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

ANNUAL REPORT 2008

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PET
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Amidst hectic activity, the Danish Neuroscience Center was nearly completed in 2008.
Photo: Poul Erik Nielsen

Introduction - 2008 in words

by Leif Østergaard

The Danish National Research Foundation's Center of Functionally Integrative Neuroscience (CFIN) has experienced immense growth since it was founded in 2001, with a four-fold increase in external funding and employees. While these resources have lead to increasing scientific quality and growing international recognition, the consolidation of this effort has become a growing challenge. Scientists who dedicate their careers to interdisciplinary research often develop research areas that bridge methods, concepts and knowledge across Faculty traditions. The development of career opportunities for interdisciplinary researchers within a traditional University structures is therefore crucial to the long-term investments in CFIN over the past decade. In July 2007, the Danish Ministry of Science, Technology and Innovation introduced the University Investment Capital (UNIK) grant program, allowing Danish universities to develop new, crosscutting activities. Early 2008, a consortium consisting of CFIN researchers and collaborators within the research cluster Cognition, Communication, and Culture (www.ccc.au.dk), the Faculties of Science and Health Sciences, Aarhus School of Business and the Royal Academy of Music were selected by the University of Aarhus to finalize one of 28 applications submitted nationwide. After thorough international reviews by leading international scientists in our field and subsequent evaluation by an international expert panel, the resulting application, MIND*Lab*, was chosen as one of only four initiatives to receive DKK 120 million for research 2009-2014. While this secures continued funding of key CFIN scientists and the pursuit of new scientific goals with our close collaborators, we currently work with the University of Aarhus to create permanent positions to support CFIN and MIND*Lab*'s aim to become a global hub for interdisciplinary neuroscience and cognition studies.

CFIN and key future MIND*Lab* activities are housed at Aarhus University Hospital, Århus Sygehus. Thanks to a visionary investment in research and industrial innovation to reduce the burden of neurological and psychiatric diseases, the Danish Neuroscience Center (DNC) was almost completed by the Central Denmark Region in 2008. In CFIN and MIND*Lab*, researcher from fields such as physics, statistics, psychology of religion, cognitive psychology and the studies of language and music, exploit their results in parallel efforts to develop sophisticated neurosurgery, combat chronic pain, refine rehabilitation after brain damage, and so on. Our Annual Reports (In this issue, see for example the section on functional haemodynamics page 24-25) highlight the tremendous translational potential of CFIN and MIND*Lab* research in terms of defining tomorrow's patient management and technology – while making it available to patients at Aarhus University Hospital today. With increasing challenges to maintain patient care with less governmental reimbursement, we are thankful that Aarhus University Hospital remain supportive of our needs for office space and facilities for advanced neuroimaging technology. In 2008, VILLUM KANN RASMUSSEN FONDEN and VELUX FONDEN generously supported the MIND*Lab* core experimental facility, partly funded as a national instrument center by the Danish Ministry of Science, Technology and Innovation in 2007. The purchase and siting of a magnetoencephalograph and a 3 Tesla MR imager is now ongoing, while TMS, EEG and psychophysics laboratories are being established. Our next challenge is to establish novel molecular imaging technologies in Denmark in order to ensure the progress of crucial research to combat neurodegenerative diseases.

In December 2008 Albert Gjedde, PET Center head and CFIN founding director 2001-2003, accepted a position as Head of the Department of Neuroscience and Pharmacology at the University of Copenhagen. Albert Gjedde has been instrumental to the development of an imaging neuroscience environment in Aarhus; an effort he will continue as an adjunct professor at the University of Aarhus. We celebrate Albert Gjedde's 15 successful years in Aarhus in a special section pages 8-13.

With this annual report we wish to highlight scientific progress and key events in 2008, and to thank CFIN scientists and collaborators, the Danish National Research Foundation, Central Denmark Region, the University of Aarhus and our other generous funding sources for their continued support.

On behalf of the CFIN scientific coordinators

Leif Østergaard

NEUROENERGETICS

by Albert Gjedde

Brain Energy Metabolism

Metabotropic monoaminergic receptors affect brain energy metabolism by regulating calcium ion sensitive metabolic pathways in the cells of the nervous systems and changing both cytosolic glycolysis and mitochondrial oxidative metabolism. Therefore we argue that changes of glycolysis and oxygen consumption reflect the variations of monoaminergic neuromodulation although the exact correlations are still very uncertain (Wong & Gjedde 2008). The question is how the changes of metabolism facilitate the integration of neuronal network activity that ultimately leads to brain function and consciousness (Iversen et al. 2008). The tentative answer is that oxidative metabolism provides a steady background of energy turnover, while glycolysis provides the temporal buffering of functional fluctuations. An additional question is how the metabotropic receptors influence the mechanisms of blood flow and energy metabolism regulation: Are blood flow, glucose delivery and consumption, and oxygen delivery and consumption affected equally, or can the relative changes of these variables be used to predict the different types of monoaminergic neuromodulation? The regulation is not limited to the monoamines, as glutamate also has metabotropic receptors. The role of these receptors in relation to the monoaminergic receptors is uncertain (Falkai et al. 2008, Wong et al. 2008).

Oxygen, Glucose Delivery, and Lumped Constant

While glucose consumption has been a standard measure of brain activity *in vivo* since 1979 it remains unclear how accurately glucose consumption can be determined with 2-deoxyglucose (2DG) or fluoro-deoxyglucose (FDG), the conventional tracers of glucose metabolism *in vivo* in animals and humans (Lerche et al. 2008). This question is closely linked to the accuracy of the lumped constant, a variable that accounts for the differences among glucose and tracer metabolism. Our new findings indicate that as much as 80% of the glucose may be phosphorylated in cells other than neurons, as well as in parts of neurons that are less oxidative than the tissue as a whole. As much as 80% of the oxygen consumption in turn appears to take place in neurons. These findings introduce the concept of spatial inhomogeneities of glycolysis, oxidative metabolism, and blood flow, and they raise the issue of which of these variables is the most accurate marker of brain activity and activation (Iversen et al. 2008).

Flow and Flow-Metabolism Coupling

Regional cerebral blood flow is, by a wide margin, the most common marker of brain activity (Gjedde 2008). Most applications give relative results of normalized data, either relative to a baseline or relative to a whole-brain average, or both. Our recent findings show that normalized values in many cases greatly misrepresent the true state of the blood flow variable (Borghammer et al. 2008a, 2008b). When real values of blood flow are determined, the findings of non-steady-states suggest that regional flow rates in the brain are coupled to glucose consumption but not to oxygen consumption, as also shown by the BOLD images of mismatch between oxidative metabolism and blood flow. The mismatch is also reflected in significant changes of the oxygen-glucose index, which appears to decline at the onset of increased activity and to rise immediately after the resumption of normal activity. New evidence indicates that the flow-metabolism coupling can be improved by inhalation of carbogen (Ashkanian et al. 2008).

Neurobiology of the ”Hard” Problem

Recent attempts to understand brain function and the mechanisms that underlie phenomena such as sensation, perception, awareness, consciousness, depend almost entirely on presumed measures of the changes of blood flow that happen when brain functions undergo a controlled change in a subject placed in the device that makes the measurements. The researchers base the statistical evaluation of the results on a general linear model of additive variables that has its ancient origins in the work of Franciscus Donders and his inference of variable cognitive processes from variable reaction times, the practice known as mental chronometry. Recent measures with magnetic encephalography of changing magnetic fields of the order of milliseconds suggest that inferences of the kind that Donders introduced could be wrong, particularly for types of brain function that are outside the primary sensory domains. The question that the current researchers inherited from phrenology and mental chronometry is still whether the mechanisms that serve different brain functions are localized to specific brain regions or whether they involve most of the brain most of the time (Ptito et al. 2008). The latter possibility raises the subsequent question of how brain functions acquire their characteristic manifestations if most of the brain is involved most of the time. The former possibility raises the subsequent question of the measurability of local changes if total activity remains

constant when work is simply switched from one activity to another in the pursuit of specific brain functions, which is the same as asking how intertwined local networks could be and still be functionally separate. Assuming that these questions to methodology will receive adequate answers, it is still not clear which questions can be posed of the organization of the brain in the cases of the alternatives proposed above. The neuroscience of the ”hard” problem remains limited to the presentation of empirical findings and subsequent speculations on the meaning of these findings.

Emotion, Cognition, and Memory

Emotions and cognition competitively have activity in specific brain networks (see page 13). We specifically addressed how this competition varies among humans and how it relates to experience, differences of personality, and advancing age (Geday & Gjedde 2008, Pallesen et al. 2008). The findings indicate that post-traumatic stress disorders can initiate a form of maladaptive plasticity in which the memories of past traumas intrude upon the considerations of the present to such an extent that it can be called pathological (Hall et al. 2008). The impact of emotions in general tend to vary in inverse proportion to the effect of drugs that increase monoaminergic tone in the ventromedial prefrontal cortex, and this is also the place where patients with Alzheimer's disease have the greatest decline of activity when they are faced with a cognitive task which normally is not sufficient to inhibit the activity associated with the memories of the past and the future. The findings also suggest that the emotionality of an experience is under the control of distributions of metabotropically excitatory and inhibitory receptors of the monoamines (Geday & Gjedde 2009), which are likely to respond to trophic factors that are sensitive to psychotherapy, as predicted by the psychoanalysts of old.

References

Geday J, Gjedde A (2009) *Monoaminergic modulation of emotional impact in the inferomedial pre-frontal cortex.* Synapse 63: 160-166 (released electronically 2008).

For 2008 references, see page 66.

SELECTED RESEARCH PROJECTS:

Per Borghammer, Joel Astrup Aanerud, Albert Gjedde: Studies of brain flow and metabolism in humans.

Anders Nykjær, Dirk Bender: AD-ANA mice.

Jakob Linnet, Arne Møller, Albert Gjedde: Clinical, psychological and neurobiological aspects of gender differences in pathological gambling.

Susanne Lerche, Ole Schmitz, Albert Gjedde: Effect of GLP-1 on glucose uptake in CNS and heart in healthy persons evaluated with PET.

Aage Olsen, Joel astrup Aanerud, Dirk Bender: Beta-amyloid imaging in older Goettingen minipigs.

Per Borghammer, Albert Gjedde: Cerebral perfusion and metabolisme in non-treated Parkinsons Disease.

Albert Gjedde, Søren Laurberg, Arne Møller: Sacral nerve stimulation.

Lynn Ho et al. : Separating micro- and macro-vascular contributions to cerebral blood flow changes using functional arterial spin labeling (PhD project).

Søren Laurberg et al.: Cerebral activation response to sacral nerve stimulation in healthy animals and patients with fecal incontinence.

Ericka Peterson et al. : Clinical, psychological and neurobiological aspects of gender differences in ludomania.

Ericka Peterson, Christopher Bailey, Per Borghammer, Arne Møller, Kim Vang Hansen, Jakob Linnet, Albert Gjedde: Sex-specific changes of CBF and $CMRO_2$ when men and woman gamble.

Bjørn Pedersen et al.: Cochlea implantation and neuroplasticity.

Per Borghammer et al.: Cerebral perfusion and metabolism in untreated Parkinson's disease.

Joel Aanerud et al.: Cerebral energy metabolism, blood flow, 5-HT1A receptor binding and accumulation of beta-amyloid plaques in Alzheimer's disease in young and old healthy volunteers.

Aage Olsen & Anders Rodell et al.: Beta-amyloid imaging in older Goettingen minipigs and cloned Danish Landrace pigs.

NEUROENERGETICS

Animal models in High-field functional MRI

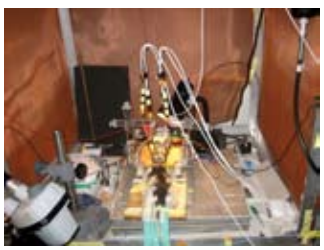
by Christopher J. Bailey

Blood oxygenation-level dependent (BOLD) functional MRI is arguably the most popular functional mapping tool for human studies. Factors contributing to this are its non-invasive nature of application, relatively good spatiotemporal resolution, coverage of large parts of the brain, and the fact that experiments can be conducted on most clinical MRI scanners by slight adjustments. However, future utility of fMRI for diagnostic and treatment purposes in humans is largely dependent on a better neurophysiological interpretation of the BOLD signal change because the conventional fMRI map reflects changes in blood oxygenation, not actual neuronal activity.

