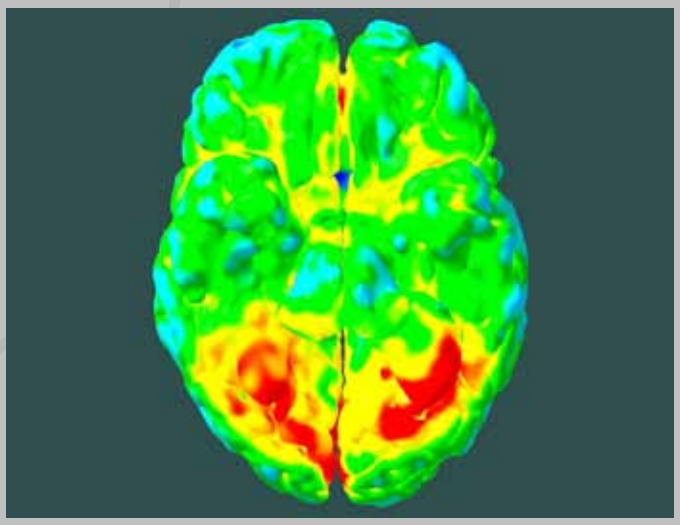

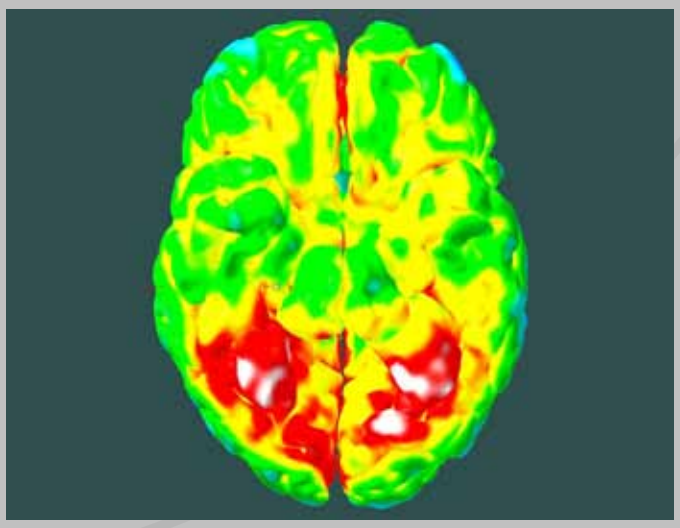

SELECTED RESEARCH PROJECTS:

Anders Rodell, Jamila Ahdidan: Longitudinal study of cerebral deformation and cognitive deficits in depression.

Anders Rodell, Albert Gjedde: Hypotime: direct calculation of parametric images in WAY-PET.

Arne Møller, Paul Cumming, Andreas Roepstorff, Albert Gjedde: Effect of mobile phones on blood flow and oxygen metabolism in the brain.

Christopher Bailey, Basavaraju Sanganahalli, Peter Herman, Albert Gjedde and Fahmeed Hyder: Quantitative imaging of the rat visual system using functional MRI at 11.7T and unit recordings.

Lise Schlunzen, Manouchehr Vafaee: Cerebral blood flow changes in healthy controls under hyperventilation.

Malene Vejby Mortensen, Albert Gjedde: Mapping of auditive processes in normal hearing, deaf, and cochlea implantees.

Malene Vejby Mortensen, Albert Gjedde: Auditory cortical responses in unilateral deafness as a model for auditory system development after pediatrics cochlear implantation.

Malene Vejby Mortensen, Albert Gjedde: Mapping of cerebral language areas prior to neurosurgery and cochlea implantation - a normal material.

Manouchehr Vafaee, Albert Gjedde: Study of cerebral blood flow in use of different anesthetics.

Manouchehr Vafaee, Mahmoud Ashkanian, Leif Østergaard: Improved oxygen uptake in the brain in stroke patients through inhalation of CO2 and O2 mix.

Manouchehr Vafaee: CBF and CMRO2 in healthy aging.

NEUROENERGETICS

The Great Energy Debate

by Albert Gjedde

Overview of CFIN Neuroenergetics Research 2001-2006

Is brain work a measure of brain function? If not, what is? Uninterrupted oxygen delivery to the mammalian brain is necessary for normal functioning of this organ, but it is not entirely clear how critical it is. It is clear that without energy there can be no work, and 99.5% of the energy turnover in brain tissue is linked directly to oxygen consumption. However, evidence obtained in the last decade of the 20th century suggests brain activity can rise without a change of oxygen consumption. However, there is other and much older evidence that conscious brain function ceases as soon as six seconds after complete interruption of oxygen delivery, without apparent depletion of key metabolites in brain tissue. Conventional mechanisms of obligatory flow-metabolism coupling fail to explain the dissociations between flow, metabolism, and brain function.

The key question raised by this conundrum is the extent to which conscious brain function is directly related to brain work. Is it possible that the majority of the work performed by the brain, as judged from the energy turnover, is not directly linked to, and therefore, cannot be an index of conscious brain function? The research of the first five years of neuroenergetics activity at the Center of Functionally Integrative Neuroscience focused on this question.

Functional brain imaging is motivated by the question raised above. Also known as brain mapping, this method has been the dominant neuroscientific tool for four decades, but the answer is as elusive as ever. If phrenology is included in the history of brain mapping, the question has been open for more than 200 years. Now, however, the practitioners of this method face an important challenge that pits the neophrenologists against the energeticists. At the core of this challenge is the emerging discipline of neuroenergetics. On both sides of the current controversy, we find physiologists and biochemists who try to fill the void left by the psychologists when they abandoned the bodily brain in favor of more spiritual notions of how the mind works. In contrast, many neuroscientists were trained by the circulation physiologists and biochemists who invented the methods that are still used to measure blood flow and brain energy metabolism in regions of the brain.

The core of the debate is the observation that blood flow rates vary greatly in apparent step with changing brain functions, while rates of brain energy metabolism, roughly in proportion to rates of ATP turnover, vary little from the normal average of healthy and awake volunteers. These observations raise the question of which of the two measures of brain activity that matters to brain function, the wide fluctuations of blood flow or the more stable rates of energy turnover?

Two additional observations compound the uncertainty. Glucose phosphorylation is the prelude to glucose oxidation to lactate or carbon dioxide, depending on the preference of the cells that use the glucose. First, it appears changes of glucose phosphorylation match the large changes of blood flow rather than the small changes of energy turnover, suggesting the fluctuations of blood flow are really unrelated to any change of energy turnover. Second, however, it paradoxically also appears that the rate of oxidative metabolism, which is coupled to the energy turnover, is matched by the rate of neurotransmitter release over a surprisingly wide range of functional states of the brain from coma to seizures. At first sight, these observations lead to the surprising conclusion that the magnitude of brain work must always be the same.

As the first messengers of brain function, neurotransmitters distribute information among the cells of nervous tissue, providing the cells with the stuff that brain work presumably is made of. The observation that neurotransmission matches brain energy metabolism over a wide range of activities suggests that brain function is more closely linked to the energetically more important changes of oxidative metabolism than to the energetically less important changes of blood flow and glycolysis. Add to this the realization that there is more than one class of cells in brain tissue, of which the glial cells known as astrocytes seem to play important roles in the regulation of blood flow rates and glycolysis, while the cells known as neurons seem to play equally important roles in the regulation of oxidative metabolism, and we are saddled with an important scientific controversy: Is the study of how the brain works more properly the study of brain energy metabolism, or are maps of experimentally induced blood flow changes the correct approach? Is information processing energetically costly to the brain, or is brain tissue hard-wired to handle changes of information processing with a minimum of real work, fortuitously coupled to the flow and glycolysis changes that happen to be very visible in the brain images?

On the one side of this controversy we find the neophrenologists who are the followers of David Ingvar and Niels A. Lassen in Scandinavia. They seek generalities in the varied patterns of localized blood flow changes in cerebral cortex and assign specific modular functions to the sites of peak change. The advantage of this position is that patterns of change are easily measurable. On the other side, we find the energeticists who are the followers of Robert G. Shulman and Louis Sokoloff in the U.S. They regard the fluctuating changes as minor in comparison with the vast underlying average activity of cerebral cortex, by now known as the “default” activity associated with a “resting” average awake state. The latter position is less defensible in practice, because it is difficult to formulate hypotheses of mechanisms of brain function from measures of metabolism that do not yield to functional pertubations in the awake default state.
It is an interesting feature of the controversy that both sides cite the work of the Swiss neuroscientist Pierre Magistretti and his coworkers, but they do so for different and in part incompatible reasons. The

work of Magistretti and his coworkers integrates the results of several different lines of inquiry into a view of the biology of astrocytes, which is perceived very differently by the participants in the great energy debate. First, astrocytes are clearly more glycolytic than neurons and hence generate more pyruvate relative to their ATP turnover than do neurons. Second, astrocytes also actively remove potassium ions and the neurotransmitters glutamate and GABA, both released to the extracellular space during neurotransmission.

The glutamate is returned to the presynaptic neurons through a series of metabolic steps that involve the astrocytes. The fate of the potassium ions is less certain, but they may use astrocytes as bridges to the vicinity of microvessels. Much has been made of the fact that the foot processes of the astrocytes extend from the synaptic cleft to the capillaries of the brain; thus, provide a cellular link between neurotransmission at the synapse and neurovascular regulation at the microvessels. It is possible that these activities are part of a more substantial role for astrocytes than previously held by neurobiologists but the evidence is incomplete.

According to the neophrenologists, the astrocytes react glycolytically to appropriate neurotransmission and also engage the neurovascular coupling to change blood flow. The reactions are held to reflect the processing of information in the synapse that the neurotransmission elicits, but they are not coupled to any significant change of oxidative metabolism because the demand for rapid removal of glutamate and potassium is so great that it can only be satisfied by glycolytic generation of ATP in the cytosol of the astrocytes, with little contribution from the much less flexible phosphorylation of ADP in the mitochondria. The neophrenologists claim that the lactate generated in the course of glycolysis in astrocytes first accumulates and then slowly diffuses from brain tissue, possibly helped by the increased blood flow, or subsequently undergoes delayed metabolism in the astrocytes, or both. According to the energeticists, the astrocytes react to neurotransmission as described above, but the experimentally induced changes of flow and metabolism are held to be small in comparison with the underlying default activity. For most of this default activity, the pyruvate and lactate resulting from glycolysis in astrocytes are an immediate source of substrate for oxidative energy metabolism of neurons, driven by activated mitochondria in the postsynaptic neurons. Thus, the controversy is also about the fate of the pyruvate and lactate generated by glycolysis. The neophrenologists focus on the fluctuating glycolytic activity of experimentally perturbed astrocytes and do not worry about the fate of the lactate, other than by claiming that it definitely is not the source of increased oxidative metabolism, while the energeticists focus on the stable glycolytic activity of astrocytes precisely because it is believed to provide a ready but not obligatory substrate for the total oxidative metabolism of neurons.

Participants in the great energy debate hold that a convergence of positions is in sight. The key to the compromise may be the consideration of timing, i.e., the difference between unsteady- and steady-states. Steady-state is a concept defined by physiologists as the circumstance in which concentrations of substrates and metabolites do not change with time because the homeostatic mechanisms of the brain regulate the fluxes of the molecules but maintain their concentrations constant. However, it is clear that the stimuli and tasks imposed by the neophrenologists during functional brain imaging experiments can be sufficiently potent to perturb the default steady-state of the normally functioning brain and hence briefly disrupt the steady-state.

The needs of ion homeostasis are more rapidly matched by the glycolytic activity of astrocytes that responds quickly to the perturbation. In contrast, the oxidative phosphorylation of ADP in the mitochondria of neurons responds much more sluggishly. The disruption of steady-state may be magnified by experimentation with atypically strong stimuli and tasks that exceed what the brain normally handles and hence may be unphysiological. It is also a factor that the experiments of the energeticists are more compatible with steady-state, because the measurements take place over much longer periods of time.

What is the consequence of such a compromise for the understanding of brain function? First, it clearly complicates matters because the patterns of brain activation mapped by functional brain imaging would be sensitive to arbitrary circumstances of the brain imaging experiment itself that are very difficult to control. Second, it diverts the focus of brain mapping from the easy measurability of blood flow change associated with astrocytic activity to the less easily measurable change of oxidative metabolism associated with neuronal activity. The hope is that the combination of the two perspectives eventually would yield a more comprehensive account of brain function than they could yield separately.

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The Danish Neuroscience Center (DNC) at Aarhus University Hospitals

by Albert Gjedde

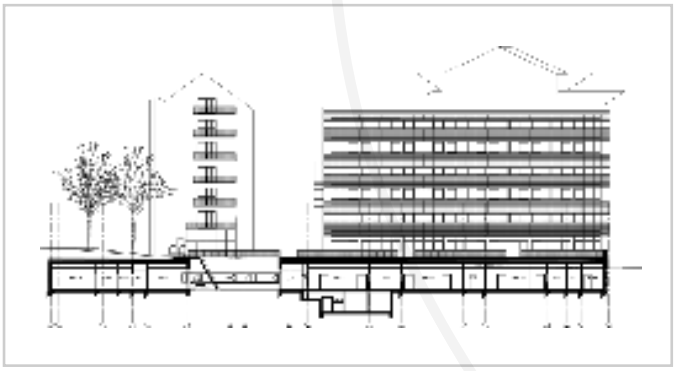
The Aarhus University Hospitals inaugurates a new laboratory building in late 2008. The Danish Neuroscience Center (DNC) completes the triangle of buildings at the topmost end of Aarhus Hospital where the majority of the neurological departments of the university hospitals are located. The building will be the home of research and innovations within neuroscience in Aarhus, to the benefit of patients and researchers alike.

The vision of the DNC is to allow teams of researchers to interact with patient populations and clinicians to understand the brain and its responses to disease and treatment. With designated space for collaborations with industry, DNC will turn this knowledge into better diagnosic tools and therapies for patients. The Danish Neuroscience Center is modelled on similar institutions in Montreal (Montreal Neurological Institute) and London (Institute of Neurology, Queen Square) that combine patient care and postgraduate education with research.

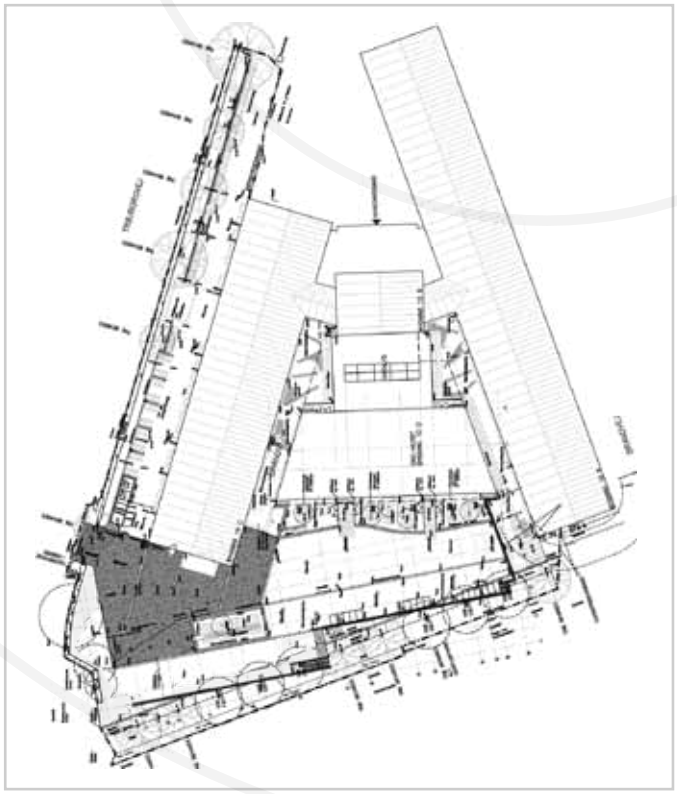
There are three goals of the activity at DNC. In random order, the first goal is to increase the understanding of brain function under normal and pathological circumstances and to reach relevant results by bringing patients, clinicians, and neuroscientists together. The second goal is to facilitate the translation of neuroscientific findings to clinical practice by direct testing and medical technology evaluation in close collaboration between researchers, clinicians, and industry. The third goal is to prepare future generations of clinician-neuroscientists who use the results of their own research to the benefit of their patients. It is the plan that clinician-neuroscientists continue to devote their efforts equally to research and clinical work after the conclusion of formal research training.

The main task of the DNC is to facilitate research, education, therapy, and innovation in all areas of neuroscience. Education and therapy must be based on an active and progressive research program to fullfil national and international criteria of academic medicine in competition with other national and international programs. In turn, it is necessary that the neuroscience at DNC is treatment-based and –oriented as linked to investigations of the effect and efficiency of specific therapies. DNC will be the seat of a graduate school of neuroscience that trains clinician-neuroscientists. The basis for this school is CFIN's School of Functionally Integrative Neuroscience Experimentation (SFINX).

For CFIN, the new laboratory building will hold two entire floors of office space and meeting rooms, situated close to collaborating clinical departments and research groups, and adjacent to extended neuroimaging facilities. Having outgrown temporary office space in various parts of Aarhus Hospital, CFIN now inhabits two separate buildings at Aarhus Hospital. CFIN is grateful for the vision and ambition of University of Aarhus and Region Midtjylland to invest in tomorrow's neuroscience and patient management.

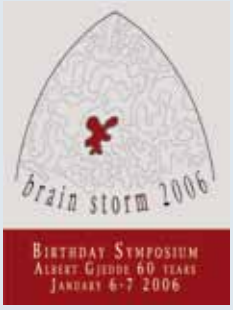


Foyer at the auditorium in DNC Building - Architect company C. F. Møller



Plan of new DNC Building - Architect company C. F. Møller

Brain Storm 2006



In January 2006, CFIN hosted the symposium BRAIN STORM 2006, to mark and celebrate Professor Albert Gjedde's 60th birthday.

Albert Gjedde, MD, DMSc, FAAAS, FRSC, is Professor of Medical Neurobiology at the University of Aarhus and Head of the Pathophysiology and Experimental Tomography (PET) Center of Aarhus University Hospitals since 1994, Adjunct Professor of Neurology and Neurosurgery at McGill University in Montreal, Canada, Radiology Consultant at the Department of Radiology, Division of Nuclear Medicine, of Johns Hopkins Medical Institutions, Baltimore, Maryland, and Visiting Professor of Diagnostic Radiology at Yale School of Medicine, New Haven, Connecticut.
He headed the McConnell Brain Imaging Center of the Montreal Neurological Institute in the period 1989-94, where he initiated a research program on the "Physiology and Pathophysiology of Neuronal Activation", funded by the Medical Research Council of Canada.
Co-founder of Center of Functionally Integrative Neuroscience (CFIN), Danish Neuroscience Center (DNC) and School of Integrative Neuroscientific Experimentation (SFINX).
His peer-reviewed reports of original research number 200 of a total of 325 publications, cited more than 6,000 times according to Science Citation Index.

The BRAIN STORM 2006 symposium brought a long list of internationally acclaimed researchers within neuroscience to visit Aarhus for two days. Among the famous speakers at the symposium were several former research colleagues of Albert Gjedde – from his time in Canada and the States – Clifford Patlak, Robert G. Schulman, Joseph D. Fenstermacher, Ronald Blasberg and many others.
The symposium was a big success and was a very well attended event with a high scientific level.

Read more at: www.cfin.au.dk/brainstorm

DNC Building facade to Nørrebrogade - Architect company C. F. Møller

NEUROTRANSMISSION

by Arne Møller

Progress in 2006

In 2006, CFIN neurotransmission research went through a profound reorganization. Paul Cumming, PhD chose to continue his scientific career in another laboratory. Arne Møller, M.D. oversaw this transition, with the completion and publication of a number of projects initiated by Paul Cumming. The research year students, Søren Dinesen Østergaard and Kasper Pedersen, submitted their reports, followed by a successful defence in March 2007. They have continued as part time employees at the center, as part of the integrated core group of translational research. In addition, Luciano Minuzzi and Mette Møller both submitted their PhD-theses (accepted and defended in 2007).

In an effort to understand the complex interplay of behavior and neurotransmission in the so-called 'reward system', CFIN studies pathological gambling in close collaboration with Jakob Linnet, PhD. Studies related to dopamine release in gambling showed exciting preliminary results and received a 1 million DKK grant to complete the studies. Two other gambling related programs started in 2006.

The CFIN neurotransmission research is currently being reorganized with more integration between in vivo and ex vivo/in vitro studies in basic (preclinical) research. A concerted effort is being made to create a multidisciplinary, integrated core group of expertise in large (pig) and small (rodent) animal studies. A preclinical motor and mood disorders imaging program with a strong emphasis in translational research is being formed with the addition of Adjmal Nahimi (research year), Pernille Jansen (post doc fellow), and projects continuing by Søren Dinesen Østergaard and Kasper Pedersen.

With enhanced exsperimental capabilities, a number of translational and integrative projects are now underway including:

Vagal Nerve Stimulation and Electroconvulsive Therapy

Two new projects encompass the longitudinal effects of electrical stimulation of the brain by vagal nerve stimulation and electroconvulsive therapy on the monoaminergic networks in depression, epilepsy and Parkinsonism in minipigs, aiming to perform follow up studies in patients. Autoradiography with relevant PET tracers will be added to the battery of ex vivo and in vitro autoradiography methods. Surgical techniques in rodents such as stereotaxic lesions or intracerebral injections are being implemented.

Alzheimer's Disease (AD)

A PhD-program has been initiated in this field. In these studies, changes in amyloid deposition in relationship with the loss of hippocampal neurons measured using a specific ligand of the serotonergic receptors will be evaluated in patients suffering from AD. The PhD student undertaking this project is Joel Astrup Aanerud, MD.