The initial demonstration of the BOLD effect was performed in rats and mice, but very rapidly the method was routinely used to study the human brain. Only in recent years has the field of animal fMRI again gained foothold in scientific practice, and is contributing to a better understanding of the BOLD signal. This has been helped along by the more widespread availability of small-bore high-field horizontal MR spectrometers, suitable for the imaging of small animals such as rodents *in vivo*. On the other hand, to relate the BOLD signal to neuronal activity, it is necessary to actually measure that activity, a task suited only for animal experimentation where invasive techniques can be used.

To understand the BOLD signal is also to understand more generally the energetics of the brain: the link between substrate delivery via the blood circulation, to the production of energy-rich phosphate bonds, and finally the release of the stored energy at sites of increased brain work. The Magnetic Resonance Research Center (MRRC) at Yale University School of Medicine, USA, is a pioneering laboratory in the field of neuroenergetics. The current director of the quantitative MR group, Dr. Fahmeed Hyder, has a particular interest in the dissemination of the BOLD signal change into its constituents (blood flow and volume, as well as oxygen consumption). As part of an ongoing collaboration between MRRC and CFIN researchers, I spent 14 months at Yale learning to apply *in vivo* imaging techniques to rats at 11.7T.

Figure 1
Experimental setups. (Left) For MR imaging in the 11.7T Bruker spectrometer, the rat is placed on a cradle that fits into the coil fixture and is inserted into the magnet bore. (Right) For recording of electrophysiological signals in the cortex, the rat is fixed onto a stereotaxic frame inside a Faraday cage.



To probe properties of the BOLD effect, one must introduce focal perturbations in the oxygenation-state, most readily achieved by stimulation of the various senses and observation of the resultant signals in the relevant brain region(s) with high temporal resolution (we used TR=1 sec). A popular protocol in the rat model is direct electrical stimulation of the forepaw, leading to signal transduction to, and BOLD response in, the contralateral primary somatosensory region. Though a strong response, the stimulation method is somewhat artificial, i.e. one not encountered by the animal in its normal life. Dr. Hyder's group has previously developed methods for the controlled deflection of the rat's whiskers, as well as the delivery of odorous gases for olfactory stimulation. My task was to complete a prototype for the delivery of visual stimuli during MR imaging, as well as during acute intracortical electrical measurements of neural activity, and to conduct a series of experiments to demonstrate the feasibility of the approach. It should be noted that we do not measure the BOLD and electrical signals simultaneously in the same rat. Instead, separate groups of rats are used, and the stimulators are designed in a way that allows near-identical conditions both inside the scanner and on the electrophysiology bench.

Figure 2 is a collage of data from two rats undergoing identical 30 second stimulation periods of green light flashes (50 msec flash duration) delivered at a rate of 1 Hz. The high spatial resolution of the fMRI data, one benefit of the very strong static magnetic field, is evident in (A). Voxels exhibiting significant ($p<.01$) stimulus-induced signal changes are overlaid on two consecutive 1 mm-thick sections through the posterior part of the rat brain. Panel (B) illustrates the BOLD response profiles in the two primary visual processing structures of the rodent brain, the visual cortex (VC) and superior colliculus (SC). The fundamentally different neuronal networks of the VC and SC manifest as distinct BOLD time courses. The electrophysiology experiment gives a complementary view of the brain's response to stimulation; for VC this is illustrated in panel (C). The broadband electrical recording is first filtered into two non-overlapping frequency bands: 1-200 Hz and 500-3000 Hz representing the local field potentials (LFP) and multi-unit activities (MUA), respectively. The LFP signal arises from the synchronous post-synaptic potentials in the vicinity (several hundred micrometers) of

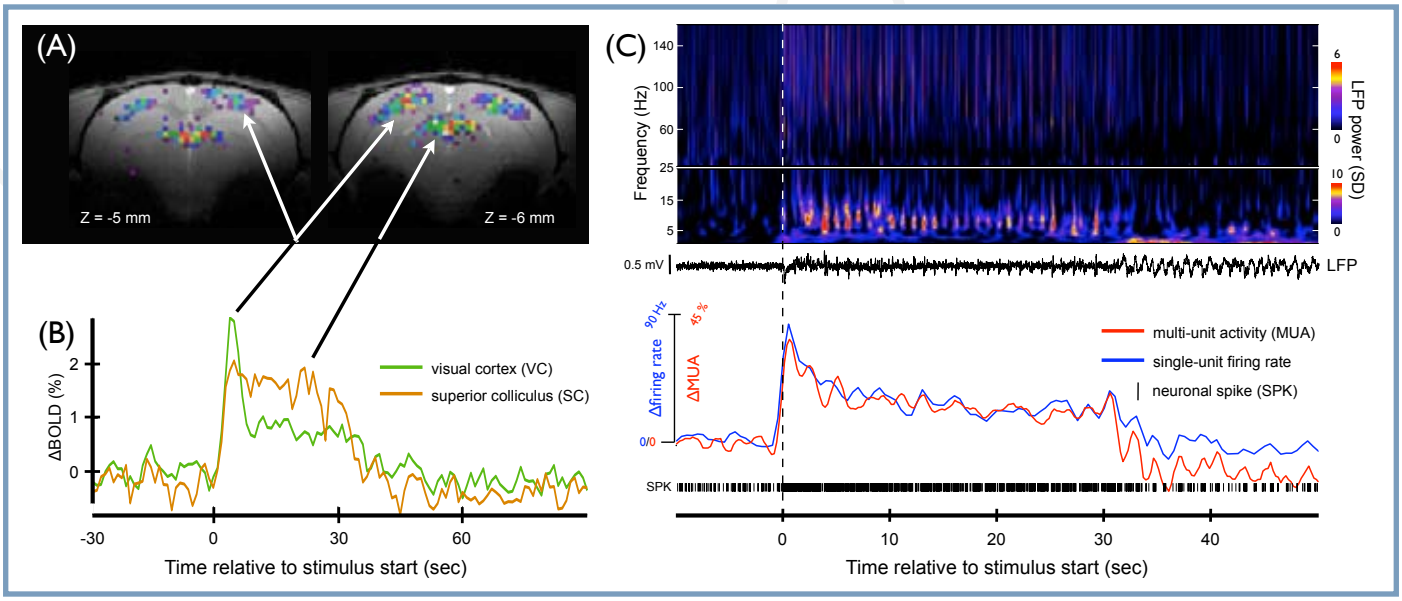


Figure 2
Comparison of results obtained with fMRI (A,B), and electrophysiological recordings (C). See text for details.

the recording electrode. The power in the MUA band, on the other hand, can be used a measure of the output, i.e. spiking, of a population of cells close (within tens to a few hundred micrometers) to the electrode. Panel (C) (bottom) illustrates this by comparing the firing rate of a single neuron (blue; black lines) to the simultaneously acquired MUA trace (red). Note that the electrical response profile in (C) bares a close resemblance to the VC BOLD trace in (B). The LFP band can be further decomposed by spectrogram analysis (panel C, top) to reveal e.g. the presence of gamma-range (60-150 Hz) responses to stimulation.

Clearly, our goal is not so much to discover new facts of the rodent visual system *per se*, but rather to use the rat's fully functional visual capacities to learn more about the BOLD response. To this end, the stimulation setup we developed was based on simple flash-stimuli, the duration, intensity and frequency of which were computer controlled. In addition, by relying on inexpensive high-luminance LEDs, we are also able to select from a variety of light wavelengths, i.e. colours. The LEDs with associated circuitry can be placed far remote from both the magnetically hostile MR environment, as well as the electrically ultra-sensitive physiology bench. The LED light was led to the rat's eyes using long fibre optic cables and a sequence of collimator and dispersion lenses; see Figure 3.

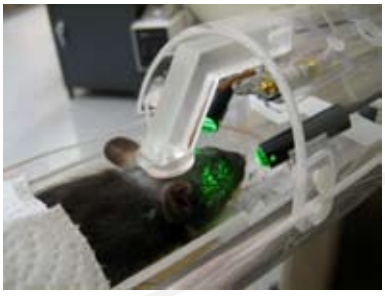


Figure 3
Visual stimulus delivery setup for high-field fMRI. The rat is placed under the transceiver coil (1.4 cm diameter), and the fibre optic cables fastened to holders (black, with custom-built lenses) that can be positioned optimally relative to the eyes.

So what can the rat visual, or other sensory system tell about the numerous contributors to the BOLD response? The key to understanding the question lies in realizing the vast amount of literature on rat brain anatomy, morphology, and physiology that make possible viable extrapolation of results from experiments such as the ones described here. This background information allows us to relate the findings in e.g. the visual system to the underlying neural and vascular architecture in a potentially very detailed manner. Neurochemical perturbation experiments, as well as genetic manipulations are examples of strategies not amenable to human research alone. The fundamentally different cortical and subcortical structures that process whisker deflections and visual information, and the associated differences in the elicited response, can help to pin down integral properties of the BOLD signal. Combinations of stimuli given simultaneously offer the opportunity to begin fMRI and neurophysiological studies of sensory integration. Much work still lies ahead before a comprehensive understanding of the BOLD response, and the neurovascular and neuroenergetic processes it reflects, can be claimed. Animal models in high-field functional MRI will play a key role in advancing this knowledge.

My Fifteen Years in Århus

by Albert Gjedde

General Perspectives

The period from 1993 to 2008 saw the creation in Aarhus of the PET Center, the Center of Functionally Integrative Neuroscience, and the Danish Neuroscience Center, in that order. For my part, the experience began with a sabbatical from McGill University during the year 1993-94, and it then followed a simple plan, the creation of a laboratory of applied neurobiology, dedicated to the study of functionally integrative neuroscience, with the ultimate goal of understanding the mechanisms in the brain that subserve the generation of consciousness. The act that is most apparent when you wake up from a deep sleep, surgical anesthesia or coma. What roles do brain energy metabolism and monoaminergic neuromodulation play in this transition, both when consciousness is lost, and when it returns?

The seeds of this program were sown in Montreal, of course, at the Montreal Neurological Institute where much of the neophrenological revolution took place, but I was never completely satisfied with the progress for reasons that were not intrinsic to the MNI. When the opportunity arose to start a program in Aarhus, I literally jumped at the prospect, particularly as the freedom to move ahead with speed and dedication seemed unlimited in this underappreciated university city. Aarhus in 1993 had a budding program of magnetic resonance imaging, briefly directed by John Hazelgrove who since returned to Philadelphia.

The new PET Center in Aarhus, which opened on October 20, 1993, was organized as a hospital department. The hospital very generously devoted somewhere between 75% and 90% of the basic budget to research.

Strategies and Realizations
First Five-Year Period: 1994-1998

The first five years from 1993 to 1998 were productive and progressive years of work in the forms of brain and liver imaging in the PET Center itself and useful collaboration with the cardiology department on heart imaging made by visiting cardiologists. The brain research of the first five years continued and completed work on themes that had been initiated in Montreal and Copenhagen, including the imaging of DOPA conversion to dopamine in normal volunteers and patients with Parkinson's disease, previously begun with Paul Cumming and Hiroto Kuwabara and others in Montreal, and the imaging of dopamine binding in striatum of healthy human volunteers and patients with psychosis, begun with Dean F. Wong at the Johns Hopkins University in Baltimore. The activity in the PET Center also saw the beginning of the valuable work of Peter Johannsen on brain function in elderly healthy volunteers and patients with Alzheimer's disease, and the work of Leif Østergaard on the measurement of relative blood flow rates in human brain by means of bolus tracking of contrast material imaged with magnetic resonance.

On the five-year anniversary, however, it was plain for all to see that the issues of the appointment of non-medical PET researchers (as well as medical staff who wanted to do research after the completion of a PhD program) in tenure track positions as well as the space available to house these researchers and their graduate students required the timely introduction of new initiatives in the direction of grants to fund researchers and grants to build the space to house them.

The first of these initiatives was the plan to apply for major funding for a center of excellence from The Danish National Research Foundation, the subsequently named Center of Functionally Integrative Neuroscience (CFIN). The execution of this plan occupied most of the second five-year period (1998-2003). The second initiative was the plan to fund the building of a new research wing adjacent to the brain-related clinical departments of the hospital, the more recently named Danish Neuroscience Center, the establishment of which occupied most of the third five-year period (2003-2008). The plan for the new wing was announced somewhat prematurely in October 1998 at the five-year anniversary event of the PET Center.

Newspaper clipping from 1998 with Albert Gjedde and Aarhus County Mayor Johannes Flensted-Jensen discussing a future Danish Neuroscience Center.
Photo: Axel Schütt

Second Five-Year Period: 1999-2003

The main focus of the second five-year period was the completion of the application for a center-of-excellence grant to The Danish National Research Foundation, and the subsequent establishment of the center when the grant was received. The imaging of DOPA metabolism and dopamine binding in health and disorders such as Parkinson's Disease and psychosis by Paul Cumming, Dean Wong and myself, and my interest in oxidative brain energy metabolism as the mechanism underlying consciousness, together with the emerging MR methods of diffusion-tensor imaging studied by Peter Vestergaard-Poulsen, and the bolus tracking of hemodynamic variables that Leif Østergaard had described during his year of PhD program study at the Massachusetts General Hospital, immediately suggested a program of four related topics centered on the theme of neuroplasticity. The PET Center still had only the tomograph donated by the Karen Elise Jensen Foundation but the program was further strengthened by the acquisition of a 3-Tesla magnet donated by the John and Birthe Meyer Foundation. Peter Vestergaard-Poulsen formulated the theme in the phrase, "neurotransmission is the architect of connectivity, neuroenergetics is the engine of neuroplasticity". Neuroenergetics is the application of the principles of bioenergetics to the brain. This phrase neatly summarized the four interrelated topics, labeled "columns" for the purposes of the grant request. The columns included Neuroenergetics devoted to measures of brain energy metabolism and flow-metabolism coupling, Neurotransmission devoted to the study of variations of dopamine synthesis, metabolism and binding in the health and diseases such as schizophrenia and Parkinson's disease, Neuroconnectivity focused on the documentation of old and new connectivity that resulted from the neuroplasticity engineered by neurotransmission and fueled by the oxidative metabolism of neuroenergetics, and Hemodynamics devoted to the study of the use of magnetic resonance to map the changing activity of brain tissue as neuroplasticity proceeded. Above these more earthly topics floated the more ghostly subject of cognition which presumably underscored the importance of the four other columns. Happily, we recruited anthropologist and neuroscientist Andreas Roepstorff to head this secret fifth column.

The center-of-excellence grant was awarded to the Center of Functionally Integrative Neuroscience (CFIN) in 2001, and it secured temporary salaries for a number of key researchers, including four of the five column coordinators.

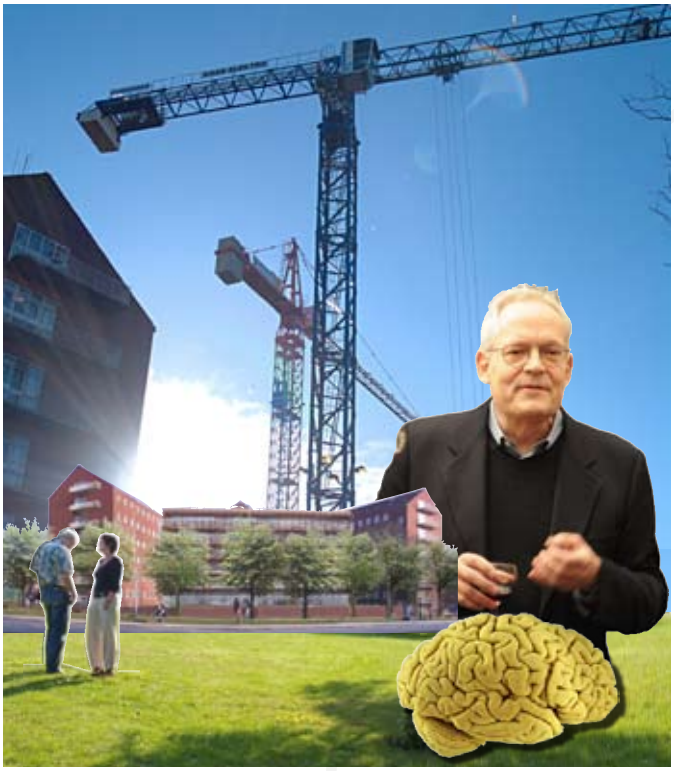
We found a temporary solution to the problem of the space available to PET and CFIN researchers in a defunct supermarket adjacent to the hospital. The building was known as the Box because it once housed a box factory. Researchers continued to study DOPA metabolism in Parkinson's disease, both the experimental variety in pigs and the idiopathic form in people, the susceptibility of brain energy metabolism to stroke and the consequences for tissue viability, the regulation of oxidative metabolism in relation to blood flow, the visual system in blindness and the auditory system in deafness, blood flow changes in depression, and the decline of cognitive functions in aging and Alzheimer's disease.

The results of much of this work were presented in preliminary form in the 10-year anniversary volume published by PET Center contributors under the common title of "In Search of Inner Life." The volume listed the 44 technical and scientific co-workers to which the staff had grown from the modest beginning of 8, as well as the satisfactory number of 18 PhD and other doctoral theses completed in the previous ten years, and the more than 200 research reports published in scientific journals in these periods. The volume also included a discussion of the grave challenges that the PET Center would face in the future when renewals or alternatives to the center-of-excellence grant and additional space for the researchers would have to be found.

Third Five-Year Period: 2004-2008

As I passed the Directorship to Leif Østergaard in 2004, the plans for the erection of the Danish Neuroscience Center drew closer to completion but the end was not yet in sight.

At the end of 2007, the PET Center's annual report listed 75 technical and scientific co-workers of all professions, including affiliated scientists. The brain research continued along the lines established in the columns of CFIN, with new insights obtained into DOPA metabolism, dopaminergic neurotransmission, and flow-metabolism coupling changes in sensation-seeking, addiction, and Parkinson's disease, and into the role of serotonergic neurotransmission in ventromedial prefrontal cortex and the limbic brain in emotions and emotional disorders. The work also contributed new understanding to the role of the hippocampus in stress, depression, and dementia, and new findings of the neuroplasticity of the primary senses of vision and hearing, with potential for novel treatments of the loss of these senses.



Albert Gjedde and Danish Neuroscience Center
Collage: Henriette Blæsild Vuust

The research accomplishments of the past fifteen years represented an impressive body of work, on which tentative conclusions can now be reached.

Major Themes of Research

Good science is known by the answers it gives rather than the questions it raises, but without questions there can be no science at all. Three interrelated sets of questions or themes characterize the work of the last 15 years, including neurotransmission, its consequences for brain energy metabolism and circulation, and the functionally integrated activity of the brain as whole in specific areas of brain function. The general question is how these three aspects of brain work interact. From the results of the last 15 years, the researchers of this effort may now conclude that the combined effects of neurotransmission and energy turnover generate the synergy required for brain functional activity to arise from neuronal networks, while the absence of one or more of these factors potentially explain all the signs of pathology that are evident in brain disorders.

Neurotransmission and Neuromodulation

Neurotransmission is the series of steps that lead from precursor transfer to brain tissue, transmitter synthesis and vesicular incorporation, transmitter release and binding, and ultimately transmitter reuptake and breakdown. As neuromodulators, the monoaminergic transmitters generally interact with metabotropic receptors in cell membrane and hence serve to regulate excitability rather than initiate depolarization. The receptors in turn tend to exist as two major subtypes that serve respectively to increase and decrease excitability when they are occupied by the monoamines to which they have affinity in the relevant concentration range. The release of the monoaminergic neuromodulators also tends to happen both as conventional synaptic release as well as by release en passant from varicosities and diffusion over extended distances by volume transmission. The question is how the different actions of ionotropic and metabotropic receptors subserve brain function. The general answer arising from the work is the realization that the disintegration of mechanisms of monoaminergic neuromodulation likewise leads to the more subtle signs and symptoms of chronic diseases in which it is the regulation of excitability that appears to fail over longer periods of time rather than the acute and complete disruption of interneuronal communication. An important aspect of the failure of this regulation is the complex interactions between the different monoamines which complicates the interpretation of findings specific to one monoamine.

Dopamine Synthesis and Parkinson's Disease

Neuromodulation is the end result of the combined action of a series of complicated biochemical steps. The question is how the limited number of symptoms of disordered dopaminergic neurotransmission arise from the huge number of potentially defective links in this chain. The findings from the last 15 years of studies of dopaminergic mechanisms in Parkinson's Disease demonstrate that the major deficiency is a loss of stored dopamine, resulting both from impaired synthesis of dopamine from DOPA and from the accelerated breakdown of the transmitter, either from failure of vesicular incorporation or from elevated monoamine oxidase activity. The work of Paul Cumming, Erik Danielsen, and Yoshitaka Kumakura played a seminal role in the efforts that led to this understanding. The role of the aromatic amino acid or DOPA decarboxylase enzyme in the homeostasis of dopamine was identified in the

first half of the period, and the role of the accelerated loss of dopamine became evident in the second half.

Dopamine Binding and Release, Addiction and Psychosis

While other neuromodulators also play important but uncertain roles, it is evident that both addiction and psychosis are disorders of dopamine binding and release which disrupt the regulation of extracellular dopamine concentrations. Pharmacological escriptions of the kinetics of binding and release indicated that it would be possible to assess dopamine release quantitatively in living human beings by means of the methods of positron emission tomography and to relate signs and symptoms of patients to variations of dopamine release. The work was essential to the correct understanding of the concept of binding potential which is the most commonly reported measure in these studies. The question is how dopamine release correlates with postsynaptic effects of the neuromodulation at different distances from the site of release. These studies tentatively gave the answer that both addiction and psychosis is associated with abnormally augmented dopamine release, the former from a baseline of perhaps too little dopamine that may be the fundamental deficiency in attention deficit and hyperactivity disorder, and the latter from a baseline of too much dopamine, probably associated with increased capacity for dopamine synthesis. In addition to Paul Cumming, the major collaborators in this effort were Pedro Rosa-Neto and Dean Wong at the Johns Hopkins University in Baltimore.

Noradrenaline, Histamine, Serotonin and Depression

While dopamine is mainly a limbic neuromodulator, serotonin is active in the neocortex where many findings indicate that a serotonin deficiency may underlie the signs and symptoms of at least some forms of major depression. Serotonin interacts with a multitude of receptors with differentiated locations but the majority increase excitability while excitability declines only for one or two. The same appears to be the case for other monoaminergic receptors. The question is how the coexistence of abundant different monoaminergic receptor subtypes extract a coherent message from a single neuromodulator. The work revealed the answer that this characteristic subdivision allows for a distribution of excitabilities among individuals with subtle differences in local cortical numbers of the two major subtypes of serotonergic and probably also noradrenergic receptors. As these subtypes are known in part to be under genetic or epigenetic control, the effects both of different baseline concentrations and of different intensities of release turn out to vary greatly among people, both healthy and depressed. Mette Møller, Donald Smith and Poul Videbæk were the key contributors to this work.

Brain Energy Metabolism

Metabotropic monoaminergic receptors affect brain energy metabolism by regulating calcium ion sensitive metabolic pathways in the cells of the nervous systems and changing both cytosolic glycolysis and mitochondrial oxidative metabolism. Changes of glycolysis and oxygen consumption hence reflect the variations of monoaminergic neuromodulation although the exact correlations are still very uncertain. The question is how the changes of metabolism facilitate the integration of neuronal network activity that ultimately leads to brain function and consciousness. The tentative answer is that oxidative metabolism provides a steady background of energy turnover in the shape of oxidative metabolism while glycolysis provides the temporal buffering that reflects the fluctuations of local maxima and minima. An additional question is how the metabotropic monoamine receptors influence the mechanisms serving blood flow and energy metabolism regulation: Are blood flow, glucose delivery and consumption, and oxygen delivery and consumption affected equally, or can the relative changes of these variables be used to predict the different types of monoaminergic neuromodulation. The regulation is not limited to the monoamines, as glutamate also has metabotropic receptors. The role of these receptors in relation to the monoaminergic receptors is uncertain.