Music

A new clinical study has been initiated in collaboration with Peter Vuust, PhD to study the effect of musical performance on the reward system of experienced musicians.

Cognition

A PET-study examining the dopaminergic cortical regulation of cognition has been initiated by Professor Hans Lou using a new specific tracer of the dopaminergic extra striatal system.

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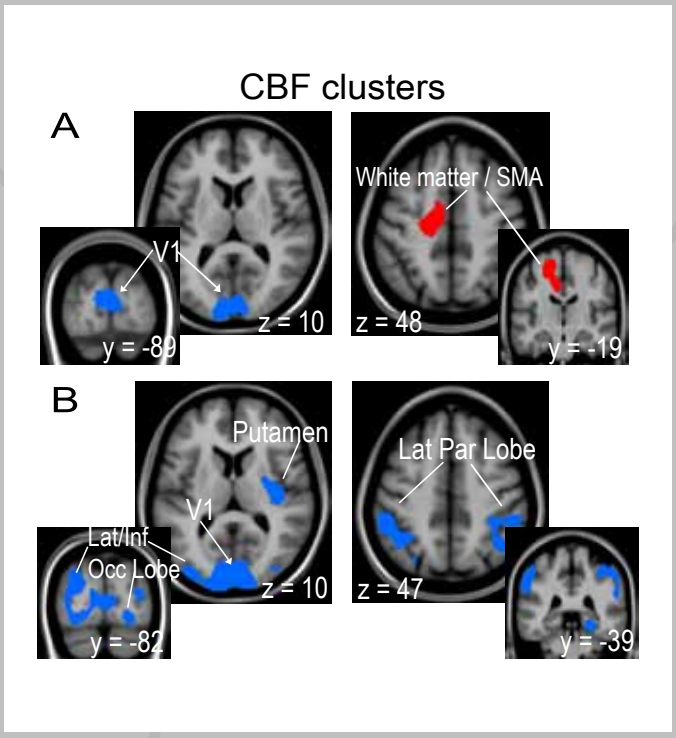

Above:
Differences in cerebral blood flow (CBF) between a group of patients with early Parkinson's Disease and healthy elderly controls.
Clusters of significantly different CBF voxels in the voxel-based analysis superimposed on an MRI atlas in Talairach space. Blue and red colors designate clusters where Parkinson's Disease patients had decreased / increased CBF compared to healthy controls. The small inset images show coronal sections of the largest significant clusters.

A. Analysis of data originally normalized to whole brain. A single cluster of decreased CBF in the V1 was found. A cluster of increased CBF was found in frontal lobe white matter expanding slightly into the SMA and anterior cingulate.
B. When normalizing the data to white matter, we found several areas of decreased CBF in PD patients in V1, inferior occipital lobe bilaterally, and right putamen / insula. There were no longer any significant clusters of increased CBF.

Courtesy: Per Borghammer, Karen Østergaard, Kristjana Yr Jonsdottir, and Albert Gjedde.

SELECTED RESEARCH PROJECTS:

Arne Møller, Jakob Linnet: The gambling reducing slot machine.

Bente Finsen (University of Southern Denmark), Paul Cumming: Expression of markers for micro glia proliferation in a rodent licien model.

Doris Doudet (University of British Columbia, Canada), Pedro Rosa Neto, Paul Cumming: Parametric mapping of monoamine markers in an ape model by MPTP induced Parkinsonism.

Jakob Linnet, Arne Møller, Andreas Roepstorff, Paul Cumming, Albert Gjedde: Pathological gambling.

Jakob Linnet, Arne Møller: Age differences in pathological gambling.

Paul Cumming, Mette Møller, Bente Pakkenberg (Bispebjerg Hospital): Stereological analysis of serotonin neurons in a pig model of ecstasy intoxication.

Per Borghammer: Parkinson's Disease judged by PET scanning including the farmacological effect of memantin.

Per Borghammer: Statistical stereotactic atlas of the brain in patients with Parkinson's Disease and healthy controls: Atrophy and neuropsychological evaluation.

Ron Kupers, Troels S. Jensen (Danish Pain Research Center), Nanna Witting (Danish Pain Research Center), Ruta Kuzminskyte: Pain and the brain.

Yoshitaka Kumakura, Albert Gjedde, Paul Cumming, G. Gründer (Mainz Universitet): Parametric mapping of dopa utilization in aging, Parkinson's Disease and Schizophrenia.

NEUROTRANSMISSION

The mystery of monoamine actions on brain function

by Albert Gjedde, Arne Møller and Paul Cumming

Overview of CFIN Neurotransmission Research 2001-2006

The monoamines are among the most active molecules in brain tissue, yet their general role in brain function are largely unknown, although the actions at the molecular level are understood in some detail.

The monoamines in brain differ from the main excitatory and inhibitory neurotransmitters glutamic acid and gamma-amino-butyric acid (GABA). They are called monoamines because they have a single amino group bound to an aromatic ring by a two-carbon chain, and they all stem from the aromatic amino acids phenylalanine, tyrosine, histidine, and tryptophan. In brain, the monoamines include the catecholamines dopamine and norepineprine as well as serotonin, melatonin, histamine, and the trace amines phenylethylamine, tyramine, and tryptamine. The most important to current research into brain function at CFIN and the PET Center include the catecholamine dopamine and the monoamine serotonin that act primarily subcortically (dopamine) or cortically (serotonin).

The importance of the monoamine transmitters derives from the nature of their transmission, which is now known as "volume" transmission (VT) to indicate that a significant fraction of the effect is established at a distance from the site of release. This makes the action of the monoamines more like that of hormones and it is sometimes called paracrine for that reason. Paracrine activity is terminated by monoamine transporters in cell membranes. The further the transporters are removed from the sites of release, the more paracrine the action is likely to be. This is true of the dopamine (DAT), serotonin (SERT), and norepinephrine (NET) transporters. In addition, there are the vesicular monoamine transporters 1 and 2 (VMAT-1 and VMAT-2) in the membrane of intracellular vesicles.

It is interesting to note that cell membrane transporters of dopamine and serotonin are particularly prominent in subcortical regions where some monoamine receptors are also located, while they are relatively scarce in cortical regions where other monoamine receptors reside. This anatomical arrangement suggests that the action of monoamines is confined to synapses and their immediate vicinity in the subcortical regions, where the transmission is sometimes called synaptic or "wired" (WT). In contrast, volume transmission appears to be important in the cortex where the cell membrane transporters are fewer. The cortical volume transmission means that the concentrations of the monoamines respond more slowly to changes of release or blockade of the transport in the cortex because they depend on the rates of diffusion over extended distances.

The Relation between Monoamine Occupancy and Brain Function

For a least a decade now, the reigning paradigm of neuroreceptor studies with PET has been the experimental modulation of the binding potential measure to show changes of monoamine concentration. The binding potential of a receptor system is determined with a radioligand. It is a steady-state measure of the ratio of radioligand molecules bound to the receptors and radioligand molecules in the tissue that are not bound to the receptors. It also equals the ratio of bound and unbound transmitter molecules, corrected for the ratio of the receptors' affinity to the radioligand and transmitter molecules. In Aarhus, we have measured the binding potentials for dopamine, serotonin and norepinephrine receptors in humans, Yorkshire landrace pigs, Göttingen minipigs, and rats.

The most important question concerning the monoamine volume transmission is how the release of monoamines relates to monoamine concentration, and how these concentrations relate to brain function. This is the question on which the work on monoamine neurotransmission at CFIN was focused in the period 2001-2006. The results vary, in part because the most popular method of modulating the monoamine concentration in brain in vivo is the blockade of the monoamine transporters with amphetamine or cocaine in subcortical regions and cortex. The unknown distance between the transporters and the sites of release and reception seriously confounds the interpretation of the results, even when results of microdialysis are available. Thus, it largely has been impossible to confirm increases of serotonin binding to its receptors in cortex after blockade of serotonin transporters with selective serotonin reuptake inhibitors (SSRI), despite evidence by microdialysis of extracellular increase of serotonin, either because the blockade occurs so far from the receptors that the increase is not representative of the change at the receptors, or because the increase is too small to affect the occupancy, or both.

In the experimental approach to dopamine volume transmission, dopamine occupancy is changed by the action of an exogenous drugs and the relation between changes of behavior and occupancy is recorded. Alternatively and potentially much more interesting, behavior undergoes a primary change without the poorly focused aid of a drug, and the accompanying change of dopamine occupancy is measured. Dopamine occupancy of its receptors is conventionally determined with an antagonist radioligand but we have tested the use of an agonist radioligand that would reflect also the affinity changes that affect the receptors when the dopamine occupancy is altered.

Our use of radioligands is based on the concept of simple competition between the radioligand and the endogenous transmitter that visibly affects the binding of the radioligand. We have tested several compounds that appear to affect behavior and the occupancy of

dopamine simultaneously, including the prototypic amphetamine as well as the recreational drugs methylene-dioxy-meth-amphetamine (MDMA or "Ecstasy") and nicotine. There seems to be a relation between the behavior and the occupancy but the relation is equivocal.

We have also tested the effect primary behavioral change on dopamine occupancy, including cocaine craving (without cocaine) and novelty seeking, both in pigs and in people. Craving, sensation-seeking, extroversion, and exploratory behavior, all appear to be associated with greater dopaminergic volume transmission. In brain disorders, schizophrenia in the openly psychotic state is also characterized by greater dopaminergic transmission, while Parkinson's disease and Attention-Deficit-Hyperactivity Disorders appear to be associated with reduced dopaminergic volume transmission, possibly because they lack the dopamine required to sustain the focus on cognitive activity. These experiments will be followed by activation studies of cerebral blood flow and oxygen consumption to establish the complete chain of events from behavior via monoamine transmission to brain energy metabolism. CFIN and the Aarhus PET Center are uniquely placed to reveal the changes of all four links in this pathway, separately as well as collectively.

In contrast to the generally excitatory effect of increased dopaminergic transmission, serotonin and norepinephrine reduce the excitability of cortical neurons. While the success of the dopamine occupancy studies is confined largely to the striatum where dopamine receptors and transporters coincide, the same success has not been evident with serotonin or norepinephrine, probably because the majority of the receptors and the transporters reside in different parts of the brain, the receptors in cortex and the transporters below cortex. To ascertain this observation, we labeled both serotonin receptors and serotonin transporters and followed their fall with age. The attempt to map serotonin occupancy changes continues with a range of differentially selective radioligands. The attempts to map norepinephrine occupancy changes are just beginning with the first selective ligand of the alpha-2-adrenoceptor, yohimbine.

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MIND - Membrane-receptors In Neuronal Disease

The Vps10p family of type-1 receptors are highly expressed in the nervous system. The receptors bind a variety of ligands, notably neurotrophins and their proforms, and participate in intracellular protein transport and signal transduction. Recent findings implicate the receptors in the mechanisms that govern neuronal degeneration and death. The MIND-center is dedicated to research in the molecular and physiological functions of the Vps10p-D receptors. MIND is a multidisciplinary neuroscience center based on a close collaboration between research groups from the Institute of Medical Biochemistry, the Department of Stereology, the Department of Molecular Biology and the PET-center at Aarhus University. The center-activities encompass basic research as well as clinical studies and integrate numerous disciplines including crystallography, protein chemistry, cell biology, and transgenic animal models. MIND is sponsored by a major grant from the Lundbeck Foundation and is lead by Professor C. Munck Petersen and Professor A. Nykjær, Inst. of Med. Biochemistry, AU.

Read more at: http://www.newmind-center.dk/index.html

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by Arne Møller

Dopaminergic neurotransmission in pathological gambling.

It has been suggested that high sensation seekers have lower activity in the dopaminergic system, which may in turn make them more susceptible to dopamine enhancing stimulants such as amphetamine, and possibly gambling. Few empirical studies, however, have tested this hypothesis.

This PET study focused on [11C]Raclopride binding potential in high sensation seekers compared to low and mid-range sensation seekers in a control version and a gambling version of the Iowa Gambling Task. From a normally distributed sample of 243 individuals we defined cut-points for high and low sensation seekers as the top and bottom 20% of the distribution. This corresponded to a score of 25 and greater for high sensation seekers, 14 and lower for low sensation seekers, and 15 – 24 for mid-range sensation seeking. In the current study we compared 8 high sensation seeking men with 12 low to normal ranging sensation seeking men.

The results showed that high sensation seekers had significantly lower binding potentials (pB) in the putamen, indicating a lower receptor availability in high sensation seekers. The finding was more significant in left putamen than in right putamen. We also found a significant negative correlation between sensation seeking and receptor availability in the left putamen, suggesting that higher sensation seeking was related with lower receptor availability.

Our results of lower receptor availability in high sensation seekers are congruent with literature reporting increased risk of developing addictive behavior, and suggest that personality traits should be accounted for in dopamine receptor studies of addictive behavior. They may also suggest, that dopamine receptor availability is a biological marker for both sensation seeking and addictive behavior, which can be used to differentiate the heterogeneity of specific sub-types of addictive behavior within addictive behavior such as pathological gambling or amphetamine dependence.

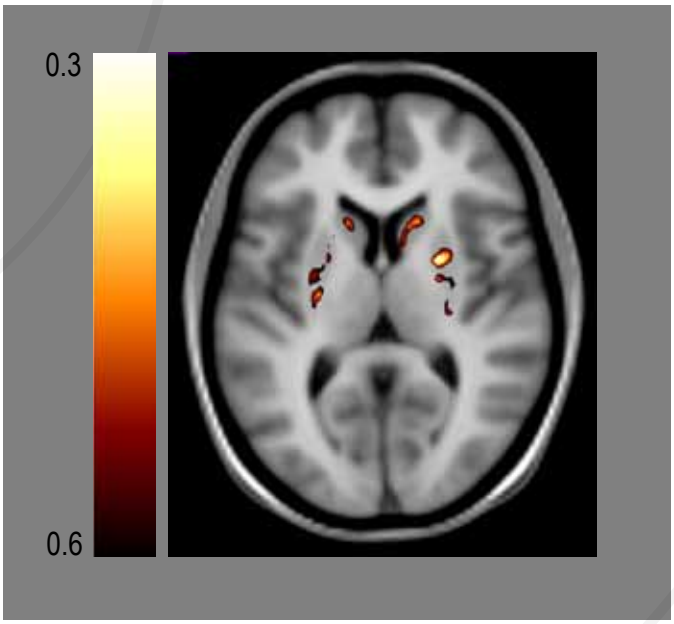

Figure 1
High sensation seekers.
Average ΔpB (baseline–gambling)
The image shows on a scale from 0.3 to 0.6, where on average the pB was HIGHER during baseline than gambling.

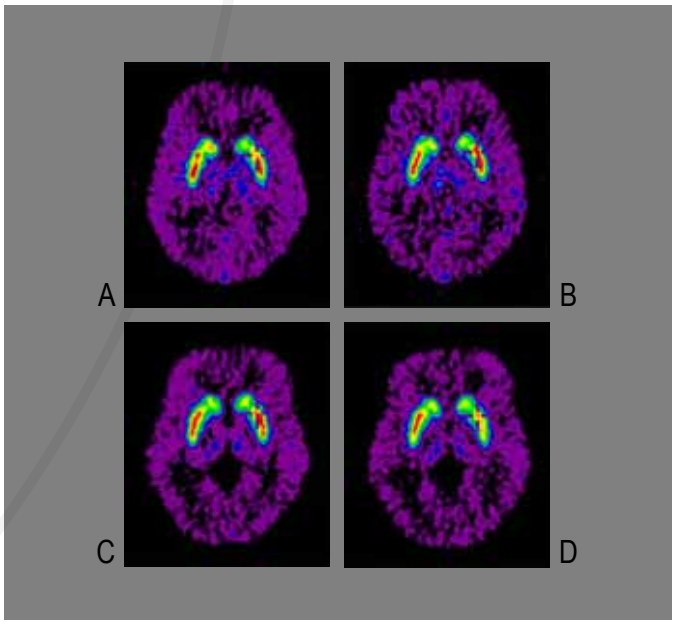

Figure 2
Binding potential (pB) in one High and one Medium sensation seeker.
Binding potentials in contrast and gambling condition in one High- and one Low sensation seeking individual.
The High sensation seeker has higher [11C]Raclopride binding potential (pB) in right putamen during contrast condition (A) seens as more red colors in the cross hair; and lower pB during gambling (B) seen as more yellow colors in cross hair, as a result of increased dopamine release.
Low sensation seeing individual has lower [11C]Raclopride binding potential during contrast condition (C) and higher pB during gambling (D), as a result of decreased dopamine release during gambling.

NEUROCONNECTIVITY

by Peter Vestergaard-Poulsen

Progress in 2006

Our research focuses on how brain connectivity, integrity, and plasticity are regulated by changes in neurotransmission – for example, in stroke and learning. This is mainly pursued by magntic resonance imaging (MRI) methods, measuring water self-diffusion which has proven to be extremely sensitive to microstructural changes on a micrometer scale. Using a combination of modeling and experimental studies of brain tissue, we study basic cellular mechanisms underlying for example ischemic changes (cell fraction, water exchange and intermolecular interactions) as well as structural connectivity in longitudinal studies in the post-ischemic brain.

Neuronal homeostatis

CFIN research has focused on comprehensive, biophysical models that may serve as a framework for extracting crucial, microstructural information from complex MRI data. In 2006, Brian Hansen and Peter Vestergaard-Poulsen completed a cellular multi-compartment model that allows for diffusional and transverse relaxation effects in compartmental heterogeneity. The model is promising in terms of accounting for qualitative and quantitative findings in normal and ischemic cell homeostasis.

A novel approach of simulating the neuron as a specific fractal model (reflecting the actual growth and structure of neurons) has been developed. This new model by Brian Hansen strongly supports the general assumption that the clinically observed changes in the diffusion weighted signal in e.g. stroke are mainly due to changes in the size of the extra-cellular space.

In our efforts to directly assess microstructural underpinnings of cortical plasticity, Sune Nørhøj Jespersen has developed a model af neuronal substructures in a collaboration between CFIN and The Mallinckrodt Institute of Radiology, Washington University, St. Louis, USA (Dr. D. Yablonski and Prof. J. Ackerman). This model has the unique feature to produce the relative density of dendrites or axons in gray and white matter of the brain. The results are being validated by established histological methods (Nissl staining, by Institute of Anatomy Aarhus University). Preliminary analysis suggest that we may indeed estimate dendrite density by non-invasive diffusion MR imaging.

Our efforts to describe water self diffusion near impermeable barriers by advanced biophysical models have now been completed by Astrid From Frøhlich (collaboration with Universitätsklinikum Freiburg für die Medizinische Fakultät der Albert-Ludwigs-Universität, Freiburg, Dr. Valerij Kiselev).

Neuronal connectivity

CFIN researchers have studied the relationship between plastic changes of the fiber bundles in white matter following ischemic stroke and motor recovery by diffusion tensor measurements and computer based three-dimensional axonal fiber tracking algorithms (Jesper Frandsen). The study showed that the developed methods can map the Wallerian degeneration process that follows an infarct. The results reveal an association between the temporal evolution of diffusion related indices, describing how water diffusion is altered in injured fibers, and motor function. These changes may reveal early degeneration of axons compared with higher sensitivity than more conventional MR imaging. Mette Møller submitted her PhD thesis: Recovery and serotonergic neurotransmission in the wake of stroke and recovery on this subject in 2006 and successfully defended her work in March 2007. Efforts to develop functional connectivity acquisitions methods and refine the fibertracking acquisition and postprocessing methods have generated important scientific and methodological progress, now used in pilot studies to apply fibertracking procedures in presurgical planning.

Ultra high field MR microimaging methods for neuroimaging research

In June 2006, two Danish National Research Foundation research centers, inSPIN and CFIN, inaugurated a state-of-the-art 16.4 Tesla imaging system, located at InSpin (Center for Insoluble Protein Structures) at the Institute of chemistry, Aarhus University. This equipment is uniquely suited to test our biophysical models by diffusion weighted imaging at an image spatial resolution down to a few micrometers (imaging of single neurons up to mouse brain in-vivo) at extreme sensitivity. Extending our collaboration with a leader in this field, Peter Vestergaard-Poulsen visited US National High Field Laboratory and McKnight Brain Institute (Dr. S. Blackband, University of Florida, USA) in October-November 2006, allowing the transfer of a cutting-edge experimental set-up and biological models to Denmark, where they are now established.

The biophysical models of dendrite density, which is a major feature of cortical plasticity, can now be applied to high-quality experimental data. The first step towards this goal, validation of the dendrite density models by histology and stereology, is the focus of the current work. In a second step, dendritic changes in hippocampal neurons after mental stress is being studied in collaboration with Center for Psychiatric research, Aarhus University Hospital in Risskov.

The inSPIN-CFIN collaboration is now sharing equipment and teaching resources (Biomedical Engineering MRI courses), initiating collaborations with industry.

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SELECTED RESEARCH PROJECTS:

Astrid From Frøhlich, Leif Østergaard, Valerij Kiselev (Freiburg Universitet, Tyskland): Fiber models of white matter in the human brain.

Astrid From Frøhlich, Leif Østergaard, Valerij Kiselev (Freiburg Universitet, Tyskland): The theory behind fiber tracking: diffusion in biological tissue.

Brian Hansen and Peter Vestergaard-Poulsen: A fractal model for description of diffusion weighted magnetic resonance imaging in brain tissue.

Jesper Frandsen, Leif Østergaard, Eva Vedel Jensen, Jens Christian Sørensen, Astrid From Frøhlich, Valerij Kiselev (University of Freiburg, Germany), Peter Vestergaard-Poulsen: 3-dimentional axonal Fibertracking.