Leif Østergaard and Albert Gjedde during the Brain Storm Symposium, January 2006.
Photo: Anders Gade

Oxygen Delivery, CMRO2, Glucose Delivery, CMRglc, and Lumped Constant

Glucose is the preeminent nutrient of brain tissue and glucose consumption has been a standard measure of brain activity *in vivo* since 1979. Oxygen delivery on the other hand supports the steady-state rate of brain energy turnover. Yet it remains entirely unclear how glucose and oxygen transfer and metabolism interact and are regulated in relation to brain activity, in part because brain activity itself does not have a clear definition in relation to energy turnover. The questions are how oxygen and glucose delivery and consumption vary temporally and spatially among the different compartments in brain tissue, and how accurately glucose consumption can be determined with 2-deoxyglucose (2DG) or fluoro-deoxyglucose (FDG), the conventional tracers of glucose metabolism *in vivo* in animals and humans. The latter question addresses the accuracy of the lumped constant, a variable that accounts for the differences among glucose and tracer metabolism. The findings indicate that as much as 80% of the glucose may be phosphorylated in cells other than neurons, as well as in parts of neurons that are less oxidative than the tissue as a whole. As much as 80% of the oxygen consumption in turn appears to take place in neurons. These findings introduce the concept of spatial inhomogeneities of glycolysis, oxidative metabolism, and blood flow, and they raise the issue of which of these variables is the most accurate marker of brain activity and activation. The main contributors to these findings include Richard Berger, Hans Erik Bøtker, and Manouchehr Vafaee.

CBF, Flow-Metabolism Coupling, Ischemia and Stroke

For the last 30 years, the most common marker of brain activity and brain activation, by a wide margin, is the presumed measure of regional blood flow rates in brain tissue, as also determined with BOLD imaging or bolus tracking of nuclear magnetic resonance. The question is how faithful a measure of brain work the blood flow rate is in reality, and how important the blood flow rate is to the preservation or restoration of brain function after interruption of the flow. The issue is also with the presumption that measure of choice in fact reflects blood flow rates. Most applications give relative results of normalized data, either relative to a baseline or relative to a whole-brain average, or both. The findings show that normalized values in many cases greatly misrepresent the true state of the blood flow variable, When real values of blood flow are determined,

Albert Gjedde and PET Center Aarhus
Photos: Århus Sygehus

the findings of non-steady-states suggest that regional flow rates in the brain are coupled to glucose consumption but not to oxygen consumption, as also shown by the BOLD images of mismatch between oxidative metabolism and blood flow. The mismatch is also reflected in significant changes of the oxygen-glucose index, which appears to decline at the onset of increased activity and to rise immediately after the resumption of normal activity. Leif Østergaard, Masaharu Sakoh and Jens Waaben made significant contributions to the understanding of these non-steady-state changes during activation and during and after brain oligemia or stroke.

Vision, Blindness, and Blindsight

Most sensations apparently represent a form of memory, first because they reflect previously experienced sensations, and second because the reentry of past sensations presumably depend on active processes of plasticity in the central nervous system. As a primary sense, vision remains a puzzle, particularly with respect to the presence of blindsight in individuals who are blind; Blindsight is an important piece of evidence that directly favors a distinction between sensation and perception in relation to consciousness. The phenomenon suggests that sensation is conscious but that perception is not. Hence humans appear to have the ability to present objects of past sensation into consciousness in specific contexts that they select or that arise from the consideration of the past or the future. Normal healthy humans cannot distinguish the two aspects but brain imaging may under some circumstances reveal a dichotomy of activation. This possibility raises the question of the proper marker of the plasticity of neuronal networks that subserves the reentry of past objects of sensation into consciousness. The main collaborator in this effort is Maurice Ptito.

Language, Hearing and Deafness

Hearing is another primary sense that is subject to plasticity and a measure of ”deaf” hearing in which a minimum of cues suffice to induce perception. As with other senses and for major elements of sensation, also sensations of sound are to a great extent self-generated, so much so that the sensations may reach pathological proportions, such as in tinnitus. The questions are at which places in the primary and secondary hearing pathways tinnitus is first generated and then heard. The form of plasticity that gives rise to pathological sensation can rightly be termed maladaptive, and the findings indicate that generation of the tinnitus experience originates in the frontal lobe while the sensation itself has its locus in the temporal lobe. In people who are born deaf or become deaf before the acquisition of language, the question is whether the plasticity necessary to sense sound and perceive language remain active until such a time that implantation of a cochlear listening computer in the inner ear can be attempted. The findings indicate that comprehension of language depends on the combination of precursors of sensation established in the left frontal lobe and associated perception associated with activity in the right temporal lobe. The co-workers most active in these demonstrations are Frank Mirz and Malene Vejby Mortensen.

Pain and Anxiety

Pain is primary sense with strong relations to anxiety and the perception of the unpleasant quality of the sensation of pain, which may not itself be conscious. The question is whether the two aspects of pain, the sensation of the pain itself and the perception of the unpleasantness can be distinguished by methods of brain imaging, as in the cases of vision and hearing. The findings suggest the same simple division of labor between the frontal lobes as origins of the reentered sensation in the case of remembered pain, and the temporoparietal lobes as the origin of the perception that accompanies the sensation. Ron Kupers is the main contributor to this effort.

Emotion, Cognition, Memory, Dementia and Alzheimer’s Disease

Emotions and cognition competitively recruit activity in medial prefrontal lobe, in association with the anterior and posterior cingulate gyri, and the limbic and hippocampal lobes that together form circles of connections around the top of the legs of the hemispheres. The existence of this network was first suggested by studies of the perception of self by Hans C. Lou and later identified in studies of oxygen consumption as the core of the cortex where introversion, the considerations of the past and the future, and the memories of associated emotions arise, in competition with the cognitive contingencies imposed by acute sensations and needs for comprehension of their significance. The question is whether this competition varies among humans and how it relates to experience, differences of personality, and advancing age. The findings indicate that post-traumatic stress disorders can initiate a form of maladaptive plasticity in which the memories of past traumas intrude upon the considerations of the present to such an extent that it can be called pathological. The impact of emotions in general tend to vary in inverse proportion to the effect of drugs that increase monoaminergic tone in the ventromedial prefrontal cortex, and this is also the place where patients with Alzheimer’s disease have the greatest decline of activity when they are faced with a cognitive task which normally is not sufficient to inhibit the activity associated with the memories of the past and the future. The findings also suggest that the emotionality of an experience is under the control of distributions of metabotropically excitatory and inhibitory receptors of the monoamines, which a likely to respond to trophic factors of plasticity, which likely are sensitive to experiences of psychotherapy, as predicted by the psychoanalysts of old. The main contributors to these insights include Jacob Geday, Peter Johannsen, and Karen Johanne Pallesen.

For full publication list see: www.cfin.au.dk/albert-fifteenyears

Albert Gjedde, Brain Storm Symposium, January 2006.
Photo: Anders Gade

NEUROTRANSMISSION

by Arne Møller

The opening of the DNC building and a much needed expansion of the PET Center is awaited with excitement by the Neurotransmission group. The improved facilities for radiochemistry and greater PET scanning capacity will greatly improve opportunities to pursue new research goals. The group looks forward to welcoming Danish basic neuroscientists at the OAK meeting on 12 - 13 June 2009 in these new surroundings.

While carrying out important support functions, the PET Center radiochemistry and veterinarian staff played a key role in research progress in 2008. Dirk Bender, head chemist at the PET Center, and Professor Doris Doudet were the driving forces in peparing a grant to image alpha-synuclein in Parkinson's Disease in order to provide a new diagnostic marker of the disease. Mette Simonsen, a PET and microPET technician is working with Aage Kristian Olsen Alstrup, the veterinarian at the PET Center, in order to determine the effects of inhalation versus injection anesthesia on the uptake of PET tracers in the rat brain. Steen Jakobsen, a PET chemist, initiated studies involving the preclinical evaluation of a new PET tracer for the alfa-1-adrenergic receptor.

It has been an exciting and productive year for the Pathological Gambling group headed by Arne Møller and Jakob Linnet. Three new research assistants have joined the group: Stine Ramsgaard Jørgensen, Victoria Wohlert and Mette Frøslev. Stine, Victoria, and Mette have worked on the project on pathological gambling and sensation seeking, where we completed the data collection in 2008. They continue to work on new and existing projects, and they are a great addition to the group.

PhD student Ericka Peterson has worked on two projects under the Pathological Gambling study initiative. First, in a study examining skin conductance response (SCR), sensation seeking, and dopaminergic neurotransmission during gambling, she has completed data acquisition for 22 subjects. The data and statistical analysis have been finalized and the results from the study are currently being prepared for publication. In a second study, "Sex-specific changes of CBF and $CMRO_2$ when men and women gamble", she has completed data acquisition and analysis for 31 subjects including 10 male healthy controls, 10 female healthy controls, 6 male pathological gamblers and 4 female pathological gamblers. A comparison of healthy male and female controls during gambling is in progress. With other studies in this initiative, we hope these studies will expand our knowledge of the complex relations between dopaminergic neurotransmission and behaviour, while these two studies, as well as others under the same initiative, will help to contribute to a better understanding of Pathological Gambling.

Another study of co-morbidity "Dopamine and depression in pathological slot machine gamblers", which received funding in 2007, has been expanded to include research on co-morbidity between pathological gambling and Parkinson's disease. After completing a Master's degree in Psychology, Mette Buhl Callesen will perform these studies as part of her PhD project.She will be studying pathological gambling and impulse control disorders in response to anti-parkinsonian drugs, a devastating side effect of dopamine agonist therapy.

Another side effect of chronic intermittent L-DOPA therapy is the development of motor complications, especially dyskinesia which consists of disabling uncontrollable aforme movements. The occurence of L-DOPA-induced dyskinesia is believed to be caused by non-physiological fluctuations in the extracellular dopamine concentration, partly due to the conversion of L-DOPA to dopamine in serotonergic neurons and subsequent uncontrolled dopamine release. Supervised by Professor Doris Doudet, medical students Mette Høltzermann and Adjmal Nahimi will collaborate with Dr. Gregers Wegeners from the Center for Basic Psychiatric Research, Risskov, to perform a combined microPET and microdialysis study in order to elucidate the role of serotonin and its 5-HT1A receptors in the development of L-DOPA-induced dyskinesia in a rat model of severe PD receiving chronic L-DOPA treatment. This will enable the correlation of the changes in binding potential from microPET to changes in extracellular dopamine concentration obtained by microdialysis.

Two PhD programs in the field of dementia have been initiated:

PhD-student Joel Fredrik Aanerud is currently conducting a study to evaluate the fate of amyloid and serotonin-1A receptors using PET in Alzheimer's patients and healthy controls. So far one fifth of the planned subjects in this study have been scanned. The study also includes an MR-protocol and additional PET-scans to compare cerebral blood flow and oxygen consumption.

Rikke Fast, a veterinarian and PhD student, is in the beginning stages of a study in which ageing dogs with symptoms of spontaneous dementia will be PET scanned with PIB, a marker of amyloid deposits in the brain.

Finally, as a follow-up of an earlier study of the role of dopamine in personality traits, a collaborative project with Dr. Yoshi Kumakura will investigate the relationship between dopamine synthesis and receptor function with sensation seeking personality in healthy volunteers.

PhD student Mette Buhl Callesen giving a talk at the OAK Meeting 2008, Odense.
Photo: Arne Møller

SELECTED RESEARCH PROJECTS:

Rikke Fast, Aage Olsen, Arne Møller, Mette Berendt: Dementia in Geriatric Canines: A Clinical and Neuroimaging Study Comparing Man and Dog.

Joel Astrup Aanerud, Arne Møller, Hans Brændgaard, Manouchehr Vafaee, Johannes Jakobsen, Leif Østergaard, Albert Gjedde: Relationship between changes in amyloid deposits and loss of hippocampal neurons.

Adjmal Nahimi, Anne M Landau, Doris Doudet, Albert Gjedde: In-vivo and in-vitro evaluation of monoaminergic innervations in a rat model of Parkinson´s Disease.

Arne Møller, Yoshitaka Kumakura, Paul Cumming, Albert Gjedde, Jakob Linnet: Low dopamine receptor availability in brain of high sensation-seeking men.

Yoshitaka Kumakura, Doris Doudet, Jakob Linnet, Arne Møller, Albert Gjedde. Role of dopamine synthesis in the sensation seeking personality constitution.

Anne M Landau, Aage Olsen, Albert Gjedde, Doris Doudet: Effects on electroconvulsive therapy in Parkinsons Disease.

Anne M Landau, Suzan Dyve, Doris Doudet, Albert Gjedde: Effects of Nervus Vagalstimulation on the brain.

Ericka Peterson, Arne Møller, Albert Gjedde, Jakob Linnet: SCR (Skin conduction reaction) and dopamine release.

Kristine Rømer Thomsen, Mette Buhl Callesen, Arne Møller, Jakob Linnet: Severity of Gambling is associated with severity of depressive symptoms in Pathological Gambling.

Jakob Linnet, Arne Møller, Kristine Rømer Thomsen, Mette Buhl Callesen: Lower event frequency and reward frequency reduce sloth machine gambling in Pathologcal Gamblers.

Jakob Linnet, Ericka Peterson, Doris Doudet, Albert Gjedde, Arne Møller: Immediate defeat: Inverse dopamine reward response in Pathological Gamblers and Non-Gamblers.

Jakob Linnet, Line G Josefsen, Howard Shaffer, Kim Mouridsen, Arne Møller: Cognitive bias in poker.

Hans Lou et al.: Dopaminergic neurotransmission in striatum during conscious awareness of sensations.

Adjmal Nahimi, Mette Høltzerman et al.: Modulation of exogenous L-DOPA derived dopamine in unilaterally lesioned animals with Parkinsonism and L-DOPA-induced dyskinesia

Arne Møller, Ericka Peterson, Doris Doudet, Albert Gjedde, Jakob Linnet: Dopaminergic neurotransmission and brain activity in ludomaniacs engaged in computerized games.

NEUROCONNECTIVITY

by Peter Vestergaard-Poulsen

Our research focuses on how brain connectivity, integrity and plasticity are regulated by changes in neurotransmission under various conditions.

Specifically, we strive to develop MR-based methods to observe the microstructural effects of neuroplastic changes in Alzheimers disease and mental stress and to develop methods to allow direct detection of neuronal activity than is currently possible by fMRI. This is mainly pursued by magnetic 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 *in vivo* and *in vitro*, we study basic neuronal cell mechanisms underlying neuroplasticity and function (cell fraction, water exchange, dendrite density and intermolecular interaction). We use state-of-the-art whole-body magnets (3T) and increasingly more ultra high-field magnets (16.4-17.5 T) due to the extreme sensitivity and image resolution attainable at this field strength (read more about this on the following pages, Ultra high-field MR imaging).

The year 2008 has brought exciting results within these fields of investigation. Brian Hansen returned to CFIN from postdoctoral studies in professor Stephen J. Blackband's lab at McKnight Brain Institute, University of Florida (UFL), USA. Brian Hansen worked with Dr. Jeremy Flint from UFL (see "New Face at CFIN" below). Thanks to a special grant program from The Danish National Research Foundation, Jeremy Flint was employed at CFIN in May 2008 and his main task is research within MR microscopy that effectively bridges methodologies and research themes across CFIN and inSPIN – both Danish National Research Foundation centers - with groups at the UFL. The results of this collaboration, e.g. demonstrating the first-ever MR imaging of alpha motor neurons in the spine, are stunning (see description in the following pages: Ultra high-field MR imaging projects). Brian Hansen has now received an assistant professor position in Ultra high-field neuroimaging at CFIN, University of Aarhus.

Two new PhD students, Louise Rydtoft and Mads Vinding, started out in 2008. As part of her Masters thesis, Louise Rydtoft showed that individual amyloid plaques *ex vivo* and *in vivo* can be detected within a reasonable scanning time at the ultra high field strength (16.4 T). In a project made possible by the EliteForsk Prize to CFIN in 2007, she will proceed to investigate how the degeneration of neurites is related to formation of amyloid plaques using a promising model of tissue microstructure developed by Sune Nørhøj Jespersen.

As a collaborative effort between inSPIN and CFIN, Mads Vinding will focus on the crucial challenge of producing high spatial and time resolution MR images of the brain and brain stem in the presence of distorting magnetic field gradients (e.g. tissue-air interfaces) that under normal circumstances prevents us from acquiring images in the prefrontal cortex, brain stem, spine etc. with sufficient spatial resolution – see the promising preliminary results in the following pages: Ultra high-field MR imaging.

NEW FACE AT CFIN

Jeremy J. Flint, was born in Webster, Texas in September 1980. He completed high-school in 1998 after graduating from Marjory Stoneman Douglass in Parkland, Florida. It was during this period that Jeremy discovered his interest in biology and made the decision to commit his life to the study of medicine.

He graduated summa cum laude from the University of Florida in 2002 with a bachelor's degree in cell and molecular neurobiology. His undergraduate thesis focused on the role of alpha-spectrin protein as a potential biomarker for injury severity following neurotrauma. In 2004, he entered graduate school at the University of Florida's Interdisciplinary Program in Biomedical Sciences. Since then, he has pursued studies focusing on the ways in which neural tissue structure and function can be measured at the cellular level using magnetic resonance microscopy.

He is currently a PhD candidate pursuing a degree in neuroscience. Jeremy is now responsible for facilitating the collaborative research efforts between University of Florida and the two Danish National Research Foundation Centers inSPIN and CFIN.

ADVANCED MR IMAGING SYMPOSIUM & WORKSHOP

Tuesday August 12th, 2008
09.00 - 16.00
University of Aarhus, Institute of Physics
Ny Munkegade, 8000 Århus C.
Physics Auditorium (Room 1523-315)

iNANO inSPIN

Joint **CFIN / iNANO / InSpin** symposium on advanced MR imaging. Topics covered will include modeling and measuring diffusion with MR, advanced pulse sequences for measuring magnetization transfer, relaxation in heterogeneous media, dynamic susceptibility weighted perfusion measurements and more.

Participation is open for all with no registration necessary, and everyone interested in any of the topics is strongly encouraged to join the discussions. Lunch will be served to registered attendees. Please send an e-mail to: sune@pet.auh.dk before August 4th, 2008.

Program:

09.00:	COFFEE
09.25:	Welcome
09.30:	**Alexander Sukstanskii**, Washington University: *3He MRI and Lung Microstructure*
10.00:	**Klaus Scheffler**, University of Basel: *Quantitative Magnetization Transfer Imaging measured with Steady State Free Precession*
10.30:	**Valerij Kiselev**, Freiburg University: *Transverse MR Relaxation in Heterogeneous Media*
11.00:	**Atle Bjornerud**, University of Oslo: *Dynamic Susceptibility Based CBV Mapping of Brain Tumors*
11.30:	**Sune Jespersen**, University of Aarhus: *Modeling Diffusion in the Brain: Obtaining Cytoarchitectural Parameters*
12.00:	LUNCH
13.00 - 16.00	Informal discussions/workshop. Coffee will be served.
16.00	Farewell

FOR FURTHER INFORMATION ON THE SYMPOSIUM & WORKSHOP:
Contact Sune Jespersen: sune@pet.auh.dk / 8949 3334

In 2008 CFIN was the host of the successful international workshop: "Advanced MR Imaging Symposium & Workshop, University of Aarhus, Tuesday, 12 August 2008" organized and chaired by Sune Nørhøj Jespersen.

Collaborators

Jeremy Flint, US National High Field Laboratory and McKnight Brain Institute

Steve Blackband, US National High Field Laboratory and McKnight Brain Institute

Esben K.U. Larsen, Jørgen Kjems et al. The Interdisciplinary Nanoscience Center (iNANO)/Dept. Molecular Biology , AU

Michael R. Horsman Dept. Experimental Clinical Oncology, AU

L. Leigland and C. Kroenke, Oregon Health and Science University, United States
Gregers Wegener, Dept Psychiatry, AU

Jens R Nyengaard, Dept. Stereology, AU

Carsten R Bjarkam, Inst. Anatomy, AU

SELECTED RESEARCH PROJECTS:

S. N. Jespersen, C. Bjarkam, J. Nyengaard, M. Chakravarty, D. Otykier, B. Hansen, N. C. Nielsen, P. Vestergaard-Poulsen. Neurite Density from Magnetic Resonance Diffusion Measurements: Comparison with Histology.

N. Buhl and S. N. Jespersen : A Simulation Framework for Diffusion Weighted MRI in Digitalized Neurons: Extracting Cytoarchitectural Parameters Using a New Theoretical Model for Diffusion.

S. N. Jespersen, M. Ashkanian, K. Mouridsen and L. Østergaard. Modelling the Regulation of CMRO2 by Flow Heterogeneity

S. N. Jespersen, L. Leigland, and C. D. Kroenke (Oregon Health and Science University) The Diffusion Tensor Reveals Gray Matter Neurite Architecture

Mads Sloth Vinding, Thomas Vosegaard, Niels Chr. Nielsen, Sune N. Jespersen, Ryan Sangill and Peter Vestergaard-Poulsen: Optimal Control MRI of the Chronic Stress Induced Neuroplasticity of the Human Hippocampus- a feasibility study.

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

Astrid From Frøhlich, Sune N Jespersen, Leif Østergaard, Valerij G Kiselev (Freiburg University Hospital). The Effect of Impermeable Boundaries of Arbitrary Geometry on the Apparent Diffusion Coefficient

Louise M. Rydtoft, Leif Østergaard, Peter Vestergaard-Poulsen, Niels Chr. Nielsen, Sune N. Jespersen: Ultra-high-field MR Studies of an Alzheimer's disease mouse model.

J. Flint, C.H. Lee, B. Hansen, M. Fey, D. Schmidig, J.D. Bui, M.A. King, P. Vestergaard-Poulsen og S.J. Blackband: Magnetic Resonance Microscopy of the Mammalian Neuron.

J. Flint, B. Hansen, P. Vestergaard-Poulsen og S.J. Blackband: Diffusion weighted magnetic resonance imaging of neuronal activity in the hippocampal slice model.

Mads Sloth Vinding, Thomas Vosegaard, Niels Chr. Nielsen, Sune N. Jespersen, Ryan Sangill and Peter Vestergaard-Poulsen. Optimal Control MRI of the Chronic Stress Induced Neuroplasticity of the Human Hippocampus- a feasibility study.

ULTRA HIGH-FIELD MR IMAGING

Projects

by Peter Vestergaard-Poulsen, Sune Nørhøj Jespersen, Brian Hansen, Ryan Sangill, Louise Rydtoft, Mads Vinding (inSPIN, CFIN), Niels Buhl, Thomas Nielsen (iNANO) and Niels Chr. Nielsen (inSPIN).

While MRI remains a crucial tool in human neuroimaging, spatial resolution (usually about 1 mm) and sensitivity (signal-to-noise ratio in MR images) often limit our ability to test methods, hypotheses or therapies within reasonable time limits. In order to understand physiological mechanisms at a cellular level and to expand our preclinical research in neurological diseases and cancer, there is therefore a need to overcome barriers to improving sensitivity and spatial resolution. These limits are partly overcome by the extreme sensitivity of high-field magnets, allowing studies at field strengths 5-10 times more powerful than clinical whole body MR imagers.

At inSPIN (Center for Insoluble Protein Structures, directed by Professor Niels Chr. Nielsen) at the Institute of Chemistry, University of Aarhus, a powerful 16.4 Tesla Nuclear Magnetic Resonance (NMR) spectrometer has been equipped with sophisticated magnetic gradient technology to perform magnetic resonance imaging. In collaboration with CFIN, the instrument has then been optimized to allow imaging at unparalleled resolution: Single cells, tissue samples, living cell cultures, as well as small rodents (mice), can be imaged at resolutions of 5 and 25 microns, respectively. Our ongoing collaboration with a leader in this field, US National High Field Laboratory and McKnight Brain Institute (Dr. S. Blackband, the University of Florida - UFL, USA) provides CFIN researchers access to a cutting-edge experimental set-up.