Niels Buhl, Sune Nørhøj Jespersen: A Simulation Framework for Diffusion Weighted MRI in Digitalized Neurons: Extracting Cytoarchitectural Parameters Using a New Theoretical Model for Diffusion.

Peter Vestergaard-Poulsen, Gregers Wegener, Niels Chr. Nielsen, Thomas Vosegaard, Sune Jespersen, Brian Hansen: The neurobiology of the brain due to mental stress - an MRI approach to detect the structural correlates of induced stress.

Peter Vestergaard-Poulsen, Brian Hansen, Martijn van Beek, Jes Bertelsen, Michael Stubberup, Joshua Skewes, Andreas Roepstorff: The structural correlates of the brain after long term meditation praxis.

Sune Nørhøj Jespersen, Dmitriy Yablonskiy, Joseph J.H. Ackerman, Chris Kroenke, Larry Bretthorst (Washington University, St. Louis): Modeling of water diffusion in the brain: establishing cytoarchitectonic parameters.

Sune N. Jespersen, C. R. Bjarkam, T. Nielsen, B. Hansen, P. Vestergaard-Poulsen: Dendrite Density from Magnetic Resonance Diffusion Measurements: Comparison with Histology.

Sune Nørhøj Jespersen, Albert Gjedde: Dopamine occupancy and dopamine transport inhibition: Lessons from a dynamic model.

NEUROCONNECTIVITY

Revealing brain microstructure and connectivity by water diffusion MRI

by Mette Møller, Jesper Frandsen, Sune Jespersen and Peter Vestergaard-Poulsen

Overview of CFIN Neuroconnectivity Research 2001-2006

Our aim is to explore the microstructural foundation of brain plasticity, and more specifically, how cells and cellular interconnections adapt to perform in neuronal networks. Our main interests are plastic changes during learning and functional reorganization as it occurs during rehabilitation after stroke and brain trauma.

MR imaging sensitized to diffusion of water molecules (Diffusion Weighted Imaging: DWI) has shown great potential in non-invasively characterising tissue micro-structure. The pronounced sensitivity of the technique to hydrophobic barriers on a microscopic scale enables us to probe cellular structures and architecture of the brain in vivo.

Our strategy is to develop advanced biophysical models and MR-based techniques to characterize the cellular characteristics and 3-dimensional organization of neurons. The general approach is to combine advanced biophysical brain tissue models and experimental studies of brain tissue in order to study basic cellular mechanisms (cell fraction, water exchange and intermolecular interactions) in longitudinal studies of the brain in-vivo as well as in-vitro.

Inferring Tissue Microstructure using theoretical models of Brain Tissue water diffusion

DWI was initially developed as a tool for detecting cell damage in acute ischemia and has now found wide-spread clinical use due to its unique diagnostic power in acute stroke management. Although DWI is highly sensitive to cellular changes in cytotoxic edema (see figure), more than a decade of research with animal experiments, human experiments, and biophysical models of brain tissue has not yet led to a comprehensive biophysical model linking the measured DWI signal to changes in cellular microstructure, nor to the processes known to be central to cellular integrity and homeostasis. Detailed knowledge of cellular viability is crucial to develop and monitor treatment of patients with acute stroke – and thereby minimize the severe neurological disabilities following brain infarcts. CFIN researchers have developed several new promising models of water diffusion in brain to improve our biophysical understanding of this link as well as improving neuroimaging methods. By utilizing the dependence of the DWI signal on the underlying tissue microstructure, these models now allow assessment of specific cellular characteristics and cytoarchitecture. By means of an established collaboration with leaders in this field (McKnight Brain Institute of the University of Florida, USA and the inSPIN center at Dept. of Chemistry, Aarhus University) we have unique expertise and cutting-edge experimental set-up for testing these diffusion models in single cell preparation and nerve tissue cultures.

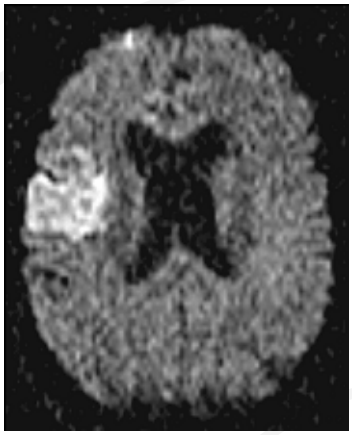

Figure 1
Diffusion weighted MR image of a patient with acute stroke in the right hemisphere

Brain Plasticity: Dynamic changes of corticospinal tracts after stroke detected by fibertracking

After ischemic damage, the adult brain can regenerate and compensate for motor deficits by plastic change, including an initial recruitment of motor pathways in the intact hemisphere, and in patients with good recovery, return of activity to the ipsi-lesional side. The integrity of nerve fiber tracts in the brain is important, not only to assess plastic changes related to functional recovery and thereby prognostic information, but also to identify future therapeutic strategies for rehabilitation of stroke patients. The integrity and connectivity of the nerve fibre tracts in the brain are also important in a long range of neurological disorders of the white matter like multiple sclerosis, Wallerian degeneration, Alexander's Disease and psychiatric diseases such as schizophrenia.

Diffusion tensor MRI (DTI) has the ability to map the nerve fiber tracts in the brain and possibly holds the potential to demonstrate whether the post ischemic adult brain has the potential to regenerate and compensate for motor deficits by plastic changes, including an initial recruitment of motor pathways in the intact hemisphere, and return of activity to the affected area. Diffusion tensor axonal fiber tracking reveals the correlation between brain plasticity and recovery of motor function during rehabilitation. However, the reorganization of fiber tracts has not previously been mapped in a longitudinal study of humans during recovery from stroke.

Figure 2
In regions with closely packed fiber bundles the water diffusion is found to be anisotropic (left image). The water self diffusion characteristics can be described by a tensor (middle image). Following the main axis in each tensor in a stepwise fashion from tensor to tensor forms the basis of fiber tracking (right image).

CFIN researchers have investigated the relationship between plastic changes of the fiber bundles in white matter following ischemic stroke and motor recovery by diffusion tensor measurements and computer based 3D axonal fiber tracking algorithms correlated with neurological motor scales. The patient study showed that our methods can map the degeneration process (Wallerian degeneration) that follows an infarct. The results reveal an association between the temporal evolution of diffusion related indices that describes how water diffusion along and across intact nerve fibers is different from injured fibers (possibly caused by the degeneration of cell membranes and the myelin layer around nerves) and motor function.These are potential early markers of ongoing degeneration of axons compared to more conventional MR imaging.

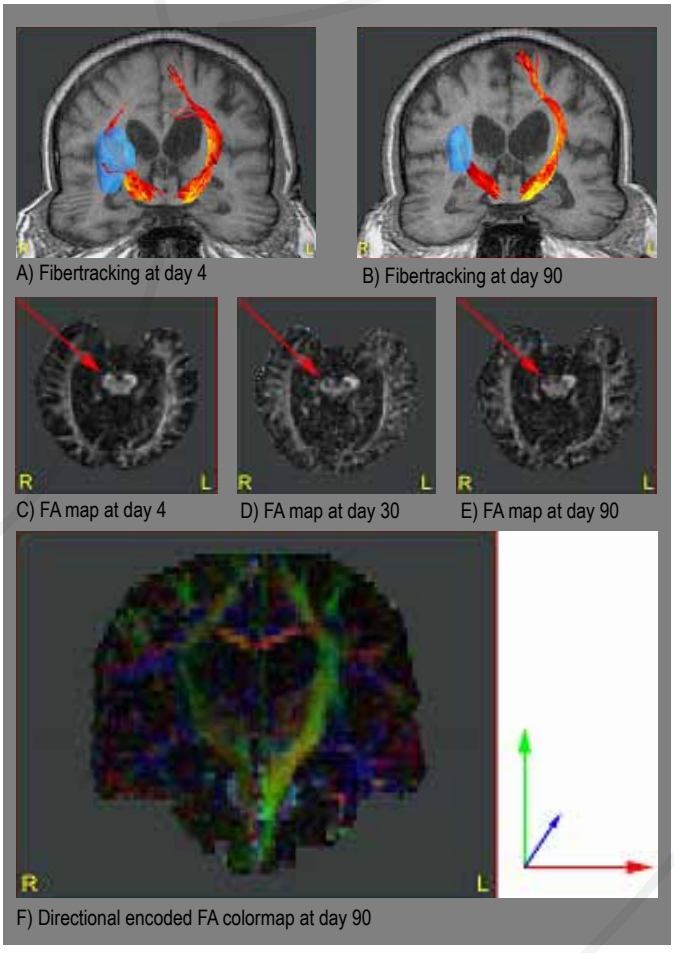

Figure 3
Temporal changes of FA values in corticospinal fibers and corresponding FA maps in a stroke patient. Panels a+b show the FA values along the tracked corticospinal fibers (high values in bright colors) and a deep MCA infarct (blue color) on the right side at day 4 and day 90. The FA values in Figures A+B were colorcoded according to the colorbar to the right of panel F. Panels C-E are FA maps showing the cerebral peduncle with low intensity on the affected right side at day 30 and 90 (red arrows). Figure F is a coronal color- FA map at day 90. (From Møller et al. 2006.)

Imaging the structural changes related to learning by high field diffusion MR microscopy

It is now widely accepted that learning can induce changes in the synaptic connections, varicosities following long term potentiation and the following microstructural changes of the dendritic tree. To develop neuroimaging in vivo markers to study these subtle microstructural changes by other means than microscope based in-vitro techniques, CFIN researchers have initiated investigations by advanced diffusion imaging and biophysical modeling using 16.4 Tesla MR microimaging equipment on a mental stress induction model already proven to induce profound changes in the dendritic material of the hippocampus (read more at page 28).

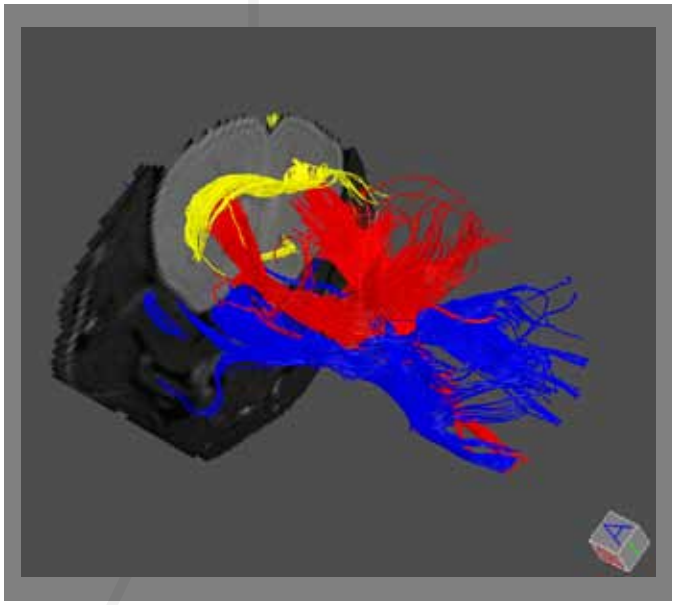

Figure 4
DTU based fiber tracking in mouse brain obtained from MRI data at 16.4 Tesla with a in-plane resolution 46 mm.
The FACT algorithm was used to produce the fiber tracts.

Collaborators

Center Insoluble Protein Structures (inSPIN), Dept Chemistry, Aarhus University, professor Niels Christian Nielsen and professor Thomas Vosegaard.
Centre for Psychiatric Research, Institute of Clinical Medicine, Aarhus University, Dr. Gregers Wegener.
Institute of Anatomy, Aarhus University, Dr. Carsten Bjarkam.
Electron Microscopy Lab., Aarhus University, Dr. Jens Randel Nyengaard.

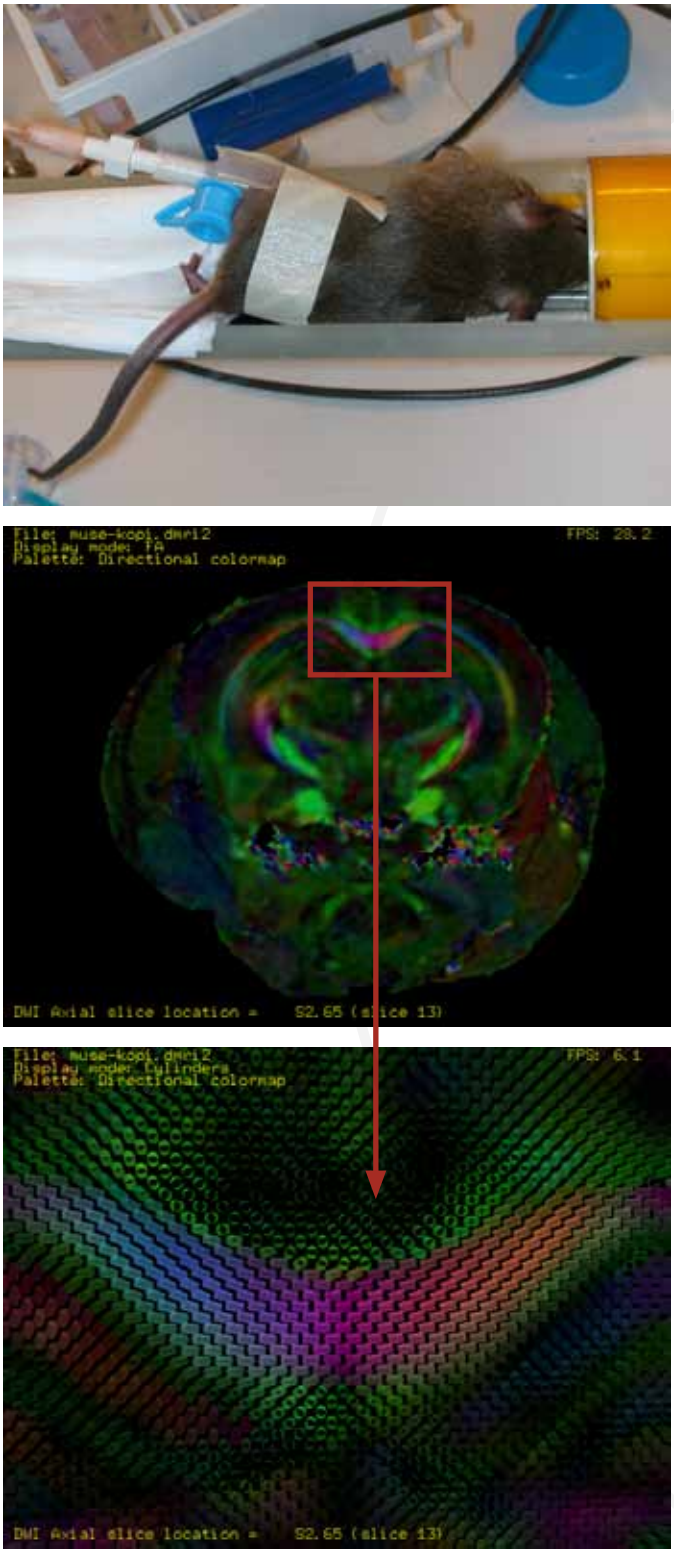

Figure 5
Diffusion anisotropy based axon directional map of the murine brain's corpus callosum obtained by diffusion tensor imaging at 16.4 Tesla.

Advanced surgery by Neuronavigation using Diffusion Tensor MRI and Axonal Fibre Tracking

Advanced neurosurgical procedures require detailed knowledge of the position and function of structures near the entry path in order to avoid damage – and thereby severe disabilities – to the patient. CFIN researchers have developed axonal fiber tracking techniques that allow imaging of white matter fiber bundles based on advanced models of water diffusion among myelin sheaths, Magnetic Resonance diffusion tensor imaging (DTI) and advanced image post processing techniques. In a fruitful collaboration encompassing neurosurgeons, physicists, computer scientists, biomedical engineers, and statisticians, a framework for efficiently using advanced neuroscience methods in the surgical treatment of patients with lesions near sensitive cortical areas (motor and language) has been developed.

Several patients that were otherwise given up by international neurosurgical experts due to extreme risk of inflicting severe neurological damage have been treated. The project will develop this technology for export to other sites and validate the utility of the technique in a simulation study involving experienced neurosurgeons.
(See info box on neurosurgery)

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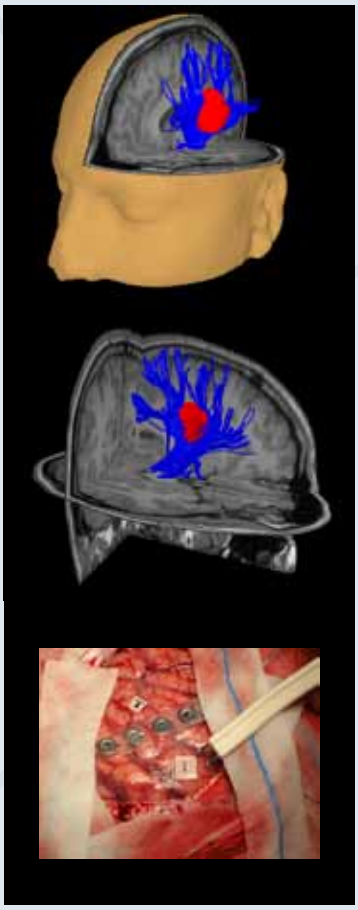
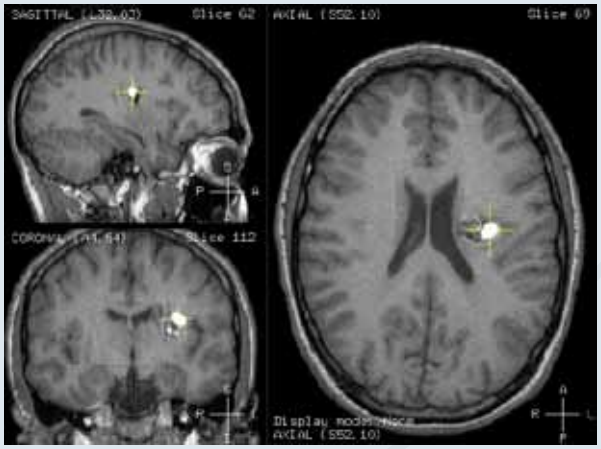
Neurosurgery

Structural MR images (bottom image) showing the abnormal vessels (angioma) of a 24 year old man, who suffered from progressing impairment of motor function and sensory function of his right arm.
Images suggested a high risk of bleedings, which would in turn cause severe disability or death. Surgical procedures would convey a high risk of damaging nerve tracts related to motor function and speech.



The DTI based 3D axonal fiber tracking images of the nerve fiber bundles adjacent to the malformation were used for planning the stereotactical procedures for this patient so that the abnormal vessels could be removed without any adverse effects to the patient.



Suzan Dyve (Dept. Neurosurgery), Anders Rodell (PET-Center, CFIN), Søren Haack (Biomedical Engineering), Ryan Sangill (Dept. Neuroradiology, CFIN), Peter Vestergaard-Poulsen (Dept. Neuroradiology, CFIN), Jesper Frandsen (Dept. Neuroradiology, CFIN), Leif Østergaard (Dept. Neuroradiology, CFIN), All Aarhus University Hospital.

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FUNCTIONAL HEMODYNAMICS

by Leif Østergaard

Progress in 2006

The ongoing work to identify and quantify mechanisms that couple the hemodynamics of cerebral vasculature to the metabolic needs of the tissue reached several crucial goals in 2006. Setting out to study the heterogeneity of capillary flows by MRI as a regulatory mechanism by which oxygen delivery may be increased, a number of methodological challenges have now been overcome.
The determination of capillary flow heterogeneity (FH) by dynamic susceptibility contrast (DSC) MRI is based on (i) precise non-invasive measurements of tracer concentrations by MRI, (ii) detection of arterial concentration time curves, and finally (iii) deconvolution of tissue concentration time curves.

Concentration measurements in dynamic susceptibility contrast MRI

Following the discovery in 2001 of nonlinearities in the concentration - ΔR2 (the 'indirect' concentration index derived from MR images) relation, a focused research effort has been carried out by CFIN researchers and Dr. Valerij Kiselev, PhD (Freiburg University) to model the underlying physics and thereby allow accurate quantification of paramagnetic substances – not only for quantitative DSC MRI, but also for quantifying BOLD imaging with the neuroenergetics and cognitive project clusters. Birgitte Kjølby completed her combined theoretical and computational approach, now allowing detailed studies of how the brains microvascular network affects the MRI signal in BOLD fMRI and DSC.

Detection of arterial concentration time curves

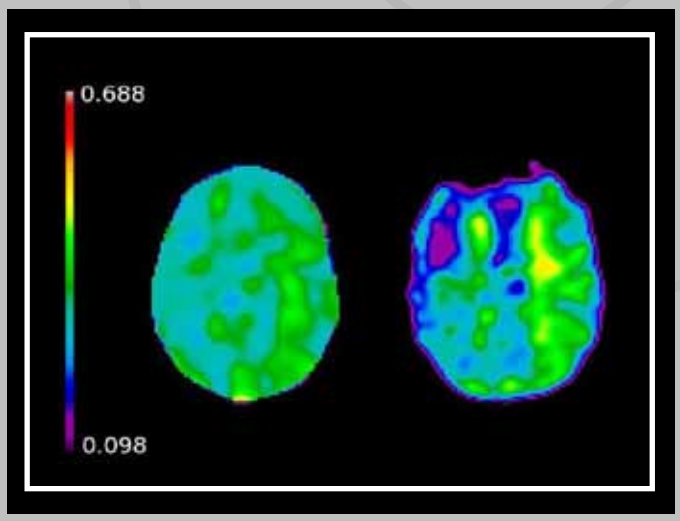
Søren Christensen - now stationed in Melbourne in a collaboration between CFIN, Royal Melbourne Hospital (Steve Davis) and Brain Research Institute, Victoria, Australia (Fernando Calamante) - pursues techniques to detect more local arterial input functions, with an aim to study FH in diseases where blood flow is compromised by vascular stenoses and occlusions. This is an important step towards studying flow heterogeneity as a regulatory mechanism in states of extremely compromised reserve capacity where flow can no longer be adjusted to meet metabolic demands.

Deconvolution Approach

Kim Mouridsen, with the statistics core group (head Karl Friston) at Functional Imaging Laboratory (FIL), University College of London, improved the quantification and detectability of abnormal FH by a novel approach utilizing prior information in a Bayesian approach. This approach, published in Magnetic Resonance in Medicine in 2006, seemingly improve our ability to extract quantitative haemodynamic information of relevance to oxygen delivery capacity. In a close collaboration between CFIN researchers Sune Jespersen, PhD, Mahmoud Ashkanaian M.D., Kim Mouridsen PhD, and Leif Østergaard, this method is currently being extended to directly assess oxygen delivery capacity and oxygen extraction, aiming to perform validation studies by positron emission tomography (PET).

Neuroinformatics: Hemodynamics and metabolic derangement in ischemia

The overwhelming data flow in neuroimaging represent a challenge to our continued integration of data across modalities and organizational levels into integrated models of human brain function. CFIN has made a strategic decision to pursue neuroinformatics and data mining methods to detect 'hidden' correlations and devise operational models of neuroimaging data. This has significantly contributed to our understanding of how haemodynamic and microstructural changes affect brain tissue vulnerability in experimental and clinical models of metabolic derangement as a result of ischemia, published by Ona Wu, PhD in 2006.
This work is now expanding, partly through the recruitment of Kim Mouridsen and Ona Wu to positions within CFIN, partly through a EU grant, positioning CFIN with a strong neuroinformatics core group.



Above:
CFIN scientists aim to develop mathematical models to describe the relation between cerebral hemodynamics and oxygen delivery. Based on this framework, MR based perfusion data predicts oxygen extraction fraction (OEF) based on microvascular flow dynamics. The Images above compare positron emission tomography (PET) based OEF measurements (left) and MRI based OEF (right) in a patient with severe carotid stenosis.

Courtesy Mahmoud Ashkanian, Sune Nørhøj Jespersen, Grethe Andersen, Kim Mouridsen, and Leif Østergaard

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Andreas Roepstorff and Leif Østergaard at CFIN Retreat 2006

SELECTED RESEARCH PROJECTS:

Birgitte Fuglsang Kjølby, Leif Østergaard, Valerij Kiselev (Freiburg Universitet, Tyskland): Relationship between relaxation and contrast concentration in DSC MRI.

Birgitte Fuglsang Kjølby, Leif Østergaard, Valerij Kiselev (Freiburg Universitet, Tyskland): Theoretical analysis and modelling of arterial input functions in DSC MRI.

Christine Sølling, Grethe Andersen, Leif Østergaard: Impact of MRI-based thrombolysis in acute stroke.

Kim Mouridsen, Sune Jespersen, Mahmoud Ashkanian, Leif Østergaard: Modelling of flow heterogenuity.

Kim Mouridsen, Kristjana Yr Jonsdóttir, Leif Østergaard: Inferential models in acute stroke.

Kim Mouridsen, Thórdís Linda Thórarinsdóttir, Kristjana Yr Jonsdóttir, Eva Vedel Jensen, Leif Østergaard: Functional Connectivity.

Louise Gyldensted, Dementia Clinic (Neurological Department, Århus Sygehus), Jamila Ahdidan, Kim Mouridsen, Anders Rodell, Søren Christensen, Peter Vestergaard Poulsen, Leif Østergaard, Carsten Gyldensted: Magnetic Ressonance Imaging (MRI) and Alzheimer's Disease.

Mahmoud Ashkanian, Grethe Andersen, Leif Østergaard, Manouchehr Vafaee: Examination of oxygen metabolisme and cerebral blood flow in the ischemic penumbra compared to healthy brain tissue, a PET study.

Mahmoud Ashkanian, Kim Mouridsen, Sune Jespersen, Grethe Andersen, Leif Østergaard: Oxygen delivery in acute stroke.

Niels Hjort, Mahmoud Ashkanian, Christine Sølling: MRI selection and monitoring of acute stroke patients for treatment with intraveneus thrombolysis.

Niels Hjort, Kim Mouridsen, Leif Østergaard: I-Know: Integrating Information from Molecule to Man: Knowledge Discovery Accelerates Drug Development and Personalized Treatment in Acute Stroke" (I-Know project under EU's 6th frame program).

Ona Wu, Kim Mouridsen, Kristjane Yr Jonsdottir, Niels Hjort, Leif Østergaard: Predictive models in acute stroke.

FUNCTIONAL HEMODYNAMICS

From models of microvascular flow to clinical stroke imaging

by Leif Østergaard

Overview of CFIN Hemodynamics Research

The formation of microvessels and subsequent regulation of cerebral blood flow (CBF) to meet metabolic demands is crucial to support not only normal brain function, but also tissue survival and subsequent functional recovery after cerebral ischemia. Since the mid-90s, CFIN neuroscientists have dedicated their work to develop methods to study cerebral haemodynamics, exploiting ultra-fast magnetic resonance imaging (MRI) techniques that allow accurate quantification of not only CBF, but also capillary density and flow dynamics. Subsequent studies of normal brain and neurological disease have greatly contributed to our understanding of cerebral ischemia and cerebral vulnerability. Also, these techniques have found widespread use in clinical research and daily patient management world-wide, underlining CFINs effort to foster translational research, bringing fundamental neuroscience to better patient management.

Cerebral Perfusion Methodology

The scientific progress in studying human cerebral haemodynamics is closely linked to the development of fast, flexible, non-invasive in vivo imaging methods and tracer kinetics for intravascular MR contrast agents. Thanks to technological break-throughs in the design and advanced neuroimaging devices, so-called echo planar imaging (EPI) allow MRI of perturbations of the cerebral vasculature at time scales comparable to that of the capillary passage of a red blood cell. By imaging the passage of standard intravenous MR contrast agent, the characteristics and temporal dynamics of the capillary circulation can thereby be studied non-invasively by methods that may be applied even in the setting of clinical neuroimaging. Flexibility and clinically applicable MRI based perfusion methodologies have been key to the progress in our understanding of neurological disease over the past decade, and remain a target of our research within neuroscience methods.

Cerebral Ischemia: A Challenge to our understanding of cerebral hemodynamics.

Acute stroke is the third leading cause of death and a major cause of severe, adult disability. The disease is fatal in every fourth patient, whereas the remaining patients suffer immediate loss of motor, sensory or cognitive functions (e.g. hemiparesis, aphasia) as regional cerebral blood flow (CBF) falls below the level necessary to support neuronal function. If blood flow is not re-established within minutes or hours, neuronal damage evolves and spreads, making the initial neurological deficits irreversible. Considerable research efforts are currently focusing on the development of therapeutic strategies that will limit neuronal death in the acute phase (within 6 hours of symptom onset). Acute patient management and development of novel therapies is, however, made difficult by the heterogeneity and poor understanding of tissue vulnerability. Aside from the need to better understand stroke pathophysiology, scientifically driven models to predict the spread of neuronal death are crucial to optimise therapeutic strategy in the acute phase – and detecting the efficacy of novel therapeutic strategies in humans.

CFIN research in the functional haemodynamics of acute cerebral ischemia

Working with the group of scientists at MGH-NMR Center, Harvard Medical School, who discovered susceptibility contrast and its use in measuring cerebral blood volume (CBV), CFIN scientists have played a key role in the successful development of magnetic resonance imaging (MRI) methods to assess cerebral haemodynamics. These methods define the diagnostic approaches now considered the standards for assessing the severity of acute ischemic lesions, and the risk of subsequent growth. The techniques combine diffusion weighted imaging (DWI - believed to reflect irreversible tissue damage through reduced water diffusion subsequent to cell swelling) and perfusion weighted imaging (PWI – reflecting CBF, CBV, and blood mean transit time (MTT) – all indices of cerebral perfusion with a possible impact on detecting tissue vulnerability and characterizing the severity of hemodynamics impairment

Perfusion pressure or MTT

With our international collaborators, we have explored the utility of the blood mean transit time, MTT, as a marker of subsequent infarction. The MTT is inversely proportional to the perfusion pressure, and thereby the severity of the hemodynamic impairment. The area of prolonged MTT was found to always contain (but often be somewhat larger than) the subsequent final infarct. The presence of areas of prolonged MTT was found to be a strong predictor of subsequent infarct growth, and has been suggested as a criterion for aggressive treatment – See Figure 1.

Cerebral Blood Flow - CBF

In animal models of acute stroke as well as in human studies using MRI, evidence has been found of ischemic CBF threshold, below which neuronal death is imminent. In a porcine MCAO stroke model developed at CFIN, the ischemic threshold below which irreversible damage occurred was found to be CBF below 60% of white matter flow, corresponding closely to an apparent diffusion coefficient (ADC – found by concurrent diffusion weighted MRI) below 80% of normal tissue values. When regional CBF was 80% of white matter for more than 6 hours, ADC was found to decline to values below 80% of normal values, suggesting that ischemic damage was progressing. In these cases, ADC-values remained above 80% of contralateral side for 3-4 hours, indicating that tissue was potentially salvageable, in agreement with the therapeutic time window of 3 hours for intravenous thrombolytic therapy in humans. These findings underline the importance of relative CBF as well as ADC measurements in the acute phases of stroke.

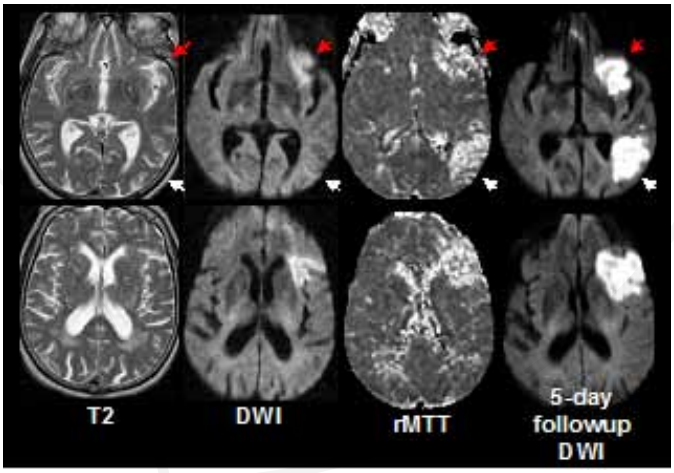

Figure 1
Structural MRI at two levels (first column) in the brain of a 78 year old woman, 3 hours after she suddenly lost the ability to speak. These images show no structural abnormalities. Diffusion weighted images (second column) show bright areas in the anterior portion of the brain, near the center involved in the formation of language. These areas are damaged and probably beyond rescue by intervention. Measurements of the blood MTT (third column) shows a larger, bright area anteriorly and posteriorly (arrows). Far right column, the extent of tissue death after 5 days is shown. The disease has spread. Notice the MTT measurements predicted this disease progression. In this patient, the measurement could thus have been used to guide treatment.

Flow Heterogeneity and Metabolism

With decreased CBF, decreasing FH has been shown to provide the means to increase oxygen extraction and thereby maintain metabolism. So far, it has only been possible to study heterogeneity by invasive high-speed microscopy of the brain surface in animals. These experiments have shown that a graded decrease in perfusion pressure causes progressive loss of high-flow red blood cells, thereby decreasing total flow heterogeneity.
To further characterize cerebral hemodyamics, we developed a kinetic theory, whereby standard perfusion measurements can be utilized to determine flow heterogeneity, the distribution of flows relative to the mean flow through the individual paths of the microvasculature of a given imaging pixel. Combining this measurement with earlier calibration constants to yield absolute flow and volume, we have shown that FH provides a direct measurement of oxygen extraction fraction. In preliminary studies, the latter technique predicted final infarct size with a high degree of certainty allowing future guidance of therapy as well as quick, cost-effective demonstration of efficacy of new therapeutic regimens in small groups of patients. Figure 2.

Water Diffusion and Residual Tissue Metabolism

To further explore the metabolic underpinnings of tissue water homeostasis and ADC, cerebral oxygen and glucose metabolism (CMRO2 and CMRglc) have been performed in a porcine middle cerebral artery occlusion (MCAO) model of acute stroke. We found that the percent decrease in CMRO2 is linearly correlated to the percent change in ADC, down to 70% of normal ADC. Below this limit, ADC decrease was accompanied by an abrupt decrease in glucose metabolism and further decrease in oxygen metabolism, signalling rapid neuronal death. Traditionally, ADC changes have been assumed to signal irreversible cell death. Our results indicate that – in the first hours following onset of ischemia – residual metabolism and possibly viable cells exist in areas of altered diffusion. Ongoing work seeks to explore this phenomenon in humans, such that quantitative DWI can be utilized as an index of residual metabolism and thereby the potential reversibility of neuronal dysfunction following treatment.

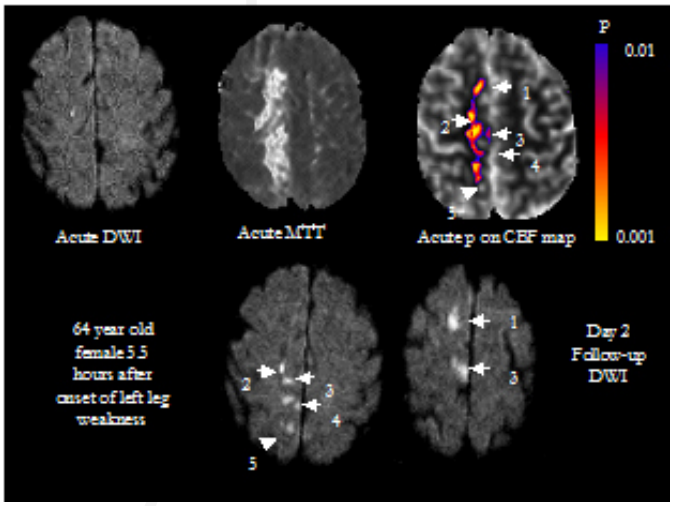

Figure 2
Patient with acute, partial closure of the anterior cerebral artery (ACA). Initially, no tissue death is present (Upper left). The image of tissue mean transit time (upper, middle), shows a large area, corresponding to the supply area of the ACA are threatened due to a decreased perfusion pressure at this initial scan, 5½ hour after onset of symptoms. Also shown is an image of CBF (upper right) where areas of homogenous flow are shown as a colour overlay. They represent areas where tissue utilises regulatory mechanisms to utilise the limited supply of oxygen reaching the area through the blood. Lower row shows the extent of tissue death after 2 days. Notice the striking similarity between areas with flow homogeneity at 5½ hour (where treatment can still be initiated) and the final tissue death. In this case, MTT predicted infarct growth, but over estimated final infarct size. .

Cerebral hemodynamics – a 2006 perspective.

With our ongoing efforts to identify the mechanisms underlying regulation of capillary density, capillary blood flow, and oxygen delivery at a capillary level, an ongoing effort to further refine perfusion methodology and biophysical modeling of blood dynamics is crucial. In a multidisciplinary effort, the basic mechanisms of MR signal formation are scrutinized, not only to quantify contrast agent concentrations

for our kinetic modeling, but also to allow future characterization of the size distributions of cerebral microvessels serving normal tissue function and functional reorganization. Meanwhile CFIN scientists work to develop robust methods of determining arterial contrast levels and impulse responses – the signature of capillary flow regulation that underly flow heterogeneity measurements - by advanced biophysical and mathematical modeling. Below, recent methodological progress and the resulting insight into the regulation of cerebral hemodynamics is outlined.

Concentration measurements in dynamic susceptibility contrast MRI

With the realization that subtle susceptibility contrast physics may impact the precision of perfusion indices derived from dynamics susceptibility contrast MRI, a focused research effort has been carried out by CFIN in collaboration with a leading scientist in the field, Dr. Valerij Kiselev, Ph.D. (Freiburg University). The resulting work by Astrid From Frøhlich and Birgitte Fuglsang Kjølby has broadened our understanding of DSC physics in biological tissue. Following the development of a combined theoretical and computational approach, an efficient simulation module now allows detailed studies of how the brains microvascular network affects the MRI signal in BOLD16 fMRI and DSC. As a spin-off of this better understanding of susceptibility physics, vascular volume and more importantly the size distribution of microvessels may now be quantified, potentially allowing noninvasive assessment of angiogenesis in neoplasms and functional reorganization.

Determining arterial input signals for flow heterogeneity measurements

CFIN researchers and collaborators found that the accuracy of perfusion estimates in general and FH measurements in particular would depend immensely on the fidelity of the unique arterial input function (AIF) chosen to represent the arterial supply of tracer to all brain tissue in the subsequent deconvolution. This led to a substantial inter-observer variability that was overcome by an automatic AIF search algorithm utilizing cluster analysis.

Decoding capillary flow dynamics: Deconvolution

Deconvoltion is the method by which dynamic images are converted into the impulse response: A detailed account of the fine temporal dynamics of tracer retention in the vasculature. In order to overcome the systematic bias by tracer arrial delays, Ona Wu devised a delay-insensitive deconvolution method. Kim Mouridsen has subsequently improved the quantification and detectability of abnormal FH by a novel approach utilizing prior information of the vasculature in a Bayesian approach. This approach is seemingly superior to previous techniques developed by CFIN scientists in terms of improving our ability to extract quantitative hemodynamic information of relevance to oxygen delivery capacity.

Bioinformatics in Neuroscience

CFIN, across columns, generates a wealth of image information across modalities (e.g. metabolic indices by PET, micro structural indices by diffusion tensor imaging (DTI), haemodynamic indices by perfusion weighted imaging (PWI)), across regions, over time. Integrating this information is immensely challenging – yet may be a crucial prerequisite for our ongoing quest to understand the brain at a number of organizational levels. In functional haemodynamic research, we have aimed to determine to what extent micro structural damage and abnormal FH predicts subsequent tissue death. Choosing a novel approach, we have modified modern bioinformatics tools to build disease models based on data mining performed on individual image voxel. By fully utilizing the potential of neuroimaging data, models of measured pathophysiological indices have provided high sensitivity and specificity in predicting tissue infarction (i.e. to account for disease progression) – and assigned quantitative importance to them. As a proof of concept, we proved the hypothesis that altering the disease model externally (in our case by administering a blood clot dissolving agent to patients, improving chance of tissue survival) would be detectable in limited samples in both humans and animal models. This approach may revolutionize our future ability to identify efficient drug candidates in a fast and cost-effective way. Current efficacy metrics involve costly trials involving the evaluation of neurological scores in thousands of patients.

CFIN Translational Research

In close collaboration with Aarhus County, the Stroke Unit, Aarhus University Hospital and Dept Neuroradiology, basic and clinical research has been undertaken in parallel, identifying the clinical utility of the tools developed under this research program.
By 2004, an acute stroke program for citizens in Aarhus County was set up, utilizing the methods and scientific insight developed throughout our research, offering the highest quality of care for stroke patients. Meanwhile, this effort has provided unique scientific data, uncovering how perfusion, diffusion, and cellular energetics underly the coupling of cellular damage to hemodynamics.

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CFIN collaboration with iNANO and inSPIN

by Leif Østergaard and Peter Vestergaard-Poulsen

Targeted nano-particles may help diagnose and treat disease

Future tools to diagnose and heal deadly vulnerable plaques, and lesions that cause heart attacks or strokes in large numbers of patients suffering from atherosclerosis every year. Novel nanoparticles that help detect tumor boundaries, helping physicians to diagnose cancer? Repairing genes that cause neurological diseases?

These are some of the visions driving a new consortium spanning experts atherosclerosis from Skejby Hospital, cancer experts from Århus Sygehus and neuroscientists from Danish Pharmaceutical company, Lundbeck, and the Danish National Research Foundations Center of Functionally Integrative Neuroscience (CFIN), Aarhus University.

Using nano-technology and molecular biology, the aim is to design probes that bind to specific cells in the human body. Detecting these nanoprobes by magnetic resonance imaging (MRI), scientists hope to better detect disease – and better target drugs to disease-prone areas.

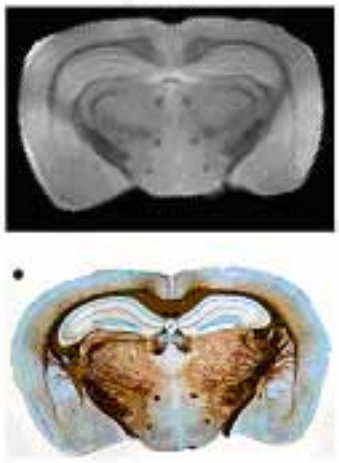
At iNANO, the group of Professor Jørgen Kjems has a long established expertise in drug delivery by nano-particles. By designing MRI visible (so-called USPIO) nano-particles with specialized surface properties, his group hopes to target cells that are specific to a certain type of atherosclerotic plaques in patients suffering vascular disease. Vulnerable plaques are plaques about to rupture – causing myocardial infarction or a cerebral stroke. By detecting these in time, we may save patients from severe disease or even death.
Another aim is to more precisely image tumors. The spread of cancer is difficult to detect my modern imaging techniques. By designing nano-particles that bind to areas where the tumor spread, scientists hope to improve early diagnosis of cancer – but also better target radiation therapy to kill all cancer cells.

Nanoscience and nanotechnology may revolutionize our ability to study living systems by non-invasive imaging techniques, and ultimately change the way we diagnose and treat disease according to one of the project coordinators.

To design nano-particles for human use, safety is crucial, and years of testing will remain before successful nano-particles will ever be used in humans. Ironically, the human body immune system has proven a powerful ally in the development of nano-particles for drug delivery and disease targeting. The body's immune system helps carrying USPIO particles to areas of disease, helping their detection. Meanwhile, the group of Thomas Vorup has developed assays to study the interaction of nano-particles with the immune system – helping the scientist optimize their design to be tolerated by the human body.