These resources are currently used to investigate the biophysical properties of tissue at a cellular level using microscopic surface coils, and to validate theoretical models of water diffusion designed to uncover brain microstructure and function by MRI. These methods are then applied in studies of structural neuroplasticity during prolonged mental stress and in the assessment of neurite and plaque density in Alzheimers disease (AD). It is our aim to develop these techniques into novel, advanced tools for imaging in humans. We pursue this aim using Optimal Control Theory in collaboration with inSPIN. In another project aiming to develop sophisticated imaging and drug delivery methods by nanotechnology and molecular biology, we design MR visible nanoprobes that bind to specific cells in the body. Such nanoprobes have the potential to revolutionize disease detection and targeting of drugs. MRI at high field strength is very sensitive to the nanoparticles' susceptibility contrast properties such that small concentrations of targeted contrast agents can be detected.

A selection of our studies is further described in the following.

MR imaging of mammalian tissue cells – first ever!

Figure 1
Example of a micro surface coil developed by Bruker, Switzerland. Left: a 50 µm surface microcoil. Right: The four-turn coil sits inside a tissue well with a diameter of 5mm and a depth of 500µm.

In an attempt to investigate the MR properties of tissue at the cellular level, prototype micro surface coils (Figure 1) with a diameter of 50-500 microns have been employed in a series of experiments. With these coils we are able to produce MR images of very high resolution at a field strength of 14.1 Tesla. Over the past year Brian Hansen and Jeremy Flint (CFIN, UFL) have developed methods to image thin tissue samples using this experimental equipment and subsequent staining and light microscopy. This allows direct comparison of tissue histology and MR microscopy images. This is the first study ever to demonstrate direct MR imaging of mammalian neurons *in situ* with histological validation (see Figure 2). The study heralds the advent of direct MR microscopy as a technique for investigating biological tissues at the cellular level.

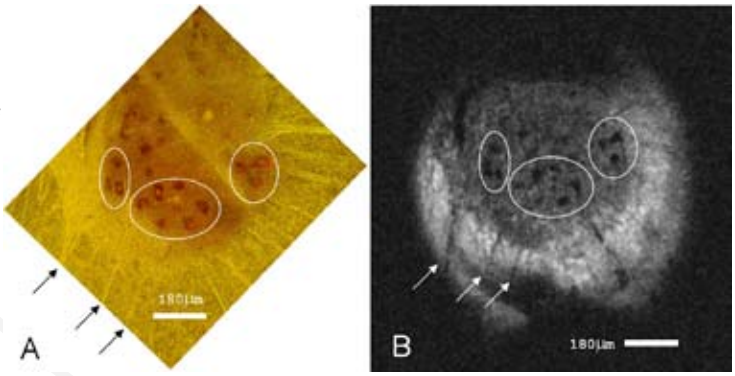


Figure 2
MR microscopy of α-motor neurons in the ventral horn of the rat spinal cord with corresponding histology. Left: Histological section showing α-motor neurons (red) (Z76409) and axonal projections at the tissue boundary of the ventral horn (arrows). Right: MR microscopy image of cell bodies and projections that correlate spatially and morphologically with those seen in our histological analysis. The image was acquired at a field strength of 14.1 T. Image resolution is 7.8 microns in-plane.

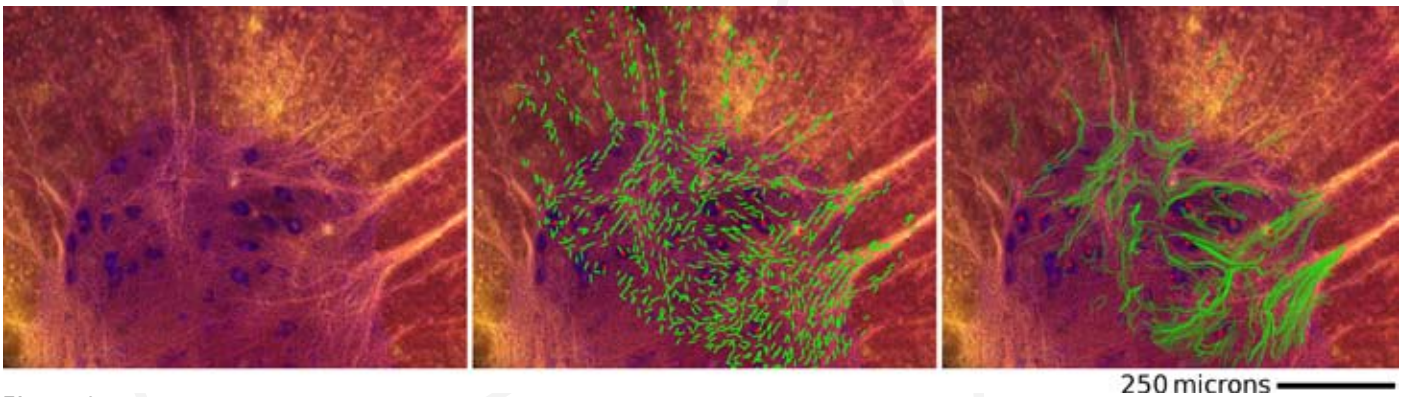


Figure 3
Comparison of tissue histology and the visualization of fiber bundles determined from the diffusion MR data. Left: Tissue histology. Middle: Overlay of diffusion orientation map (green bars) onto correlative histology. Cell bodies of α-motor neurons (purple) are marked in the orientation map with dots (red) and were used for coregistration of the data. Right: Overlay of the diffusion tensor tractography data calculated using the FACT algorithm.

One important application of diffusion weighted MR is the visualization of structural connectivity in the brain's white matter. The current method uses Diffusion Tensor Imaging (DTI) and Diffusion Tensor Tractography (DTT) to visualize fiber bundles in brain tissue. In this study, we developed a method of employing histological analysis combined with magnetic resonance microscopy (MRM) as a means of validating DTT methods (see Figure 3). Fiber tract orientation and inter-voxel connectivity can be verified by our histological method, and therefore no ambiguity exists as to the spatial positions of white mater tracts prior to the DTT analysis. In the future this method will be employed when generating DTT analysis algorithms in order to yield ever more accurate tractography.

The Diffusion Tensor Reveals Gray Matter Architecture

The anisotropy of water diffusion in the white matter of the brain is thought to mainly reflect underlying tissue anisotropy in the presence of myelinated fiber tracts. Diffusion anisotropy has also been observed in the cortex [1]. The origin of this gray matter anisotropy remains unknown.

Sune N. Jespersen has in collaboration with L. Leigland and C. Kroenke at Oregon Health and Science University, United States established and validated a model that quantitatively relates the diffusion tensor to tissue cytoarchitecture. The basic assumption underlying this result is the separation of the diffusion signal into two biophysical components, one component from a distribution of compartments with azimuthal symmetry describing diffusion in neural processes (such as dendrites and axons), and an isotropic component describing diffusion everywhere else (Jespersen et al. 2007). The theoretical findings were corroborated by ROI analysis of an MRI diffusion experiment (using a 11.7 Tesla Bruker magnet) and direct histological measurements of neurite orientations obtained from histology of a postmortem ferret brain (see figure 4). This result aids the interpretation of the diffusion tensor in terms of tissue microstructure and architecture, and will be used in CFINs studies of plasticity and normal development of the brains' gray and white matter. We are currently using the framework to study the maturation of cytoarchitecture in the cortex of developing ferrets.

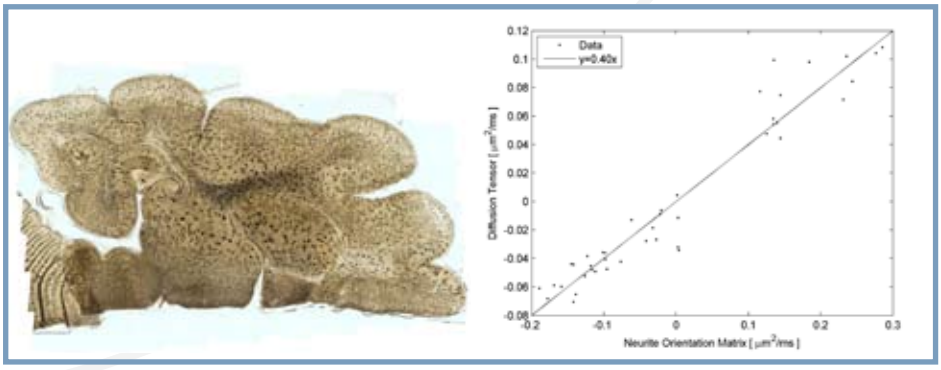


Figure 4
To the left a histological image of a ferret brain, with an indication of regions of interest in the cortex. The figure to the right demonstrates the excellent agreement between histology (along the x-axis) and MRI (along a y-axis). The actual values reflect eigenvalues of the MRI diffusion tensor and the orientation matrix of neurite distribution.

Ultra high field MR Studies of an Alzheimer's Disease Mouse Model

Alzheimer's disease (AD) is the most common cause of dementia. The degeneration of neurites in relation to the formation of amyloid plaques is a central feature in the neuropathology of AD, which is believed to closely correlate with the progressive cognitive impairment.
Preliminary MRI studies of plaque deposition in a mouse model *in vivo* and *ex vivo* have led to successful detection of individual amyloid plaques *ex vivo* within a reasonable scanning time, approximately 1.5 hours at 16.4 T. A part of the project will be focused on further *in vivo* optimization and refinement of the methods as well as advanced imaging techniques and (ii) combination with novel detection methods (e.g., 19F MRI based on 19F containing amyloid-binding organic compounds).

CFIN researchers recently developed a model (Jespersen et. al. 2007) that permits separate modeling of neurite density based on diffusion weighted MRI. An essential part of the project – led by Louise Rydtoft - will be dedicated to adapting the method for shorter imaging time and to simplify the model to allow easy, yet robust determination of the neurite density. Conditions known to alter neurite density will then be used to validate and optimize the sensitivity of the method. After this validation, the method will be applied to a mouse model of AD. Direct detection of neurite density is currently only possible through elaborate histological techniques. Further development and validation of the technique will hopefully result in an important tool in experimental study of models of neurological disorders - and ultimately in humans.

MRI of individual neuritic plaques has great potential as a non-invasive biological marker of disease progression and evaluation of potential therapeutic agents as well as providing interesting new insight to the AD mechanism when correlated with the neuritic density measurements.

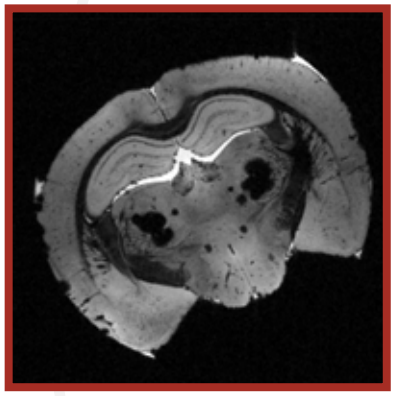


Figure 5
In vitro T2*-weighted MRI of an 13-month-old transgenic mouse showing substantial plaque deposition at 16.4 T. Image resolution: 40 µm3 (FLASH, TE/TR: 40/300 ms, θ: 31˚, NEX: 500.)

Targeted contrast agents

In a project supported by the NABIIT program, The Interdisciplinary Nanoscience Center (iNANO)/Dept. Molecular Biology has established production of ultra small superparamagnetic iron oxide (USPIO) contrast particles (Esben K.U. Larsen, Jørgen Kjems et al.) These are now being functionalized by targeting their surface to bind to specific targets, for example tumor specific proteins. When USPIO particles are taken up by immune cells, particle size and coating play an important role. The tumor accumulation of differently sized USPIO particles is currently being investigated in a murine tumor model at Dept. Experimental Clinical Oncology by Thomas Nielsen and Michael R. Horsman using the 3 T MR scanner at CFIN (Figure 6). These studies will continue at the 16.4 T magnet, which allows very high image resolution to be used in the investigation of USPIO uptake in both tumor and abdominal viscera, an important step in

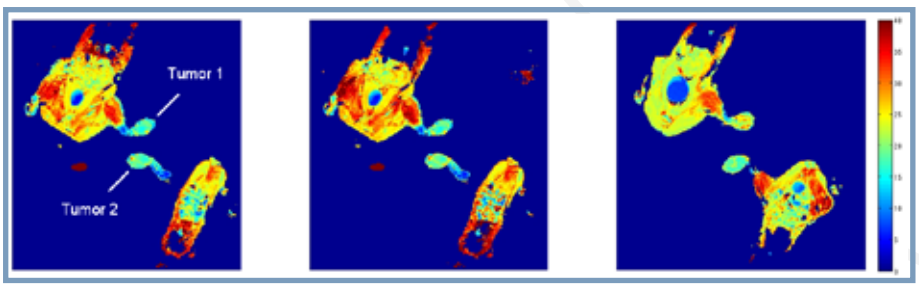


Figure 6
R2 maps from 3 T MRI of two mice, each with a 200 mm3 tumor implanted in a rear foot (indicated). Left: before injection of two different kinds of USPIO particles; middle: immediately after injection; right: 1 day after injection. In tumor 1, the USPIO particles are accumulated and cause an R2 increase after 1 day.

understandinging the pharmacokinetics of the particles. Furthermore, MRI at this field strength is very sensitive to the particles' susceptibility contrast properties, allowing very small concentrations of targeted contrast agents to be detected.