In a parallel effort, the group of Finn Skov Pedersen has chosen a more subtle approach to image specific cells. Aiming to 'repair' deficient cells in disease by gene therapy, the successful targeting of the treatment is also monitored by making the cells produce their own nano-particles, ferritin. This will improve our chances to follow the success of gene thrapy while we optimize it for human use.

At inSPIN (Center for Insoluble Protein Structures) at the Institute of Chemistry, Aarhus University, the Center's powerful 16.4 Tesla Nuclear Magnetic Resonance (NMR) spectrometer has been equipped to perform MRI. In collaboration with the Danish National Research Foundations Center of Functionally Integrative Neuroscience (CFIN), magnetic gradients have been acquired and optimized, allowing imaging at unparalleled resolution: Cell cultures and small animals can be imaged at a resolution of down to 5 and 25, respectively microns. This sensitivity will allow the detection of novel nanoparticles as they are developed and optimized in living systems. One project within this research field is concerned with measuring brain plasticity, i.e. structural changes of brain cells and their connections as observed e.g. during learning or prolonged states of mental stress, by combining our biophysical diffusion models with high-quality DWI data sets. The first step towards this goal, validation of the models with histology and stereology, is the focus of the current work. Preliminary results are shown in the figures below.



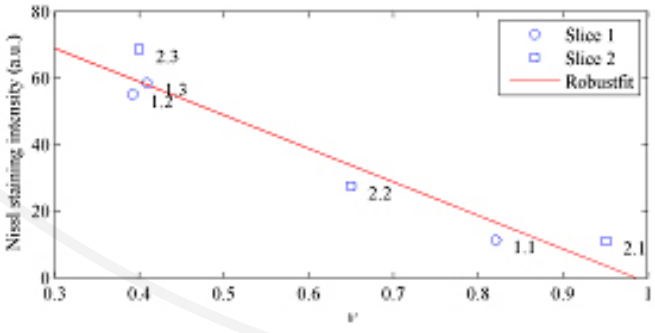


Figure 1
Left:
MR image (top) and corresponding histological section of the murine brain (bottom).

Graph below:
Measured inverse linear correlation (as expected) between the model derived neurite density and cell body density as determined from histology.
(Courtesy of Sune N. Jespersen)

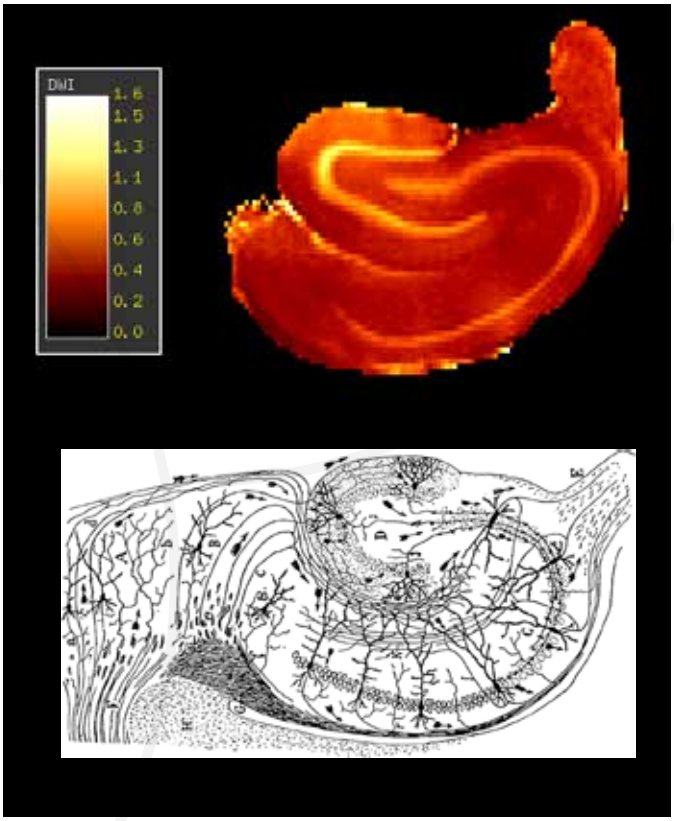


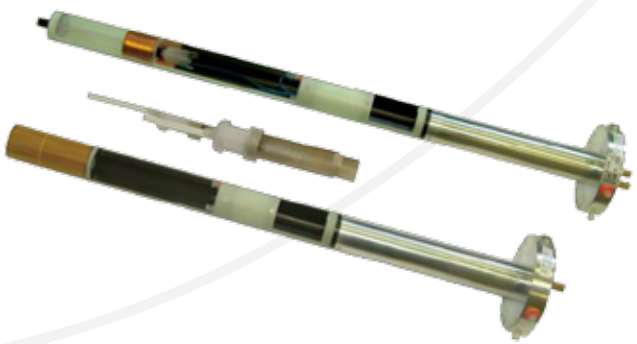
Figure 2
Above ADC map of rat hippocampus at 17 Tesla at 46 micrometer in-plane resolution.
Below is shown Ramon y Cajal's drawing of the neural circuitry of the rodent hippocampus (Histologie du Systeme Nerveux de l'Homme et des Vertebretes, Vols. 1 and 2. A. Maloine. Paris. 1911).

Notice the high levels of diffusion in cell layers.

Sune Jespersen in the lab putting a sample in the probe for 16.4 Tesla scan

The project is funded by the Danish Council for Strategic Research's Program Commission on Nanoscience, Biotechnology and IT (NABIIT) by 9.000.000 DKK.

Read more at:
www.inano.dk
www.inspin.dk



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Basic research becomes cutting edge patient management

by Leif Østergaard

In 1996, CFIN researchers working with scientists at Harvard Medical School, developed mathematical models and MRI based methods to determine cerebral blood flow (CBF) non-invasively. The resulting method, perfusion MRI, is easily applicable on most current MRI systems, and has since found widespread use in the study and diagnosis of neurological diseases.

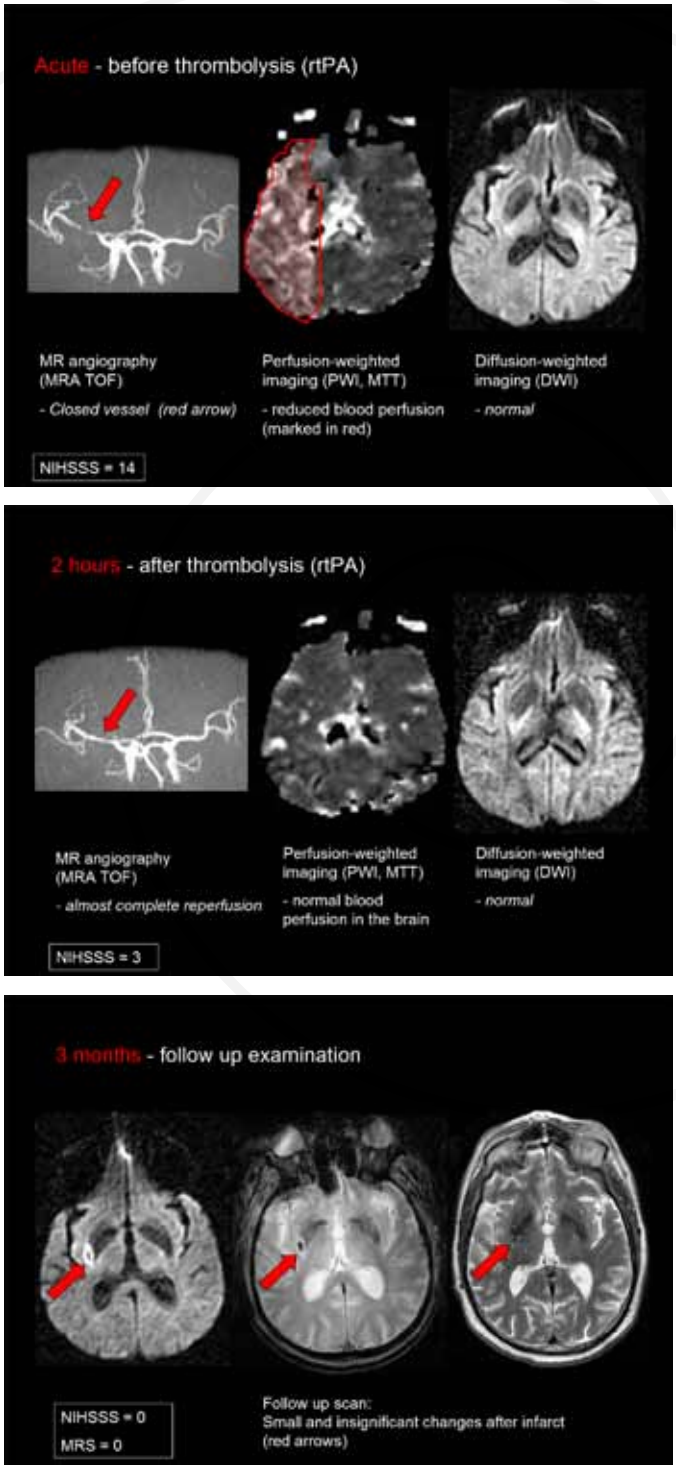
By 1998, the methods were validated by PET in Aarhus, and the first experience in acute stroke patients showed promising results. Whereas diffusion MRI demonstrated tissue damage by the stroke, the new method revealed extensive areas of poorly perfused tissue in most acute patients. Without treatment re-establishing blood-flow, this tissue would be the site of infarct growth, worsening the disabilities of the patient. The so-called perfusion-diffusion mismatch or 'tissue-at-risk' soon became the target of treatment by therapies aimed at dissolving the blood clot (thrombolysis). Future treatment by thrombolysis beyond 3 hours after symptom onset is based on the demonstration of 'perfusion-diffusion mismatch', applying the original methodology by either MRI or CT.

Patients in Region Midtjylland would soon benefit from this ground-breaking research. When the first thrombolytic agent (alteplase, administered intravenously within 3 hours to dissolve the blood-clot) was approved by the Danish National Board of Health, Aarhus could offer stroke patients cutting edge diagnosis, treatment, and care while scientists at CFIN gained new insight into this severe disease. Not only was CFIN research and the clinical launch of alteplase treatment closely coordinated, but funding, staff and equipment from CFIN and Århus Sygehus were combined over a 2-year period to create a leap forward in research and patient management that would otherwise have been impossible.

The results of the study show that Århus Sygehus was able to offer the new treatment to more patients than almost any center in the world – and that the MRI methods secured safe and individualized treatment of the patients. Due to this success, the advanced MRI diagnosis and alteplase treatment is now being offered routinely.

The results have received international recognition. The European Union now funds an international consortium headed by CFIN researchers, aimed to make perfusion imaging technology available to all medical institutions.

Stroke is the second most common cause of death in the EU, and the most frequent cause of adult disability. Of the 75% of victims surviving the stroke, half are unable to live independently in their own homes due to disabilities. In 2003, annual expenses related to stroke in the EU were estimated to total 34 billion Euros (www.heartstats.org). Due to the ageing population, the incidence of stroke is expected to double over the next 50 years.



Collaborators

Dept. Neuroradiology (Carsten Gyldensted, Leif Sørensen)
Dept. Neurology (Grethe Andersen, Paul von Weitzel-Mudersbach)

I-Know **– Integrating Information from Molecule to Man: Knowledge Discovery Accelerates Drug Development and Personalized Treatment in Acute Stroke.**

Leif Østergaard coordinates a EU project where leading European stroke researchers join with Danish companies to disseminate research and create innovation. ***I-Know*** is a knowledge discovery IT -based tool designed to aid early stroke diagnosis, stroke treatment, drug development, and identification of risk factors as targets in disease prevention for the benefit of European industry and citizens.

Acute stroke is a major socioeconomic burden in the EU. The disabilities following the disease develop rapidly and prompt treatment of patients is imperative. Currently a drug dissolving the blood clot (rtPA – thrombolysis) is the only established treatment, but this is only implemented at highly specialised centers. There is consequently a strong geographical inequality in the availability of this treatment - nationally and internationally within the EU. At the same time, there is an intense search by pharmaceutical industry and academic biomedical research to identify drugs that will stop the tissue damage progressing after acute stroke.

The knowledge discovery tool, ***I-Know*** will:

- Provide instant, user-friendly IT-based diagnosis and therapeutic guidance, reducing the infrastructural, economic, and educational barriers currently hindering advanced stroke treatment at less specialized units.
- Use advanced data mining techniques to model disease progression based on large multinational databases providing state-of-the-art diagnosis of every EU citizen irrespective of knowledge barriers.
- Provide a platform for modeling beneficial or adverse effects recorded during clinical trials, allowing optimal use of preclinical data in subsequent individualized patient management.
- Be designed to integrate data across descriptive levels to devise disease models that will bring scientific progress to stroke research.

Participants

CFIN

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- Lars Rissgaard Ribe
- Kim Mouridsen
- Niels Hjort
- Kristjana Yr Jonsdottir

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- Systematic Software Engineering A/S (Denmark)
- Dimac A/S (Denmark)

The project is funded by 23.000.000 DKK by EU
Read more at www.i-know-stroke.eu

COGNITION RESEARCH

by Andreas Roepstorff

Progress in 2006

2006 saw the completion of the first three CFIN PhD candidates with a strong cognitive profile.
Peter Vuust's work on perception of polyrhythmic structures grows out of an ongoing collaboration between CFIN and the Royal Academy of Music.

In her thesis project, Nicoline Hall investigated the interaction between emotion, voluntary and involuntary memory both using PET scanning and various forms of reports in collaboration with researchers at the Institute of Psychology. One of the challenges was to develop a paradigm that could reliably generate involuntary memories. This was done by asking subjects to associate words with pictures, and subsequently present these and other words in the scanning environment. The research may have implications for understanding and treatment of post traumatic stress disorders and other conditions characterized by recuring emotionally loaded involuntary memories. Nicoline has continued her research career as a post. doc. at the Research Unit for Functional Disorders, Aarhus University.

Finally, Mikkel Wallentin has been investigating neural processing of sentences with spatial semantics in a collaboration between the Center for Semiotics and CFIN. He is currently continuing this work, which is detailed elsewhere on these pages, in a post.doc. project jointly sponsored by the Research Council for Cognition and Culture, CFIN, Linguistic Graduate School North, and the Faculty of Humanities.

Mikkel's work on spatial semantics complements the other on-going linguistic research projects at CFIN. Ken Ramshøj Christensen, who in 2006 was awarded a 'young talented researcher' prize by Aarhus University for his PhD (2005) began a post.doc. project on structure and complexity in language, cognition and brain. This research, which mainly studies problems of syntax, is co-financed by Research Council for Cognition and Communication, CFIN and Linguistic Graduate School North. It involves a close collaboration with Douglas Saddy, University of Reading, UK.

Finally Kamila Sip, who is in the middle of her PhD project on neuropragmatics and deception in a collaboration between CFIN and Department of Linguistics, is currently at the Functional Imaging Laboratory, UCL, London to work with professor Chris Frith.

These research projects are exemplary of the cognitive research at CFIN. Through close collaborations with relevant research environments, we attempt to identify central problems or questions within well-established research traditions. The aim is to instrumentalize these in a format, which is compatible with the highly specific requirement afforded by the neurocognitive research paradigms. This double anchoring of projects provides some guarantee for the relevance of the findings, both with respect to elucidating mechanisms of the brain and to identifying particular workings of the mind.

One area of research, which shows a promising synthesis between mechanisms of the brain and of the mind, is predictive coding. This line of investigation has ramifications into neuroscience, artificial intelligence, philosophy of mind, and cognitive psychology. It examines the claim that rather than passively processing information from the environment, the brain is concerned about predicting the received stimuli, based on hierarchical models of causes and effects in the surroundings. In February 2006, we made this the topic of a focused international workshop "Predictive Coding and the Mind" with participation of, among others, Karl Friston, Marc Raichle, Chris Eliasmith, Risto Näätänen, and Lars Kai Hansen. This perspective on the brain has been developed in close collaboration with CFIN associate Jakob Hohwy, who recently took up a position at Department of Philosophy, Monash University, Melbourne. It will be further examined through a joint co-sponsored PhD student affiliated with Department of Philosophy and with CFIN.

CFIN's experience of and expertise with implementing interdisciplinary research projects has attracted international attention. Andreas Roepstorff has been the chairman of a working group established by HERA (Humanities in the European Research Arena) to outline how "Understanding and Misunderstanding" could become an international, interdisciplinary research programme. The report was selected for development and implementation by European Science Foundation. He is part of a group established by the Norwegian Research Council to outline a Norwegian research programme on ethical, legal, and social aspects of biotechnology, nanotechnology, and cognitive science. Finally, he has become member of the Scientific Committee for ESF's EUROCORES project Consciousness in a Natural and Cultural Context as a consequence of the BASIC research project. At a local level, he chairs the new research cluster Cognition, Communication, and Culture at Aarhus University, which, anchored at a priority research area at Faculty of Humanities, links researchers across all faculties. He also coordinates the interdisciplinary Niels Bohr professor project 'Interacting Minds - a biological basis' which involves Chris and Uta Frith.

Context sensitivity and predictive coding

Andreas Roepstorff and Jakob Hohwy have organized the international workshop, Predictive Coding and the Mind, February 2006, and a theoretical framework has been written up (Hohwy et al., under review; Hohwy and Roepstorff, 2006). We have suggested that predictive coding underlies processing of rhythmic activity (Vuust et al., submitted). We have secured funding for a phd student to look at the selforganising brain in the context of predictive coding (with Faculty of Humanities and Danish Agency for Science, Technology and Innovation). Experimental work on agency and prediction in motor control under Functional Electrical Therapy has been finalised, and is currently being written up as part of PhD thesis by Simona Iftime and MSc thesis by Rune Vingborg. The work has been further integrated into international research through the EUROCORES project

"BASIC (Brain, Agency, Intersubjectivity, Consciousness) headed by Andreas Roepstorff and through his reserach stay at Functional Imaging Laboratory, UCL, London, September 2006 – April 2007.

Communication and Brain function

Our investigations on the 'overlapping systems' hypothesis, which predicts activation of 'spatial' brain regions during sentence processing with spatial semantics have continued in collaboration with Institute of Cognitive Neuroscience, UCL (Wallentin et al., 2006), and Mikkel Wallentin has joined the group as post.doc. upon completion of his PhD. Kamila Sip is currently pursuing her PhD study on neuropragmatics at Functional Imaging Laboratory, Institute of Neurology, UCL. First data sets have been analysed and are ready for presentations. Ken Ramshøj Christensen has joined the group as post.doc. sponsored mainly by the Research Council for Communication and Culture. The work has made an impact on the European research agenda through the work of the workgroup "Understanding and Misunderstanding" chaired by Andreas Roepstorff. The resulting report commissioned by Humanities in the European Research Arena, has been selected to be developed by ESF for a European research platform.

Symbol systems and particulars of human cognition

The work on musical aesthetic and rhythmic processing has been continued (Vuust et al., 2006a) (Green et al., 2006; Vuust et al., 2006b) Research has received further input from a new PhD student, Uffe Schiøtt, Department of History of Religion, who performs a brain imaging study of 'prayer'.

Contextualising neuroscience

Work has progressed through the European Meetings of Mind project (Roepstorff, 2006) and studies of knowledge is made in brain imaging environments (Roepstorff, 2007). The work has gained a strengthened international dimension through Andreas Roepstorff's stay as associated Researcher at BIOS, LSE September 2006- April 2007.

SELECTED RESEARCH PROJECTS:

Andreas Roepstorff: The brain in context and communication.

Andreas Roepstorff, Peter Vestergaard-Poulsen, Martijn van Beek: Attention control: brain activity during meditation.

Chris Frith, Uta Frith, Andreas Roepstorff: Interacting minds - a biological basis.

Jakob Geday, Albert Gjedde, Ron Kupers: Effect of emotional valense on social perception.

Joshua Skewes, Andreas Roepstorff og Dan Zahavi: Agency, Self and Other, and Interdisciplinary investigation.

Kamila Ewa Sip, Andreas Roepstorff, Bill McGregor, Chris Frith: Neuropragmatics of deception.

Karen Johanne Pallesen, Synnøve Carlson, Antti Korvenoja, Christopher Bailey, Albert Gjedde: Memory work of musical chords in the brain in musicians and non-musicians, studied with fMRI.

Karen Johanne Pallesen, Synnøve Carlson, Albert Gjedde, Elvira Brattico, Christopher Bailey, Antti Korvenoja: Cognitive down regulation of emotional neural work of musical chords in musicians and non-musicians, studied with fMRI.

Mikkel Wallentin, Andreas Roepstorff, Svend Østergaard: Cognition, communication and context.

Mikkel Wallentin, Andreas Roepstorff, Leif Østergaard, Arne Møller, Jakob Linnet: Chess.

Morten Overgaard, Andreas Roepstorff, Sanne Lodahl: Introspective conditions.

Nicoline Hall, Albert Gjedde, Ron Kupers: Neural mechanisms behind emotional memory.

Nicoline Hall, Albert Gjedde, Ron Kupers: Neural mechanisms behind voluntary and involuntary memory.

Peter Vuust, Chris Frith, Mikkel Wallentin, Andreas Roepstorff, Leif Østergaard: Music and Language: an fMRI study of human plasticity.

Peter Vuust, Mari Tervaniemi, Elvira Brattico, Sakari Leino: Representation of musical syntax in the human brain.

Peter Vuust, Malene Vejby Mortensen, Albert Gjedde, Therese Ovesen, Andreas Roepstorff, Eckart Altenmüller, Leif Østergaard: Musical training of cochlear implantees: A PET-study.