Advanced MR Imaging using Optimal Control Theory

In a collaboration between inSPIN and CFIN, Mads Sloth Vinding and coworkers investigate the use of Optimal Control Theory (OCT) to enhance experiments by addressing field homogeneity and spatial selectivity for reduction of fold-over artifacts in small Field-of-View (FOV)/high resolution MRI pulse sequences, and to develop and improve localized spectroscopy in inhomogeneous fields. In particular 2D spatial selective excitation pulses for small FOVs are currently in high demand for CFIN experiments. With these pulses we can - theoretically - obtain a higher spatial resolution than by any other MRI method. OCT does not only have the potential to enhance RF pulses with energy and time constraints, but the optimization procedure may also help compensate for degrading field inhomogeneities and poor coil sensitivities. Functional and diffusion weighted MRI which are based on the fast Echo Planar Imaging sequence have inherently low spatial resolution and they are very prone to susceptibility differences. By utilizing OCT it is expected that these difficulties are greatly reduced. We envisage a great potential for optimal control as a means to improve both resolution and sensitivity in a long range of MRI and MRS applications.

Mads Vinding, Louise Munk Rydtoft, and Peter Vestergaard-Poulsen at CFIN Retreat, September 2008.
Photo: Henriette Blæsild Vuust

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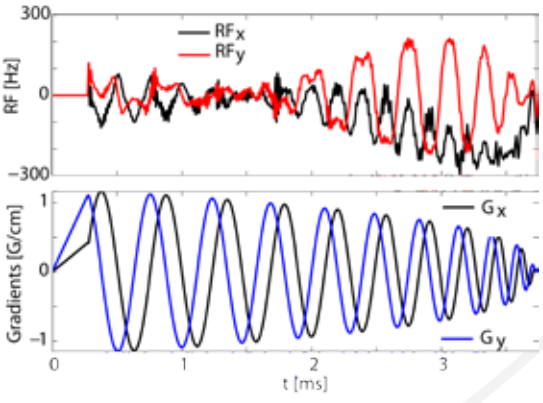

Figure 7A
(Top) An optimized RF waveform modulated in both amplitude and phase. (Bottom) The gradient waveform running simultaneously with the RF waveform.
The pulse is 3.7 ms long.

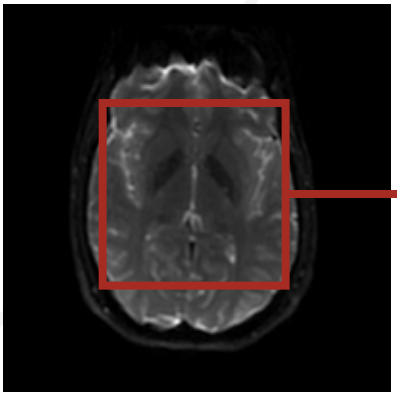

Figure 7B
A conventional single-shot diffusion weighted image
(FOV: 24 cm, matrix: 128 x 128)

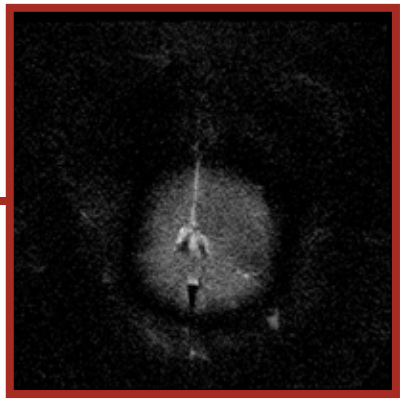

Figure 7C
The 2D spatial selection from the pulse in Figure 7A
(FOV: 12 cm, matrix: 256x 256, Ø: 4 cm)

NEUROPHYSICS

Diffusion in Biological Tissue: A Theoretical Approach

by Astrid Frøhlich Staanum

The nuclear magnetic resonance (NMR) signal derives from the magnetic properties of water molecules. The water molecules move randomly around (diffuse) in the brain tissue and by applying so-called diffusion weighted pulse sequences, the NMR signal can be sensitized to the motion of water molecules. Due to the biophysical properties of water diffusion, the diffusion weighted signal is sensitive to structures at a distance scale similar to that of cells. Diffusion weighted MRI may therefore act as a 'microscope' by which we can optain microstructural information about biological tissue in a non-invasive manner, which is extremely important in the study of neurodegenerative and ischemic disease mechanisms. Using my background as a theoretical physicist, my PhD project was designed to develop theoretical means of interpreting the relation between tissue microstructure and the measured diffusion weighted signal.

In biological tissue, the logarithm of the diffusion weighted signal, ln S, depends non-linearly on the b-value (a measure for the strength of the diffusion weighting). This dependence has often been interpreted as a manifestation of two physically distinct compartments in the tissue, leading to a biexponential description of the signal. This model fits experimental data (sizes) well, but fails to yield realistic weights of the tissue compartments. An alternative interpretation suggest that it is the restricting boundaries of the cellular structure that cause the biexponential behavior of the signal. In this context we discuss the role of the so-called cumulant expansion of the signal, which is valid *ab initio* and yields ln S in the form $\ln S = - Db+Ab^2+Cb^3+.....$ The cumulant expansion of the signal was used as the underlying basis of all four studies collected in this work.

Part I: The effects of impermeable boundaries on the diffusion weighted MR signal

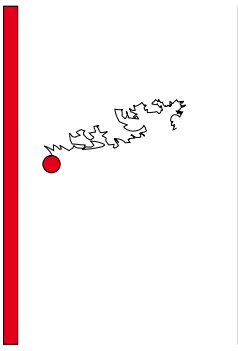

Figure 1
In study I and II we studied diffusion between two impermeable walls.

In the first study we considered diffusion between two impermeable planes (figure 1), measured with the so-called pulsed gradient spin-echo sequence with narrow pulses, for which the exact signal is known, in order to analyze the convergence of the cumulant expansion. We calculated all coefficients in the cumulant expansion. Termination of this expansion to a finite number of terms provides an excellent accuracy for small b-values, but cannot be used for large values (it diverges). We determined the range of b-values in which the cumulant expansion converges and compared the terminated cumulant expansion with the exact signal. We found that the cumulant expansion of the diffusion-weighted signal in the presence of impermeable boundaries can be used for practically relevant b-values and in this range it can be approximated by its first two terms with a good accuracy [1] (figure 2). These two terms are specified by the apparent diffusion coefficient (ADC) and the apparent diffusional kurtosis, respectively.

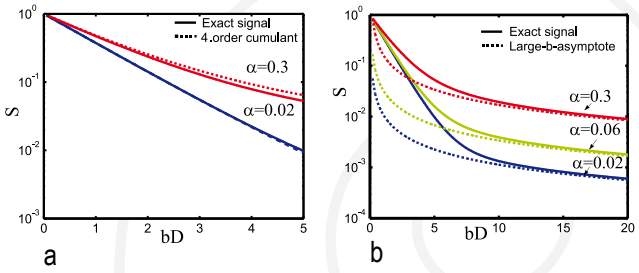

Figure 2a
The diffusion weighted signal as a function of *bD*. The cumulant expansion with two terms (the fourth order cumulant) makes a good approximation to the exact analytical signal and provides information about the geometry of the tissue. $\alpha = \sqrt{D_0 t}/a$

Figure 2b
The exact signal together with the large-b asymptote, which was also found in study I. The large-b behavior sets up at bD≈8 and here the signal is proportional to 1/(bD).

Part II: The Apparent Diffusion Coefficient in heterogeneous media

In the second part of this work we aimed to develop a better understanding of the velocity cumulants together with a technique for calculating them. This technique was used to evaluate the leading term of the cumulant expansion, which defines the ADC.
The short-time behavior of the ADC is known to provide a measure of the specific surface, S/V, of porous samples filled with an NMR-detectable fluid:

$$D_{app}(t) = D_0\left(1 - c \cdot \frac{S\sqrt{D_0 t}}{V}\right)$$

Here, D_0 is the diffusion coefficient of unrestricted diffusion and the constant, c, depends on the pulse sequence.
The potential applications of this method to living tissues such as neuronal fibers are of great interest. However, the medium surrounding neuronal fibers is not homogeneous

as in porous media and this might give rise to a temporal behaviour of the diffusion coefficient similar to the behavior caused by the impermeable surface studied. To address this problem, we expressed the velocity autocorrelation function for the molecular diffusion near a reflective wall in terms of the microscopic diffusion properties in the bulk medium, without making any simplified assumptions concerning the nature of diffusion in the medium. Given these properties, the apparent diffusion coefficient can be found for an arbitrary pulse sequence by a straightforward integration [2]. We used the result to discuss the principal application of this model to neuronal fibers, and found that in order to determine their surface-to-volume ratio, diffusion measurements should be complemented with an account for the possible difference in spatial organization of cells close to and far from the fibers (figure 3).

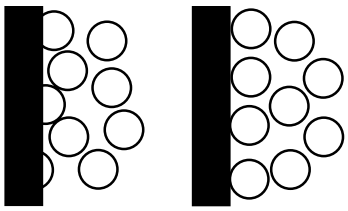

Figure 3
Two possible effects of an impermeable boundary in a medium filled with some structural units (cells or pores). In the left drawing, the boundary does not perturb the statistical properties of the medium, which could be the case in a porous medium. In the right drawing, the boundary perturbs the statistical properties. This is the case in brain tissue, since the cells correlate with the boundary possition.

Part III: The diffusion signal from arbitrarily shaped microscopic objects

In this part we extended the approach from Part II to derive an expression for the second order velocity cumulant, from which the ADC can be determined for an arbitrary three-dimensional geometry, assuming that the medium within the restricting geometry is homogeneous. We showed that for a given pulse sequence, the second order velocity cumulant can be expressed as a double surface integral of the probability to diffuse between two surface points [3]. This result enables a fast calculation of the ADC for an arbitrary time course of the diffusion-sensitizing gradient.

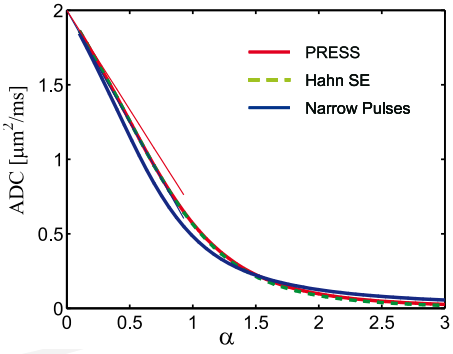

Figure 4
The ADC as a function of $\alpha = \sqrt{D_0 t}/a$ for diffusion in a cylinder, measured with three different pulse sequences. The three ADC curves are almost identical. Very similar results were found for diffusion within a sphere and for diffusion between two planes.

Explicit examples were given for diffusion within three basic geometries for different pulse sequences. The ADCs measured with the Stejskal-Tanner pulse sequence and a more realistic pulse sequence with slice selection gradient and eddy current compensation were found to yield almost identical results. This is helpful for the interpretation of experimental data across pulse sequences. The application of the ADC results were discussed with respect to determination of the microscopic structure of brain white matter.

Part IV: Diffusion kurtosis imaging

In the last study we demonstrated how the technique introduced in Part II can be used to calculate higher order velocity cumulants. More specifically, we applied it to calculate the quadratic term in b in the cumulant expansion (the apparent diffusional kurtosis). As shown in Part I, this term is important for characterizing the diffusion weighted signal. This is in agreement with results from experimental studies [4,5].