Randi Abrahamsen, Sanne Lodahl, Andreas Roepstorff a.o.: Imaging pain.

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BASIC – Brain, Agency, Self, Intersubjectivity, Consciousness

This research project brings together some of the most philosophically minded neuroscientists and some of the most empirically minded philosophers in a joint examination of consciousness. It explores the hypothesis that there are intrinsic links between agency, self, and intersubjectivity, and that this may be seen both at the level of brain processes and in conscious experience. The project grows out of a collaboration between Dan Zahavi at Center for Subjectivity Research, University of Copenhagen and Andreas Roepstorff (project leader) at CFIN, both sponsored by the Danish National Research Foundation. This has allowed to bring together a group of neuroscientists (Marc Raichle, Chris Frith, Patrick Haggard, Tony Jack, Kai Voegeley, Vittorio Gallese, Tatjana Nazir, Marc Jeannerod) and philosophers (Shaun Gallagher, Evan Thompson and Albert Newen). The project is part of CNCC, European Science Foundation's Eurocores project Consciousness in a Natural and Cultural Context. The Danish part of the research has received additional funding from the Research Council for Cognition and Culture.

Cognition, Communication and Culture

CCC, or Cognition, Communication, and Culture, is a novel research cluster at Aarhus University formed by researchers across the faculties of humanities, social science, theology, and health sciences. CCC is one of three official research focus areas at the Faculty of Humanities, but with its strong inter-faculty profile, it serves as forum for exchange of ideas and as a network for interdisciplinary cross-fertilisation across the university.
The cluster is organised around five topics:
Cognition and the Brain, coordinated by Albert Gjedde and Leif Østergaard, CFIN
Explanation and Evidence in a Mental and Neural Context, coordinated by Uffe Juul Jensen, Dept. of Philosophy
Comparative Linguistics, coordinated by Sten Vikner, Dep. of English
Memory and Cognition, coordinated by Dorthe Berntsen, Institute of Psychology
Culture and Cognition, coordinated by Armin Geertz, Department for the History of Religion.

The Cluster is headed by Andreas Roepstorff.

Chris Frith as Niels Bohr professor: Interacting Minds – a Biological Basis

In recent years it has become increasingly clear that a key to the particularities of human cognition and consciousness is the ability for humans to interact and to share understandings both of the outside world and of inner mental states. Partly for methodological reasons, partly due to certain styles of reasoning in 20th Century psychology and philosophy of mind, this line of inquiry has not been mainstream. However, this picture is rapidly changing. A combination of conceptual developments and novel experimental approaches are currently redefining the focus of research in a number of areas, and an understanding of how human interaction is instantiated in brains is becoming a key issue in cognitive neuroscience. At an applied level, the understanding of the basis for human interaction seems a prerequisite for understanding also a number of clinical situations such as autism and schizophrenia.

With the close interdisciplinary collaboration between brain scientists, clinicians and researchers of human cognition and communication, CFIN is ideally placed for this line of investigation. This has led to the research project 'Interacting Minds - a Biological Basis' which will run 2007-2011.The aim is to examine the links between the human capacity for minds to interact and the putative biological substrate, which enables this to happen.

Due to generous support from the Danish National Research Foundation and from Aarhus University, it has been possible to attract to the project the emiment British researchers Chris and Uta Frith. Individually and jointly, they have for the last decades been spearheading the investigation of interacting in terms of basic research, development of new concepts, and methodologies, and clinical applications. Uta Frith, who has been key in theoretically and clinically linking theory-of-mind deficits with clinical syndromes like autism, will be appointed Aarhus University Research Foundation Professor, and Chris Frith, who has spearheaded the use of brain imaging to study higher cognitive functioning, has been appointed Niels Bohr Professor at Aarhus University.

Chris and Uta Frith each have an outstanding academic record and worldwide reputation within their respective scientific fields i.e. functional brain imaging as applied to a range of higher cognitive processes, and investigations of the neurocognitive basis of developmental disorders, such as autism. They have previously demonstrated that a conjunction of these approaches allows for an innovative systematic examination of the neuro-cognitive basis of human interaction.

Chris Frith is born in England in 1942 and educated at Christ's College Cambridge and London University (natural sciences and psychology). He is Professor of neuropsychology at Welcome Department of Imaging Neuroscience and assistant director of Leopold Müller Functional Imaging Laboratory in London.
Uta Frith is Professor at the Institute of Cognitive Neuroscience & Department of Psychology, University College in London.

The project is shared between the faculties of Humanities and Health Sciences, and it interacts with a number of researchers across the university, from history of religion and anthropology to psychology, and psyschiatry. It will employ a set of tightly integrated approaches including conceptual examination, brain imaging data, behavioural experiments, and clinical investigations. As research and teaching activities involve inter-faculty collaboration, it will break novel grounds in establishing pathways for a flow of students across institutional borders within the university and with other teaching institutions in the Aarhus area (e.g. Royal Academy of Music, School of Engineering).

Chris and Uta Frith

COGNITION RESEARCH

Language and space

by Mikkel Wallentin

Standard theories of neural language processing argue that distinct regions of the brain are involved in language comprehension and production in a modular fashion. This has been the basis for research in neurolinguistics, more or less since Paul Broca in 1861 published evidence for a left inferior frontal brain region involved in language production (now commonly known as Broca's area). The explanatory power of this model, however, has turned out to be limited in certain respects. Firstly, modularity has been difficult to establish, since patients with Broca's region lesions usually also have comprehension deficits. Secondly, neuroimaging experiments on healthy subjects have revealed a diverse pattern of brain activations in relation to linguistic stimuli. And lastly, language comprehension may, strictly speaking, not be separable from other cognitive functions, such as memory and perception. Language must be learned and processed through the senses, and meaning is only accessible through an interaction of perceptual input and stored memories. Everyday utterances such as: "Are you picking him up today?" show this very clearly. Without a perceptual monitoring of the surroundings we cannot tell if the addressed "you" is actually you, and without searching both semantic and episodic memory stores, it is not possible to know what "pick up" means (is it a "hand movement"?), who "he" is, and when "today" (now, in 5 minutes or 23.59?) is. In other words, such a sentence is meaningless without context.

The "overlapping systems" theory of language function, therefore, argues that linguistic meaning construction crucially relies on contextual information provided by "non-linguistic" cognitive systems, such as perception and memory. According to this theory, a strictly modular linguistic system cannot function. Personal pronouns like "he/she/it" are among the most commonly used words in language, and a valid theory of language comprehension must therefore address how such words are processed by the brain.

Processing of spatial information is a good test case for examining an "overlapping systems" model in a neurocognitive framework. Spatial prepositions (e.g. "over", "in", "toward") are the most important carriers of spatial information in language. But like the personal pronouns this small class of words only carries a very schematic notion of the spatial relations they depict. This allows for spatiodynamic "metaphors" to be widely used in language to express even abstract, nonspatial scenarios (e.g. "The result approaches significance") as well as more concretely spatial scenarios. Cognitive linguists have, on the basis of these observations, named spatial cognition as one of the basic constituents of semantics. From a neurocognitive point of view, much is already known about the neuronal underpinnings of spatial cognition, due to decades of study in both humans and in animal models. Particularly, posterior parietal cortex has been found to play an important role in spatial working memory as part of a "dorsal stream" network for spatiodynamic processing.

In a collaboration between CFIN, Center for Semiotics at University of Aarhus, and Institute of Cognitive Neuroscience at University College London, we have conducted a series of studies to examime whether linguistic processing of spatial relations call on the same posterior parietal neural system involved in processing spatial relations set up through nonlinguistic input.

In one study, (Wallentin, Roepstorff, Glover, & Burgess, 2006) working memory evoked by linguistic cues for spatial and non-spatial aspects of a visual scene was investigated. Subjects were asked to indicate the relative positions of people or objects (referenced by the personal pronouns) in a previously shown image. Our results indicate that dorsoposterior precuneus supports spatial WM during linguistic processing. Good performers had higher activity in precuneus as a function of increased "effort" (higher response time) compared to poor performers during the spatial task, whereas the opposite was found for a nonspatial task, providing further evidence for specifically spatial WM in dorsoposterior precuneus.

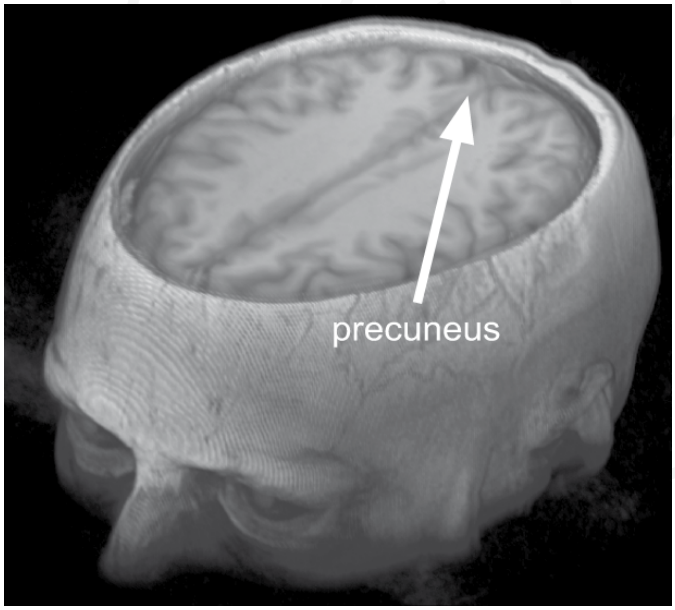

Figure 1.
Precuneus is located in the dorsoposterior part of the parietal lobe. This region is known to play a key role in spatial attention and working memory processes. Damage to this region often leads to deficits in these processes, such as hemispatial neglect.

Lunch reading in the shade - Mikkel Wallentin at Human Brain Mapping 2006 in Florence, Italy

In a second study, (Wallentin, Weed, Østergaard, Mouridsen, & Roepstorff, in press) subjects read simple sentences, which again presented two persons in relation to each other, and again subjects were asked to evaluate spatial (e.g. “Was he turned towards her?”) and equally concrete nonspatial content (e.g. “Was he older than her?”). We found that recall of the spatial content relative to the non-spatial content resulted in higher BOLD response in a dorsoposterior network of brain regions, most significantly in precuneus, strikingly overlapping the network found in the first experiment with recall of spatial aspects of images depicting similar scenarios.

Together these findings support a neurocognitive model of language function, where sentences establish meaning by interacting with the perceptual and working memory networks of the brain.

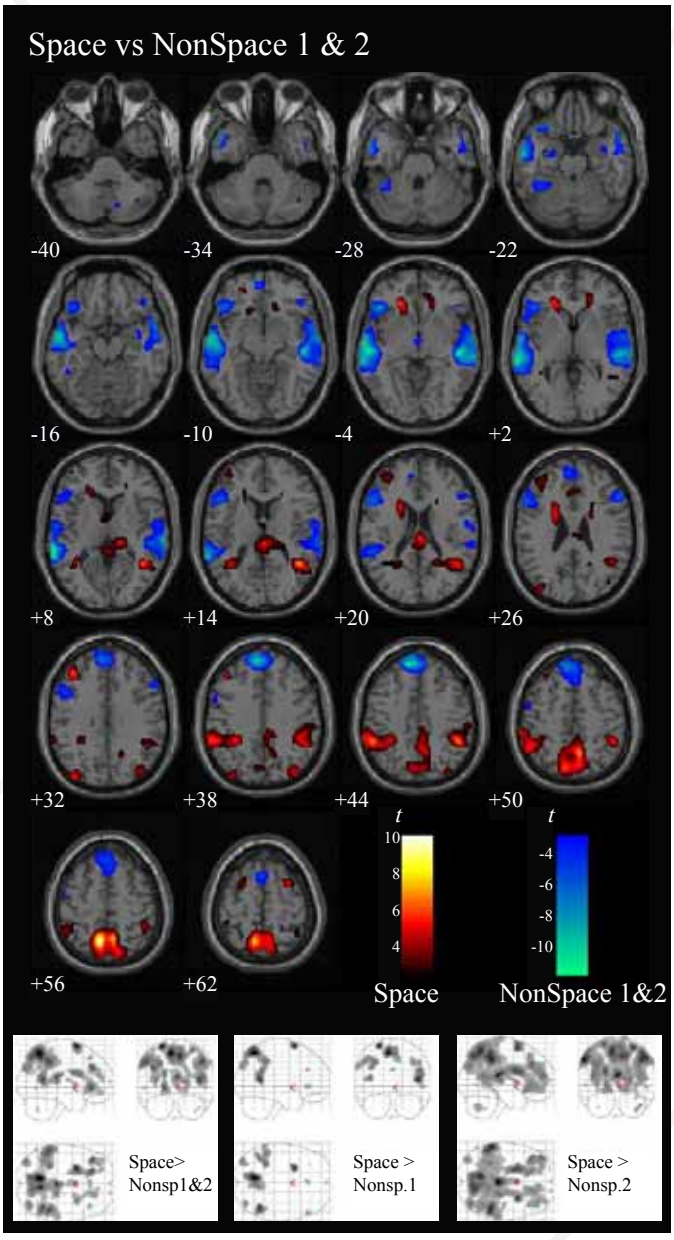

Figure 2.
Recall of space relative to recall of two nonspatial tasks, thresholded at P<0.05, FDR-corrected.
Main contrast of space is seen against the collapsed effect of the two nonspatial contrasts. Effects, however, are similar when contrasted only with one or the other.
Glass brains show: LEFT: Space-NonSpace 1 & 2; MIDDLE: Space-Non-Space 1; RIGHT: Space-NonSpace 2, all at P<0.05, FDR-corrected.

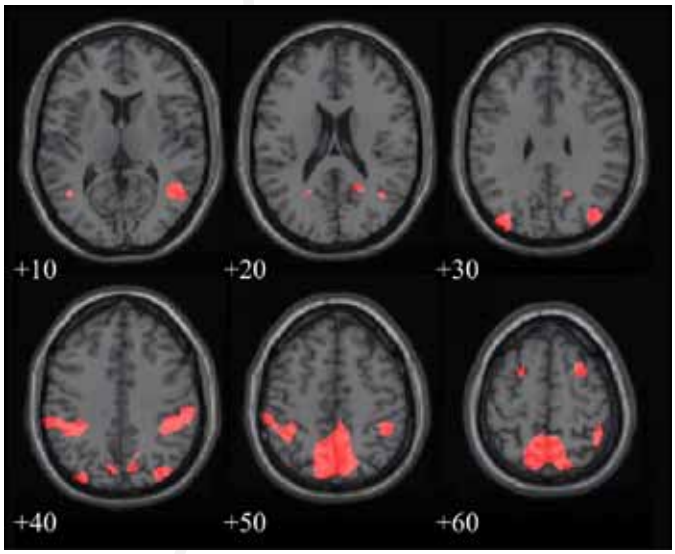

Figure 3.
Recall of spatial content from language relies on the same network of brain regions found to be involved in recall of spatial aspects of an image (see Wallentin et al. 2006). The figure shows overlapping voxels from the [Space>NonSpace1 & NonSpace2] contrast from this study and the [Space>NonSpace] contrast from Wallentin et al. (2006) study, both thresholded at P<0.05, FDR-corrected.

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COGNITION RESEARCH

Music and brain

by Peter Vuust

Contrary to music research, traditionally belonging to the field of humanities, brain research offers a scientific method of examining some of the basic questions concerning music such as why humans have the ability to communicate through music and what influence culture has on this ability (Cross, 2003; Huron, 2001; Krumhansl et al., 2000). The methodical and experimental aim of this research is to create an understanding of the way in which core human competencies such as music, communication, and language will affect the effective and functional connections of the brain and how factors such as competence, emotion, consciousness/awareness, and knowledge influence both actions and perception. This involves experimental studies using brain scanning techniques and conceptual studies of cognitive semiotics, linguistics, psychology, and theoretical neurobiology. Thus research questions and methods are of fundamental multidisciplinary nature; therefore, multiinstitutional co-operations using the resources and specialist knowledge from different fields are prerequisites.

This is the background for the current collaboration between the Center of Functionally Integrative Neuroscience (CFIN) and the Royal Academy of Music (DJM), and it is the main point of DJMs focus area: Musical perception, cognition and learning, in which the relationship between music and subject is brought into focus.

Current research projects within this field:

Music and Language

The overall aim of this project is to contribute to mapping of the human brain. In particular, knowledge about the relationship between the neural processing of music and language is important to a range of different issues including the ongoing political debate about the potential transfer effect of music training to other cognitive domains (Schellenberg; Schellenberg, 2004). Clinically, this research may have far reaching consequences for rehabilitation in relation to language disorders, neurosurgery, and cochlear implantees.

Musical syntax in the human brain

In Western tonal music, the rules of harmony determine the order and hierarchical importance of events in a musical piece. For example, the tonic chord, built on the first note of the diatonic scale, is usually placed at the end of chord sequences. A brain response termed the early right anterior negativity (ERAN) is elicited when a harmonically incongruous chord is inserted within or at the end of a musical sequence (Koelsch et al., 2000; Koelsch et al., 2001; Koelsch and Mulder, 2002). We recently conducted a study to test whether the ERAN reflects the processing of harmony rather than the building of a tonal context and whether the ERAN is also elicited by violations of the tuning of the sounds upon which harmony is based (Leino et al., 2006).

Musical training of cochlear implantees

The purpose of the present project is to test the hypothesis that musical training of cochlear implantees enhances the auditory system and thereby understanding of speech. We are aiming at: 1) finding an efficient method to better cochlear implantees' perception of spoken language, and 2) investigating brain areas responsible for the analysis of complex sounds in speech and music.

Predictive coding of music

During the last decades, models of music processing in the brain mainly addressed the specificity of brain modules involved in the processing of different musical components. We argue that the theory of predictive coding explains the functional integration involved in musical processing. We have provided evidence for a neural network involved in the processing of rhythmic incongruence, consisting of the mismatch negativity (MMNm), which has the properties of an error term, and a P3a component, which is interpretable as a subsequent evaluation (Vuust et al., 2006a).

Assessing musical potential in infants

Early exposure to musical training is a necessary but unfortunately not sufficient condition for achieving musical expertise. A reliable assessment of musical potential in infants could spare many fruitless music lessons in some and inspire others with a real potential for a musical career. Behavioural measures of musical potential in general are not very well validated in a wider population and may not apply to infants, in so far that these tests are built on verbal communication. Therefore, it would be of great value to have an objective measure of musical talent. The mismatch negativity (the MMNm) as measured by magnetic encephalography (MEG) (or electro encephalography (EEG) has proven to be a strong indicator of musical expertise in adults. Superiority in the auditory processing of different musical parameters such as pitch, rhythm, intensity, sound source localization, and timbre have been found in musicians as compared to non-musicians (Koelsch et al., 1999; Seppanen et al., 2006; Tervaniemi et al., 2001; Tervaniemi et al., 2006; Van Zuijen et al., 2004). The ensuing project proposes: 1) to develop adequate behavioural measures for measuring musical abilities and potential in infants, and 2) to test whether this measure correlates with psychophysical measures (MMNm) of their musical abilities.

Musical Learning and Liking

This project examines the neuronal substrate and dynamics as the brain learns and recognizes music and melodies. Empirical behavioral studies have shown that learning – i.e. how well one knows a given piece of music - to a certain extent determines how well one likes the music. The so-called Wundt inverted-U curve effect between knowing and liking (Szpunar et al., 2004) predicts that few as well as multiple exposures to a piece of music is associated with a low score for 'liking' the piece. The neural correlates to this psychological effect are, however, unknown. We hypothesize that brain activity

during melody perception will depend on how well known the melody is. The actual presentation frequency, the memory rating as well as the associated brain activity pattern will correlate with the subjective rating. For seldom heard melodies, many brain regions should show activation, including higher level auditory areas, association areas, and areas supporting a heightened attention function, i.e. primarily in frontal cortex. Well known melodies should activate a lesser total extent of areas, since the cognitive burden will have lightened and become more automatic. Additional brain regions will probably show up for the perception of well known melodies, i.e. memory areas such as the hippocampus.

Musical competence and heart stethoscopy

The perspective in this study is an increased understanding of how pitch recognition and rhythmic skills relate to auscultation of the heart and thus eventually contribute to improvement of auscultation skills. In addition, the study will add knowledge about specialized musical training for medical doctors and musical tests and training at different levels of medical expertise.

Dopamine release in Musicians: a natural high

Using the radioactive ligand [11C]raclopride, this study investigates dopamine neurotransmission in relation to concert playing in expert musicians contrasted to a control situation in which the musicians play scales. We hypothesize that the binding of raclopride decreases in the concert playing condition indicating an increase in endogenous dopamine release in the basal ganglia.
The possible implication of dopamine release in response to musical performance may be an important example of self-stimulation. Further understanding of the neurobiological basis of such self-stimulation of the dopamine system could potentially contribute to improving assessment and treatment methods in addictive behaviour such as drug abuse and pathological gambling, as well as clarifying the specificity and interaction of dopamine.

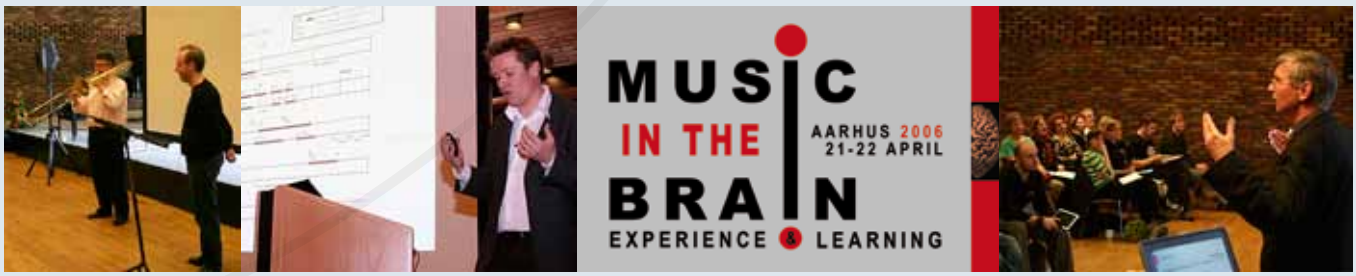
Music in the Brain – meeting and network

The collaboration between CFIN and DJM has recently resulted in the formation of the international research network “Music in the brain”. Music in the Brain was founded by a number of research institutions in the city of Aarhus working within this field. It aims to facilitate contacts between different scientific approaches to studying music and the brain, and to introduce this scientific field to a broader audience within the Danish music community. The activities of the network include a biannual meeting at the Royal Academy of Music in Aarhus, where international researchers as well as prominent people from the Danish music community are invited to speak. The first meeting entitled “Experience and Learning” took place in april 2006 with the participation of international top researchers including Isabelle Peretz, Mireille Besson, Eckard Altenmüller and Gottfried Schlaug, and was attended by more than 150 guests from different countries.

The meeting aimed at introducing this scientific field to a broader audience in Denmark. Specifically there was a discussion of intriguing questions related to musical competence, for example: “what characterizes the musical brain?”, and “what happens in the brain during musical learning?”

This field of research is particularly relevant to the music academies. On the other hand, neurobiological studies of human cognition can benefit greatly from the collaboration with musical academies, which provide education and knowledge about musical practice to the highest artistic level and music teaching on all levels. The collaboration has therefore already resulted in internationally acknowledged studies with implications and promising perspectives both for basic research in cognitive neuroscience as well as for clinical use.

Read more at: www.musicinthebrain.dk



CFIN staff

Head of CFIN - Professor Leif Østergaard

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Doris Doudet
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Sune Nørhøj Jespersen
Kristjana Yr Jonsdottir
Malene Vejby Mortensen
Kim Mouridsen (PhD degree 28.04.06.)
Anders Bertil Rodell
Donald F. Smith
Manouchehr Seyedi Vafaee
Peter Vuust (PhD degree 02.02.06.)
Mikkel Wallentin (PhD degree 06.06.06.)

PhD students:
Joel Fredrik Astrup Aanerud
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Christopher Bailey
Per Borghammer
Søren Christensen
Jesper Frandsen
Astrid From Frøhlich
Jacob Geday
Anders Green
Louise Gyldensted
Nicoline Marie Hall (PhD degree 01.11.06.)
Brian Hansen
Niels Hjort
Birgitte Fuglsang Kjølby
Luciano Minuzzi
Mette Møller
Thomas Nielsen
Karen Johanne Pallesen
Ericka Peterson
Lars Riisgaard Ribe
Uffe Schiøtt
Kamila Ewa Sip
Christine Sølling
Kristian Tylén, Guest Researcher

New faces at CFIN

Jakob Linnet has his Masters (Cand. Psych.) and Ph.D. in psychology from University of Copenhagen. He is a licensed clinical psychologist and has a Post Doctoral degree from Harvard University. Since 2001 professor Linnet has focused his research on pathological gambling. His research concentrates on the clinical and neurobiological basis for heterogeneity of pathological gambling, and involves clinical assessment of pathological gambling, neurobiological correlates of cognitive, and behavioral impairment of decision making, and dopaminergic neurotransmission during gambling.

Professor Doris Doudet, PhD, on sabbatical from the University of British Columbia, Vancouver, Canada, joins the PET Center as a new CFIN researcher April 1, 2007. Doris is a neuroscientist with special interests in neurotransmission and Parkinson's disease. She is Professor at the Division of Neurology, Department of Medicine, University of British Columbia (UBC), since 2003. Doris has no less than two PhD degrees in Neurosciences-Neurobiology (1983) and Human Neurophysiology (1985), from Universitées Bordeaux I and II, respectively. Before the current appointments, Doris held posts as Visiting Scientist at Johns Hopkins University (1986-87) and the Laboratory of Cerebral Metabolism (1988-93) of the National Institutes of Mental Health, Bethesda, where she continued as Guest Researcher when she moved to UBC, first as Assistant Professor (1993-2000) and since 2004 as Associate Head of Research at the Department of Medicine.

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Rune Vingborg

Research Assistants:
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Line Gebauer
Sanne Lodahl
Anders Bay Neumann
Kristine Rømer Thomsen

Technical Staff:
Lili Elgaard, Radiographer
Michael Geneser, Radiographer
Kim Vang Hansen, Imaging Analyst
Poul Erik Nielsen, System Administrator
Ryan Sangill, MR Physicist
Dora Zeidler, Research Radiographer

Administrative Staff:
Mai Drustrup, Secretary
Michele Gammeltoft, Secretary
Palle Monefeldt, Logistics Coordinator
Henriette Blæsild Vuust, Communications Coordinator

CFIN Retreat at Sandbjerg Gods, August 2006

Facts about CFIN

Teaching

CFIN has in 2006 continued to work on establishing pre-graduate cross-disciplinary teaching at the University of Aarhus. In 2005 CFIN coordinated gathering of courses and teaching from all five faculties at the university and initiated the making of a course catalogue called NEUROVIDEN 2005/2006. This catalog offered teaching in neuroimaging, cognition, brain research and similar topics. In 2006/2007 the course catalogue has become web-based.
Read more at: http://www.cfin.au.dk/neuroviden-06-07

In regards to postgraduate teaching the research school SFINX (Graduate School of Functionally Integrative Neuroscientific Experimentation) was started in the beginning of 2006. Head of the PET-center at Aarhus University Hospital, Professor Albert Gjedde is the primary force behind the new research school that offers courses, workshops and seminars within the neuroscientific area.
Read more at: http://www.cfin.au.dk/SFINX

Leif Østergaard:
- A-course in Diagnostic Radiology, Aarhus, February 2006: *Acute MR at stroke: Diffusion and perfusion MRI*
- Postgraduate teaching for psychiatrists, Risskov, September 2006: *Neuroimaging: Magnetic Resonnance*

Albert Gjedde:
- *PET-skanningens rolle I neuroonkologien*. Neuro oncology A-course, Aarhus Sygehus, October 2006.
- *Cerebrovascular Diseases*. A-course, Aarhus Sygehus, November 2006.
- *Vedligeholdelse af basal somatisk viden.* Psychiatric Hospital, Risskov, 11 September 2006.

SFINX weekly workshops, Graduate School of Functionally Integrative Neuroscientific Experimentation, Aarhus University Hospitals:
- *Brain Energy Metabolism*, February 2006.
- *Substrate Transport in Brain*, February 2006.
- *ATP Homeostasis (hydrolysis of phosphocreatine and glycolysis)*, February 2006.
- *ATP Homeostasis (oxidative phosphorylation)*, February 2006.
- *Metabolic Compartmentation*, March 2006.
- *Ion Homeostasis During Activation*, March 2006.
- *Brain Energy Metabolism During Activation*, March 2006.
- *Substrate Delivery During Activation*
- *ATP Homeostasis During Activation*, April 2006.
- *Metabolic Compartmentation During Activation*, May 2006.

Andreas Roepstorff:
- *Ethnographies of Knowledge*, May-June 2006, with Simon Cohn

Peter Vestergaard-Poulsen:
- Magnetic Resonance Imaging (course leader). PhD course, Faculuty of Health Sciences, Aarhus University

Other CFIN researchers:
- *Magnetic Resonance Imaging I*, 20 November 2006 - 1 December 2006, Aarhus, DK.
- *Introduction to Matlab*, 22 May 2006 - 24 May 2006, CFIN, Aarhus, DK.
- *Magnetic Resonance Imaging I*, 27 February 2006 - 6 March 2006, Aarhus, DK.
- *Biophysics II*, 1 February 2006 - 1 June 2006, Aarhus, DK.
- A-course, Neurologi speciallæge-uddannelsen, Sundhedsstyrelsen: *Cerebrovaskulære Sygdomme*.
- Medico-ingenør uddannelsen, Aarhus Universitet, linie for biomedicinsk teknik: *MR ved akut apopleksi*.
- Instructor (spring06 and fall06) on courses *Statistisk fysik* and *Faststoffysik* at the Institute for Fysics, Aarhus University.
- Lecturer and course coordinator of the course *Biofysik II* under the Biomedical Engineering education, Aarhus University.

Invited lectures

In 2006, CFIN researchers have been invited to give lectures at the following events.

Leif Østergaard:
- Brain Storm 2006, 6-7 January 2006, Aarhus: *Assessing tissue viability by MRI and neuroinformatics*.
- Scandinavian Perfusion Day, 7 February 2006, Aarhus: *MR-metoder og principper ved stroke*.
- Staff-meeting, February 2006, Neurocentret, Aalborg Universitet: *Tværdisciplinær Neuroforskning: Erfaringer fra Århus*
- Staff-meeting, Royal Melbourne Hospital, March 2006: *Perfusion and Diffusion MRI in Stroke: Predictive Models*
- European Congress of Radiology, 3-7 March 2006, Vienna, Austria: *Diffusion and Perfusion MR imaging of the brain: Imaging techniques, protocols and post-processing*.
- Dansk Psykiatrisk Selskabs Årsmøde, 16-17 March 2006, Nyborg: *Musik og Hjernen*.
- International Society for Magnetic Resonance in Medicine (ISMRM) 14th Annual Meeting, 6-12 May 2006, Seattle, Washington, U.S.A.: *Perfusion Imaging*
- International Society for Magnetic Resonance in Medicine
- (ISMRM) 14th Annual Meeting, 6-12 May 2006, Seattle, Washington, U.S.A.: *Theory of MR perfusion Measurements*
- International Summer School on MRI and MRS, 24-28 June 2006, Poiana Brasov, Rumania: *Basics of Diffusion and Perfusion MRI*

- International Summer School on MRI and MRS, 24-28 June 2006, Poiana Brasov, Rumænien: *Clinical Applications of Diffusion and Perfusion MRI*
- European Society for Neuroradiology (ESNR), Geneva, 13-16 September 2006: *Tissue Characterization: Perfusion MRI in Stroke*.
- European Society for Neuroradiology (ESNR), Geneva, 13-16 September 2006: *Stroke Imaging* (Symposium organized by Schering AG)
- European Society for Magnetic Resonance in Medicine and Biology (ESMRMB) Annual Meeting, 21-23 September 2006, Warsaw, Polen: *Brain MRI: Anatomy, landmarks and territories*
- European Society for Magnetic Resonance in Medicine and Biology (ESMRMB) MR Lectures on Perfusion and Flow, 28-30 September 2006, Copenhagen: *Perfusion Imaging*.
- Forskningens Dag, Århus Sygehus, 29 September 2006, Aarhus: *Cellulær og Molekylær MR Imaging med målrettede nano-partikler*.
- European Society for Magnetic Resonance in Medicine and Biology (ESMRMB) School of MRI, 5-7 October 2006, Heidelberg, Germany: *Perfusion Imaging*
- Staff-Meeting (Neurology/Neuroradiology), Karolinska Sjukhuset, Huddinge: *Brain Perfusion MR in Dementia*.
- Nordic Network on Imaging in Medicine and Biology, 17-19 November 2006, Turku, Finland: *Cross-disciplinary Research and Neuroimaging at The Danish National Research Foundations Center of Functionally Integrative Neuroscience (CFIN), Aarhus, Denmark*
- Nordic Network on Imaging in Medicine and Biology, 17-19 November 2006, Turku, Finland: *Prediction of Stroke Damage Using MRI*
- International Symposium and Training Academy, German Stroke Competence Network, 24-25 November 2006, Berlin, Germany: *Cerebral Blood Flow and Perfusion Imaging*
- 12th Kuopio Bio-NMR Workshop, 11-13 December 2006, Kuopio, Finland: Stroke Imaging: *Predicting tissue outcome*.

Albert Gjedde:
- *Regulation of Brain Oxidative Metabolism*. Panum Institut. February 2006.
- *Neuroenergetics of anticipation*. Predictive Coding and the Mind Prospectives (CCC) and Graduate School of Functionally Integrative Neuroscientific Experimentation (SFINX) International Workshop, Aarhus University, DK. February 2006.
- *Flow-metabolism coupling during brain activation in humans*. European Winter Conference of Brain Research, Switzerland. March 2006.
- *Dopamine release in vivo*. Dansk Selskab for Biologisk Psykiatri i Århus, DK. March 2006.
- *Brain and Sexuality*. Brain Awareness Week, Copenhagen University, DK. March 2006.
- *Modularity of Brain*. Predictive Coding and the Mind Prospectives (CCC) and Graduate School of Functionally Integrative Neuroscientific Experimentation (SFINX) International Workshop, Aarhus University, DK. March 2006.
- *Hjerner kan spå, især om fremtiden*. Guest on "Meet the Scientist" (Politiken), Aarhus University, DK. April 2006.
- *In vivo measurement of dopamine release under the influence of drugs, hyperactivity and gambling*. Scandinavian College of Neuropsychopharmacology 47th Meeting, Helsingør, DK. May 2006.
- *PET-skanning af skelettet: Det er der mange ben i*. Danish Orthopaedic Society Annual Meeting, Odense, DK. May 2006.
- *Glæden er hårdt arbejde: Hjernen er en problemløser og problemernes løsning belønnes med glæde*. The Brain Injury Resource Centre, Funen county, DK. May 2006.
- *In vivo measurement of dopamine release under the influence of drugs, and in,hyperactivity and gambling*. 5th Annual Danish Brain Research Laboratories Meeting. June 2006.
- *What´s in a Binding Potential? How Much Binding and How Much Potential?* Neuroreceptor Mapping, Copenhagen, DK. July 2006.
- *Coupling of brain function to metabolism: evaluation of energy requirements*. Gordon Research Conference on Brain Energy Metabolism, Oxford University, UK. August 2006.
- *Karbaner, bedøvelse og tankevækkelse*. Georg Cold Retirement Symposium, Aarhus University, DK. August 2006.
- *PET-skanning og neurotransmission*. Psychiatric Hospital, Risskov, DK. September 2006.
- *Brains and Emotions*. Danish Neuropsychological Society Annual Meeting, Odense, DK. September 2006.
- *Brain Metabolism and Non-Ionizing Radiation*. Biomagnetics Workshop, Aalborg University, DK. September 2006.
- *Få biokemiske forklaringer på, hvad der gør os sunde og glade*. Danish Technological Institute, Taastrup, DK. September 2006.
- *End of phrenology: Is brain work energy-demanding?* Danish Medical Society, Copenhagen, DK. October 2006.
- *Brain Mechanisms of Depression*. Eli Lilly A/S, Copenhagen, DK. October 2006.

Andreas Roepstorff:
- *Mind the Hype*, Rathenau Institute, Brain plotting, Amsterdam, NL, 10 December 2006.
- *The brain in context and communication*, Alva Noë, The brain and consciousness in context, University of California, Berkeley, US, 2 December 2006.
- *Understanding and Misunderstanding: Cognition, Mind Culture*, Finnish Academy, Humanities in the European Research Area, Helsinki, FI, 23 November 2006.
- *BASIC: Brain - Agency - Intersubjectivity - Self & Consciousness*, European Science Foundation, CNCC launch conference, København, 14 November 2006.

- *The neuroturn: challenging anthropology or anthropological challenge?*, Department of Anthropology, University of Oxford, Oxford, GB, 27 October 2006.
- *Neurocosmology: a new master narrative in the 21 Century?*, British Museum & Anthropology, University College London, Making Things Better. Cosmologies of Wellbeing, London, GB, 10 October 2006.
- *From Neurophilosophy to Neurocosmology*, plenarforedrag Society for Philosophy, Psychiatry and Psychology, Philosophy, Psychiatry and the Neurosciences, NL, 1 July 2006.
- *Bevidsthed, Kognition og Kommunikation*, Aarhus Universitet, Forskningens Døgn, 5 May 2006.
- *Stress og depression, et socialt perspektiv*, Teknologirådet, Forskere og borgere i dialog, forskningens døgn, 5 May 2006.
- *Præstationsfremmende stoffer- et socialt perspektiv*, Teknologirådet, Forskere og borgere i dialog, forskningens døgn, DK, 5 May 2006.
- *Fra Hjernevindinger til Hjernevendinger*, Studenterkredsen, Aarhus, DK, 6 April 2006.
- *Kognition, Kommunikation og Kultur*, Humanistisk Fakultet, Aarhus Universitet, Det rådgivende arbejdsmarkedspanel, DK, 16 March 2006.
- *Snyd, bedrag og tillid*, Dansk Selskab for Neuroforskning, Din hjerne er en bedrager, København, DK, 13 March 2006.
- *Mission impossible: et forsvar for mottologien*, Humanistisk Fakultets Årsfest, Århus, DK, 23 January 2006.
- *Predictive models or modelling prediction*. Predictive Coding and the Mind. Aarhus Universitet, 10 February 2006 (med Jakob Hohwy)
- *Ascription of agency and emotional resonance in religious and quasi religious experience*. Religion and Emotion, Collegium Helveticum, Zürich, Schweiz, 3-4 February 2006.
- *Brain, Pragmatics and Deception*. Interpersonal Deception, Detection, Neuroimaging, and Pragmatic Inference. Aarhus, 26-27 January 2006.
- *The brain in context - contextualising integrative neuroscience*. Brain Storm 2006 – Birthday symposium for Albert Gjedde. 7 January 2006.

Arne Møller:
- *Brug af PET, mikroPET og røntgen-video ved dyreeksperimentelle undersøgelser*. 30 August 2006.
- *PET in rodents*. Skejby Sygehus, 28 September 2006.

Peter Vuust:
- *I got rhythm or have I?*: Musik og hjernen. Forskningens døgn, Danmark, 10 May 2006.
- *Is Musical Competence Left Lateralized - Pre-attentive MEG Responses to Incongruent Rhythms*. Conference on Music Perception & Cognition (ICMPC8), Chicago, USA, 4 August 2006.
- *Music and the brain*. Opening of Danish Science Festival 2006, 30 March 2006.
- *Music in the Brain: experience*. Chair. Music in the brain: Experience and Learning, Danmark, 21 April 2006.
- *Musik og hjerne*. Dansk musikpædagogisk Forenings lærerkonference, 2006, 5 October 2006.
- *Musikalsk stimulering af småbørn med høretab*. Fredericiaskolen (specialskole for hørehæmmede), 29 November 2006.
- *Neural Processing of Polyrhythm*. Music in the brain 2006: Experience and Learning, Aarhus, Danmark, 22 April 2006.
- *Neural Processing of Polyrhythm*. Cognitive Brain Research Unit (CBRU), 9 May 2006.
- *Prediction in Music*. Predictive Coding and the Mind: Prospects and Perspectives - International Workshop, 9 February 2006.
- *What practice does to the brain: Brain studies with implications for music(ians) and sport (athletes*). Sporting Sounds, Aarhus, Danmark, 28 September 2006.
- *What practise does to the brain?* Sibelius Academy, Finland, 9 May 2006.

Other CFIN researchers:
- 5 April 2006. Stroke Day at Neuroradiology and Neurological departments, Aarhus Hospital. Talk about experiences from the Aarhus Hospital use of thrombolysis.
- 29 October 2006. Joint World Congress on Stroke in Cape Town. Oral presentation: *Implementing MRI based selection criteria for thrombolysis in acute stroke within the 3 hour window. Efficacy over a 2 year period*.
- 7 February 2006. Skandinavisk Perfusionsdag 2006, Aarhus Universitet: *Indsigt i patofysiologi med avanceret MR*.
- Lecture at Selskabet Danske Neuropsykologers annual meeting in Odense 2006: *Emotioners effekt på voluntære og involuntære erindringer*.
- Lecture at Forskningsklinikken for Funktionelle Lidelser og Psykosomatik, Århus 2006: *Spontan og viljestyret emotionel hukommelse*.
- *A Theoretical Model of Water Diffusion in Brain Tissue*, ISMRM 2006.
- *Modeling of Water Diffusion in the Brain*, The Danish National Research Foundation – Status Meeting, November 2006.

Conferences

CFIN researchers have participated in the following congresses and conferences during 2006:

Leif Østergaard:
- European Congress of Radiology, 3-7 March 2006, Vienna, Austria
- International Society for Magnetic Resonance in Medicine (ISMRM) 14th Annual Meeting, 6-12 May 2006, Seattle, Washington, U.S.A.

- 16th European Stroke Conference, 16-19 May 2006, Brussels, Belgium
- Organization for Human Brain Mapping 12th Annual Meeting, 11-15 June 2006, Florence, Italy
- Gordon Research Conference on Brain Energy Metabolism and Blood Flow, 20-25 August 2006, Magdalen College, Oxford, England.
- European Society for Neuroradiology (ESNR), 13-16 September 2006, Geneva, Switzerland
- European Society for Magnetic Resonance in Medicine and Biology (ESMRMB) Annual Meeting, 21-23 September 2006, Warsaw, Polen.
- Joint World Congress on Stroke 2006, Cape Town, South Africa, 26-29 October 2006.
- IST Event 2006, November 21-23 2006, Helsinki, Finland.

Albert Gjedde:
- European Medical Research Council Meeting, Austria. April 2006.
- Danish Society for Neuroscience, Sandbjerg, DK. May 2006.
- Human Brain Mapping, Florence, Italy. June 2006.
- American Epilepsy Society. June 2006.
- 6th International Symposium on Functional Neuroreceptor Mapping, Copenhagen, DK. July 2006.
- Gordon Research Conference, Magdalen College, Oxford, England. August 2006.
- Society for Neuroscience, Atlanta, USA. October 2006.

Andreas Roepstorff:
- Vital Politics , BIOS, LSE, London, GB, 9 September 2006 (giving the lecture Before the Fact: From Meetings of Minds to Neurodystopiae)
- Human Brain Mapping, Florence, Italy 11-15 June 2006.
- Society for Philosophy, Psychiatry and Psychology, Philosophy, Psychiatry and the Neurosciences, Leiden, Holland, June 2006.

Peter Vestergaard-Poulsen:
- International Society for Magnetic Resonance in Medicine (ISMRM) 14th Annual Meeting, May 2006, Seattle, Washington, U.S.A.

Peter Vuust:
- Conference on Music Perception & Cognition (ICMPC8), Chicago, USA, 4 August 2006.
- Danish Science Festival 2006, 30 March 2006.
- Music in the brain: Experience and Learning, Danmark, 21-22 April 2006.
- Human Brain Mapping, Florence, Italy 11-15 June 2006.
- Dansk musikpædagogisk Forenings lærerkonference, 2006, 5 October 2006.
- Predictive Coding and the Mind: Prospects and Perspectives - International Workshop, 9 February 2006.

Other CFIN researchers:
- Ph.D Day, Aarhus University, Denmark, 13 January 2006.
- 21-23 September 2006 ESMRMB 23. Annual meeting i Warsaw, Polen.
- 29 October 2006. Joint World Congress on Stroke in Cape Town.
- 29 September 2006. Research Day at Århus Sygehus (Forskningens Dag)
- 12th Annual Meeting, Human Brain Mapping, June 11-15, Florence, Italy.
- ISMRM 14th Scientific Meeting and Exhibition, 6-12 May 2006, Seattle, WA, USA.
- Gordon Research Conference on Cerebral Metabolism and Bloodflow, 20-25 August 2006, Magdalen College, Oxford.
- Society for Neuroscience 2006, Atlanta, USA, 14-18 October 2006.
- The Movement Disorder Society's 10th international congress of Parkinson's disease and Movement Disorders, Kyoto, Japan, 28 October - 2 November 2006.
- International Stroke Conference 2006, American Stroke Association, Orlando, Florida, February 2006.
- 15th European Stroke Conference, Brussels, Belgium, May 2006
- International Symposium on Biomedical Magnetic Resonance Imaging and Spectroscopy at Very High Fields, 16-18 February 2006, Würzburg, Germany.
- Perspectives on Memory and cognition, Aarhus University 2006: *Interaction between recall strategy and memory properties. A comparison of involuntary and voluntary memory for emotional pictures.*

Human Brain Mapping 2006 in Florence, Italy

Meeting organization

CFIN researchers have participated in organizing the following scientific meetings in 2006:

Leif Østergaard:
- *Brain Storm 2006*, 6-7 January 2006, Århus, Denmark (Scientific organizer)
- *Scandinavian Perfusion Day*, 7 February 2006, Århus, Denmark (Scientific organizer)
- International Society for Magnetic Resonance in Medicine (ISMRM) 14th Annual Meeting, 6-12 May 2006, Seattle, Washington, U.S.A. (Chairman, Education Committee, Second Chair, Scientific Program Committee)
- European Society for Magnetic Resonance in Medicine and Biology (ESMRMB) Annual Meeting, 21-23 September 2006, Warsaw (Member of Scientific Program Committee)
- Nordic Network on Imaging in Medicine and Biology, 17-19 November 2006, Turku, Finland (Member of Organizing Committee)

Andreas Roepstorff:
- *Predictive Coding and the Mind – Prospects and Perspectives*. International workshop, Aarhus, 9-10 February 2006.
- CCC seminars: monthly international seminars on Cognition, Communication and Culture.

Peter Vuust:
- *Music in the brain 2006*: Experience and Learning (21-23 April 2006).

Radio / TV / newspress

CFIN researchers have participated in the following in 2006:

- Danmarks Radio, P1 Apropos (journalist Bjarke Stender):
- Leif Østergaard, *Smilets Fysiologi* (The physiology of the smile, radio program 27 March 2006)
- Danmarks Radio, P1 Apropos (journalist Gitte Førby): Leif Østergaard, *Fritid og Tidsfordriv* (Spare time and killing time, radioprogram 10 April 2006)

- Albert Gjedde, *Fund, forskere og fortolkninger*. Jyllandsposten, kronik 15 September 2006.
- Albert Gjedde, *Religion og science fiction*. Jyllandsposten, kronik 31 January 2006.

- DR2, Viden om: Arne Møller, *Afhængighedens gåde*. 24 October 2006.
- DR Morgenradio: Arne Møller, *Spil på Forskningens Døgn*. 4 May 2006.
- *Mobiltelefoner påvirker hjernens stofskifte* / Arne Møller. Dagens Medicin. 2006 ; nr. 35, 23-11. s. 10
- *Hjerneforskere vil skabe spilreducerende maskine* / Arne Møller. Dagens Medicin. 2006 ; nr. 35, 23-11. s. 12
- *Forskere jagter dopamin som bevidsthedsstof* / Arne Møller. Dagens Medicin. 2006 ; nr. 35, 23-11.

- Peter Vuust, *Bolero*. DR - P2, 4 February 2006. (radio program).
- Peter Vuust, *Bønnen i hjernen*, P1, DR, 14 August 2006. (radio program).
- Peter Vuust, *Hvor tonedøv kan man være?* DR, 31 October 2006. (radio program).
- Peter Vuust, *Kulturnyt*. DR - P2, 9 February 2006. (radio program).
- Peter Vuust, *Dagens Danmark*. DR1, 26 February 2006. (tv program).
- Peter Vuust, *God Morgen P3*. DR - P3, 21 April 2006. (radio program).
- Peter Vuust, *Citatet*. Berlingske Tidende, 27 January 2006. (interview for newspaper).
- Peter Vuust, *Den musikalske hjerne er interessant*. Århus Stiftstidende, 20 April 2006. (interview for newspaper).
- Peter Vuust, *Mozart for fuld musik*, 26 January 2006. (interview for newspaper).
- Peter Vuust, *Mozart-effekten 13 år efter*, 14 January 2006. (interview for newspaper).
- Peter Vuust, *Musik er et sprog kun musikere taler*. Politiken, 12 February 2006. (interview for newspaper).
- Peter Vuust, *Musik er fitness for hjernen*. Jyllandsposten, 30 March 2006. (interview for newspaper).
- Peter Vuust, *Musik gør hjernen glad*. Julie Lund Zafiri. Jydske Vestkysten, 7 October 2006. (interview for newspaper).
- Peter Vuust, *Musik gør os klogere*. Kristeligt Dagblad, 17 March 2006. (interview for newspaper).
- Peter Vuust, *Musik hjælper døve*. Jyllandsposten, 2 February 2006. (interview for newspaper).
- Peter Vuust, *Musik i hjernen*. Aarhus Stiftstidende, 2 February 2006. (interview for newspaper).
- Peter Vuust, *Musik og Hjerne*. Dan Johnsen. Modus - Dansk Musikpædagogisk medlemsblad, 4 April 2006. (interview for newspaper).
- Peter Vuust, *Musik åbner ørerne på hjerneforskere*. Jyllandsposten, 5 May 2006. (interview for newspaper).
- Peter Vuust, *Måske er der noget om Mozart-effekten*, 26 January 2006. (interview for newspaper).
- Peter Vuust, *Sangen er menighedens svar på Guds tiltale: Ingen gudstjeneste uden musik. Hvorfor er orglet blevet kirkens instrument? Og hvorfor ligger salmerne altid for højt?* Kristeligt Dagblad, 2 December 2006. (interview for newspaper).
- Peter Vuust, *Som mors hjerte slog*. Politiken, 21 May 2006. (interview for newspaper).
- Peter Vuust, *Succes kan læres*. Suna Haugaard. Århus Stiftstidende, 29 October 2006. (interview for newspaper).

Boards / Committees / Editorials

CFIN researchers are involved in the following:

Leif Østergaard:
- Member of work group on organizing image diagnostics in the Masterplan for the reorganization of hospitals in Aarhus.
- Member of Scientific Program Committee, European Society for Magnetic Resonance in Medicine and Biology (ESMRMB)
- Member of Annual Meeting Program Committee (AMPC), International Society for Magnetic Resonance in Medicine (ISMRM)
- Member of Board of Trustees, ISMRM
- Member of Education Committee, ISMRM with responsibility for MR e-learning for doctors and physics in Third World countries

Albert Gjedde:
- Adjunct Professor, Department of Neurology and Neurosurgery, McGill University, Montreal, Quebec, Canada.
- Member, Royal Society of Canada.
- Member, Centre de recherche en sciences neurologiques, Université de Montréal, Montréal, Québec, Canada.
- Visiting Professorship, Yale University, USA.
- Chairman, Research Advisory Committee, Royal Library of Denmark.
- Member, Medical Research Council, Ministry of Science and Technology, Denmark.
- Member, the Scientific Advisory Board, Arvid Carlsson Institute, University of Gothenburg, Gothenburg, Sweden.
- Member, The Danish Committee on Scientific Dishonesty.
- Member, The European Medical Research Council.
- Member, The Nordic Organisation of Medical Research Councils.
- Vice President 2008 of the Gordon Research Conference on Brain Energy Metabolism and President-Elect of same for 2010

Additional Peer Review/ Albert Gjedde:
- Academy of Finland.
- Deutsche Forschungsgemeinschaft.

Andreas Roepstorff:
- Project leader, BASIC (Brain, Agency, Self, Intersubjectivity, Consciousness), a ESF EUROCORES CNCC Project, 27 November 2006 - 27 November 2009.
- Member, Scientific Committe, EUROCORES Project CNCC (Consciousness in a Natural and a Cultural Context), 14 November 2006 - 14 November 2009.
- Formand for programgruppen Understanding and Misunderstanding: Cognition, Mind and Culture, Humanities in the European Research Agenda, 1 May 2006 - 1 January 2007.
- Member, Scientific Committee, 9th Internatinal Conference on Philosophy, Psychiatry and Psychology, 1 January 2006 - 1 July 2006.
- Medlem af "Utvalget for planlegging av nytt forskningsprogram om etiske, juridiske og samfunnmessige aspekter ved bioteknologi, nanoteknologi og kognitiv vitenskap", Forskningsstyrelsen, Norge. (December 2006 - April 2007).
- Medlem af ph.d. komite: Niels Nygård, "Arkitektonisk Kvalitet", Arkitektskolen i Aarhus.

Peter Vestergaard-Poulsen:
- Member of Studienævnet for Biomedicinsk Teknik (Board of Studies for Biomedical Engineering), Faculty of Health Sciences, Aarhus University.

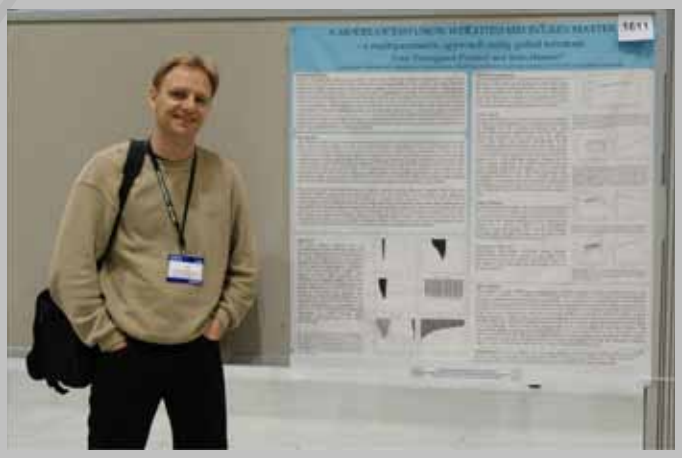
Research stays abroad

Andreas Roepstorff:
- Interacting Minds: from brain research to Biopower, Wellcome Department of Imaging Neuroscience, UCL og BIOS, LSE (1 September 2006 – 1 April 2007)

Peter Vestergaard-Poulsen:
- McKnight Brain Institute, University of Florida, Gainesville, USA (October/November 2006, The Blackband High Field lab., Prof. Steve Blackband)
- Radiological Sciences Laboratory, Stanford University, USA (Stefan Skare)

Astrid From Frøhlich:
- Medical Physics, Department of Diagnostic Radiology, Freiburg University Hospital. Two year stay (from July 2004 – July 2006)

Søren Christensen:
- Royal Melbourne Hospital, Melbourne, Australia (Professor S. Davis) (from 2004 -)



Peter Vestergaard-Poulsen at ISMRM Conference 2006 in Seattle, USA

International scientific partners

- Institut National de la Santé et de Recherche Medicale / Université Claude Bernard, Lyon, Frankrig (Professor Norbert Nighoghossian)
- Fundació Privada Institut d'Investigació Biomédica de Girona, Girona, Spanien (Professor Salvador Pedraza)
- University of Cambridge , Cambridge, England (Professor Jean-Claude Baron)
- Universitätsklinikum Hamburg-Eppendorf, Hamburg, Tyskland (Professor Jens Fiehler)
- Universitätsklinikum Freiburg für die Medizinische Fakultät der Albert-Ludwigs-Universität, Freiburg, Tyskland (Dr. Valerij Kiselev)
- Royal Melbourne Hospital, Melbourne, Australien (Professor S. Davis)
- MGH Athinoula A. Martinos Center, Massachusetts General Hospital, Boston, U.S.A. (Dr. O. Wu)
- Brain Research Institute, Heidelberg West, Victoria, Australia (Dr. F. Calamante)
- McKnight Brain Institute, University of Florida, USA (Professor Steve Blackband)
- Mallinckrodt Institute of Radiology, Washington University, St. Louis, USA (Dr. D. Yablonski and Professor J. Ackerman)
- Dan Zahavi, Center for Subjektivitetsforskning, Københavns Universitet
- Morten Overgaard, Neurocenter Hammel
- Chris Frith, UCL, London, UK
- Uta Frith, UCL, London, UK
- Patrick Haggard, UCL, London, UK
- Nikolas Rose, LSE, London, UK
- Morten Kringelbach, Oxford University, UK
- Harvey Whitehouse, Oxford University, UK
- Doug Saddy, Reading Universitet, UK
- Simon Cohn, Goldsmith College, London
- Celia Lury, Goldsmith College, London
- Jules Davidoff, Goldsmith College, London
- Evan Thompson, University of Toronto, Canada
- Marc Raichle, Washington University, St. Louis, US
- Anthony Jack, Washington University, St. Louis, US
- Alva Noë, University of California, Berkeley, US
- Kai Vogeley, Köln Universitet, Tyskland
- Albert Newen, Tübingen University, Germany
- Vittorio Gallese, Parma University, Italy
- Tatjana Nazir, Lyon University, France
- Jakob Hohwy, Monash University, Melbourne, Australien
- McKnight Brain Institute, University of Florida, Gainesville, Florida, USA (Professor Steve Blackband)
- Mari Tervaniemi, Cognitive Brain Research Unit, Department of Psychology, University of Helsinki (CBRU) and Helsinki Brain Research Center, Helsinki, Finland
- Elvira Brattico, CBRU and Helsinki Brain Research Center, Helsinki, Finland
- Sakari Leino, CBRU and Helsinki Brain Research Center, Helsinki, Finland
- Eckart Altenmüller, Institut für Musikphysiologie und Musiker-medizin, Hannover, Germany
- Karl Friston, Functional Imaging Laboratory (FIL), Wellcome Centre of Cognitive Neuroscience, UCL, UK
- Risto Näätänen Cognitive Brain Research Unit, Department of Psychology, University of Helsinki (CBRU) and Helsinki Brain Research Center, Helsinki, Finland
- Satu Pakarin, CBRU and Helsinki Brain Research Center, Helsinki, Finland
- Professor Roger Dean, Vice-Chancellor and President, University of Canberra, ACT 2601, Australia; Fellow of the Australian Academy of the Humanities (FAHA).
- Antoine Bechara, University of Iowa, USA

Industriel partners

- Systematic Software Engineering A/S , Århus, Denmark
- Dimac A/S, Højbjerg, Danmark
- Nordic Neurolab, Bergen, Norge
- GlaxoSmithKline, Cambridge, England
- Schering AG, Berlin, Tyskland.
- GE Medical Systems, Milwaukee, U.S.A.

Completed Ph.D. theses, 2006

- Peter Vuust, M.Sc., M.A. Neural processing of polyrhythmic structures in music. 2 February 2006.
- Kim Mouridsen, M.Sc. Statistical Analysis and Optimization of Perfusion Weighted MRI. 28 April 2006.
- Mikkel Wallentin, M.A. Neural processing of sentences with spatial meaning. 6 June 2006.
- Nicoline Hall, M.Sc. What springs to mind. An investigation into the neural and phenomenological characteristics of involuntary and voluntary conscious memories. 1 November 2006.

Andreas Roepstorff - Brain Storm 2006 in Aarhus, Denmark

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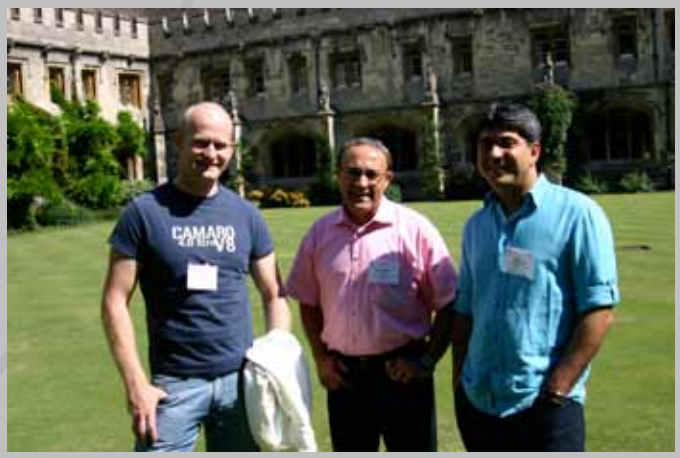


Per Borghammer, Manou Vafaee & Mahmoud Ashkanian
at Gordon Research Conference on Brain Energy Metabolism and Blood Flow 2006, Oxford, England

Bibliometry

by Leif Østergaard

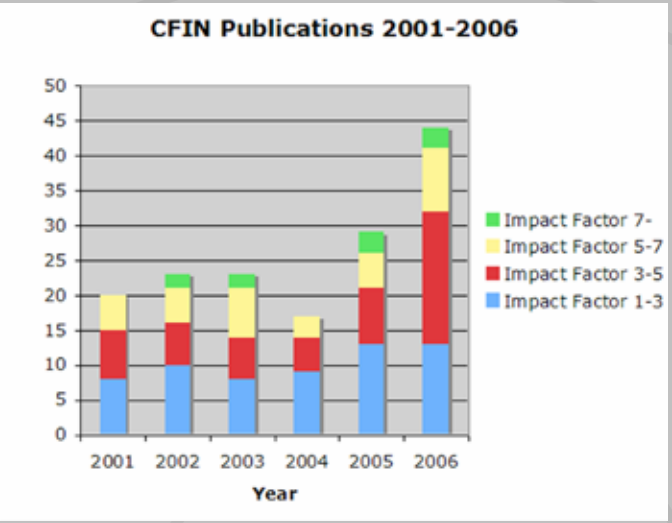
Table 1 shows the number of CFIN publications in journals with peer review 2001-2006, categorized according to the Journal Impact Factor as recorded March 28th, 2007.

Table 1	2001	2002	2003	2004	2005	2006
Impact Factor 0-1	6	4	12	8	8	3
Impact Factor 1-3	8	10	8	9	13	13
Impact Factor 3-5	7	6	6	5	8	19
Impact Factor 5-7	5	5	7	3	5	9
Impact Factor 7-	0	2	2	0	3	3
Total	26	27	35	25	37	47

Manuscripts in the 0-1 range were published in journals with language other than English (1 Polish, 8 Danish journals), in new international journals for which Impact Factor is not yet recorded, or in international journals with impact factors in the range 0.312-0.98 (11 journals).

The figure shows the total number of publications 2001-2006, with each column subdivided according to Journal Impact Factor. Only Manuscripts with Journal Impact Factor > 1.0 are shown.

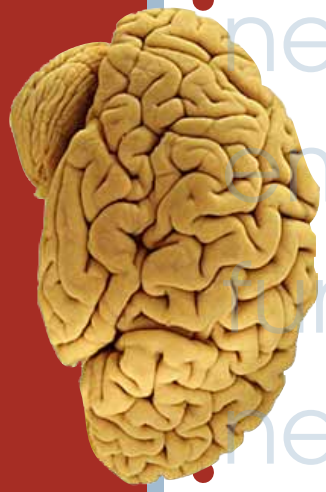
Two prominent features are noted:
While CFIN was founded July 1st 2001, the total number of publications (and their distribution) remained essentially constant until 2004. This is the typical pattern of a 'start-up' center where relatively few, established senior scientists, initiate a number of new projects with Ph.D. students who typically need 2-3 year to complete this task, with an additional one-year delay before their results appear in print. While this partly explains the rapid growth in publications 2004-2006, the successful recruitment of talented scientists and successful attraction of new grants is an important prerequisite for current and future growth.



The increase in the total number of CFIN publications has occurred primarily in journals with Journal Impact Factor > 3. Although it remains a primary goal to increase the number of publications in the few journals in our field with Journal Impact Factor > 7, this metric only to some extent reflects the subsequent impact of a manuscript. Let alone the question of whether less is more (should we strive for few manuscripts in important journals?), long term citation statistics of manuscripts published in journals with even low Journal Impact Factors is probably important to further address 'scientific productivity'.

Aarhus University

The Neurocenter at Aarhus University Hospital



neuroinformatics

emotion

functional hemodynamics

neurotransmission

brain

MEG

neuroconnectivity

fMRI

neuroenergetics

subject

stroke