The theoretical studies of diffusion by using basic models, as presented in this work, has demonstrated the usefulness of the cumulant expansion and its potential to provide insight into relations between the signal and the microstructure of complex media. The ability to probe tissue microstructure at a length scale of micrometers, may in the future provide the means of studying cellular changes in the development of severe neurological and psychiatric disorders.

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FUNCTIONAL HEMODYNAMICS

by Leif Østergaard

The functional hemodynamics group studies the coupling of capillary flow dynamics to brain function – and in particular its role in the functional recovery after neuronal damage resulting from stroke, brain trauma, cardiac arrest etc. In a parallel effort, the neuroscientific tools developed to pursue these research questions, are being exploited in clinical studies offering cutting-edge MRI based stroke patient management at Aarhus University Hospital, and in projects that develop innovative technology to support drug development and clinical decision-making in stroke patients.

Neurovascular coupling in chronic stroke

The neurovascular coupling is profoundly disturbed during cortical reorganization after acute stroke, reflecting adaptations of the vasculature and neuronal activation patterns. In 2008, Jacob Blicher MD, PhD and Leif Østergaard started a collaborative effort with the Oxford Centre for FMRI of the Brain (FMRIB) and leading experts within cortical plasticity (Dr. Heidi Johansen-Berg) and advanced functional imaging techniques (Prof. Peter Jezzard). Manus J. Donahue, PhD and postdoctoral MR physicist at FMRIB has developed innovative MR techniques to simultaneously measure changes in cerebral blood volume (CBV), blood flow (CBF) and blood oxygen level dependent (BOLD) contrast during functional activations[1, 2]. These techniques allow detailed modeling of oxygen metabolism and are now being combined with spectroscopic techniques in patients with chronic stroke, in order to quantify neurovascular coupling during cortical reorganization.

From Basic Science to Bedside: Translating CFIN research into better patient management.

CFIN researchers have developed methods that allow rapid assessment of blood flow disturbances by magnetic resonance techniques. These methods are now widely used in neuroscience and is gaining increased attention as a tool to for improved clinical management of acute stroke patient.

Challenged by the need to translate basic research and sophisticated methods into better patient management, the Departments of Neurology (Dr. Grethe Andersen and colleagues) and Neuroradiology (Prof. Carsten Gyldensted and colleagues) utilized these discoveries when introducing MR guided thrombolytic treatment to stroke patients admitted to Aarhus University Hospital, Århus Sygehus within 3 hours of symptom onset. While CFIN scientists developed software to allow the use of CFIN perfusion methods in time critical stroke management (The software is distributed from the CFIN website www.cfin.au.dk/software/penguin), CFIN MD, PhD students took part in acute patient management while collecting data for their basic stroke and neuroscience related research (see PhD project overviews by Niels Hjort, MD, PhD and Mahmoud Ashkanian, MD, PhD).

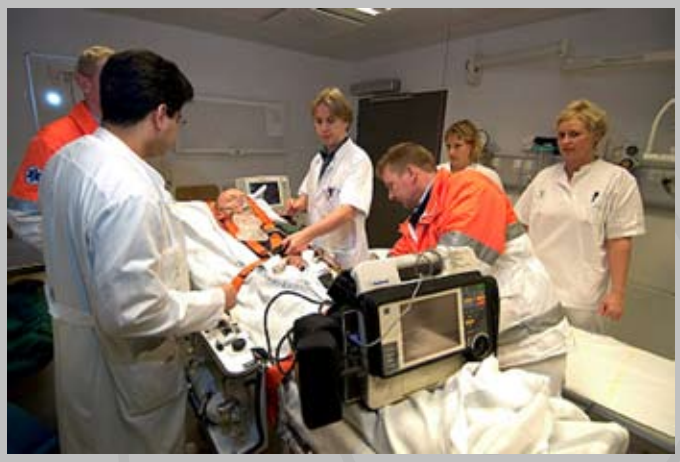

Figure 1
The Acute Stroke team receiving a patient at Aarhus University Hospital.

Christine Sølling MD, PhD took on the task of documenting the benefits of this advanced patient management over traditional thrombolytic treatment based on conventional CT to exclude hemorrhage. Her study included patients enrolled 2003-2007 and demonstrated that the novel MR approach was feasible in 88% of admitted patients. Surprisingly, despite the longer scan time for MRI (15-20 minutes as opposed to 5 minutes by CT), the more advanced imaging did not delay treatment[3]:
On the contrary, the additional diagnostic information seemingly improve patient outcome by avoiding thrombolytic treatment in patients with very high risk:benefit ratio: MRI demonstrates patients with extensive brain tissue damage at admission, as well as patient without risk of developing acute damage despite symptoms – in both cases thrombolytic treatment is believed to have little benefit while carrying a risk of adverse effects (intracranial hemorrhage). Also, patients with seizures (these can result from a stroke, visible by MRI but not conventional CT – but also be part of other medical conditions in which thrombolytic treatment should be avoided) could safely be offered thrombolytic treatment using the MRI information obtained at admission[4]. Surprisingly, the introduction of acute thrombolytic treatment with acute MRI was of considerable benefit to patients *not* diagnosed with a

stroke (these represent about 30-40% of patients admitted to a stroke unit): Their length of hospitalization was reduced by 50% - causing reduced hospital costs[5] .

The logistics and results developed in Aarhus have attracted international attention. With the support of Bayer-Schering AG, CFIN has produced an educational CD-ROM, containing a movie demonstrating patient referral logistics, stroke team check-lists, CFIN software for fast MRI data analysis, and scientific slide prtesentations. The CD-ROM is now being distributed world-wide, further disseminating our results.

Figure 2
Stroke MRI - Time is brain CD-ROM cover. The CD-ROM was produced by CFIN with support from Bayer-Schering AG.

From Basic Science to Innovation: Clinical Decision Support and Accelerated Drug Development

The advanced neuroimaging methods developed by CFIN researchers may change patient management – yet may be too complex to allow use beyond highly specialized university hospitals. CFIN coordinates the ***I-Know*** project under the European Commisson's 6th Framework ICT Programme, aiming to develop Clinical Decision Support software that support advanced diagnostics and stroke treatment by personnel at most hospitals with stroke patient referral. The ***I-Know*** project joins leading European stroke experts from Cambridge, Hamburg, Lyon, Girona, Freiburg, and Aarhus in developing advanced models of the progression of brain damage immediately after acute stroke. Having collected and classified a large database of patient imaging data, genetic

SELECTED RESEARCH PROJECTS:

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

Peter Johannsen, Elisabeth Petersen, Kim Mouridsen, Leif Østergaard: Perfusion and Predictive Models in Hereditary Frontal Dementia.

Birgitte Fuglsang Kjølby, Leif Østergaard, Valerij Kiselev (Freiburg University, Germany): 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.

Rikke Beese Dalby, Leif Østergaard, Raben Rosenberg, Poul Videbech: Perfusion and connectivity in late-onset dementia.

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

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, Jean-Claude Baron, 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, Kristjana Ýr Jonsdottir, Kim Mouridsen, Lars Ribe, 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 framework program).

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

Figure 3
The ***I-Know*** software will ultimately offer fully automated post-processing of MR images that are subsequently compared to a large patient database with known infarct growth patterns. The stroke physician can thereby determine the prognosis for ultimate brain damage with the combined knowledge of a large, expert-classified database. We hope this will improve patient acces to treatment as well as the quality of individualized stroke therapy.

profile and clinical/biochemical findings, the project now develops sophisticated models to simulate the progression of brain damage[6]. With this embedded knowledge of the stroke experts and hundreds of previous stroke cases, the software will provides automated image analysis and expert diagnostic support, supporting acute treatment of patients irrespective of infrastructural boundaries. With the statistical power of neuroinformatics and neuroimaging techniques, the technology is believed to allow the detection of efficacy signals in small patient cohorts, supporting cost-effective development of new drugs. Typical clinical testing of a stroke drug involve over 1000 patients and costs in the excess of one hundred million Euro. In comparison, the ***I-Know*** technology may theoretically identify efficacious drug candidates in early Phase II trials in 30-50 patients, greatly reducing development costs of Pharmaceutical Industry.

Stroke imaging holds immense potential in terms of studies of stroke pathophysiology and individualized treatment. A lack of standadized criteria to assess stroke images, however, represent a challenge to the convergence of scientific results and clinical practice. In March 2008, the ***I-Know*** consortium held a scientific symposium with ASIST-Japan, a succesful national network for standardization of processing and visualization of stroke data who – like CFIN and ***I-Know*** – distributes free-ware (Perfusion Mismatch Analyzer – PMA) for stroke data analysis, internationally.

Sponsored by a Norwegian software company, Nordic Imaging Lab, a succesful and well-attended meeting with presentations by the ***I-Know*** and ASIST networks was held at the Norwegian Embassy in Tokyo, with participation from leading medical imaging companies and key, presenting ASIST leaders. With a strong wish from the ASIST network to collaborate with the ***I-Know*** Consotium, and to develop common perfusion and image visualization standards, Dr. Kudo visited Aarhus in July to develop common standards for the ***I-Know*** and PMA software platforms.

The investigator meeting hosted by the Lyon team. Among the investigators are Professor Norbert Nighoghossian and Professor Trouillas (second and third from left), Professor Salvador Pedraza and Joaquin Serena, Girona (6th and 8th from left, front), Anders Truelsen, Systematic A/S (7th from left, back) and Drs Jens Fiehler and Susanne Siemonsen, Hamburg (seecond and third from left) and Josef Alaweh, Cambridge University (5th from left). The Danish ***I-Know*** consisted of Erik Søndergaard, Irene Klærke Mikkelsen, Chrisine Sølling, Lars Ribe, Kim Mouridsen and Niels Hjort.

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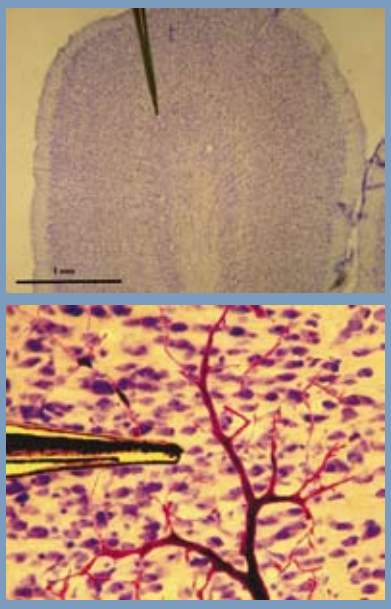
NEW COLLABORATION

CFIN has entered a collaboration lead by Kurt Vestager Gothelf, Danish National Research Foundation's Center for DNA Nanotechnology (CDNA) at iNANO.

The Danish Council for Strategic Researchs programme commission for Nanotechnology, Biotechnology and Information Technology (NABIIT) has awarded DDK 9 million to a consortium consisting of CDNA (Kurt Vestager Gothelf, Jørgen Kjems, Elena Ferapontova) CFIN (Arne Møller, Leif Østergaard), Center for Experimental Neuroscience (Jens Christian Sørensen, Carsten Bjarkam), Unisense A/S, and Lundbeck A/S.

The project aims to develop electrochemical sensors for real-time detection of neurotransmitter release in living brain tissue. Using sensor technology developed by Unisense (www.unisense.com) and highly specific receptor ligands, the consortium will attempt to develop advanced tools for experimental neuroscience and functional neurosurgery.



Oxygen brain tissue and APOX-sensor in tissue.
Photos: Unisense A/S / Courtesy Dr. Jeff Thompson.

NEW FACE AT CFIN

Jakob Blicher, MD, PhD received his MD from University of Aarhus in 2004. After that he started his PhD project at the newly opened research unit at Hammel Neurorehabilitation Center. Here Jakob studied rehabilitation of motoric function after stroke with special studies of cerebral and spinal excitability changes after stroke and in training of patients. He has primarily used methods like transcraniel magnetic stimulation (TMS) and spinal reflex examinations.

In 2008 Jakob started in a post.doc position at CFIN initially associated to the Oxford Center for Functional MRI of the Brain (FMRIB). He is currently working with FMRIB on new fMRI methods to improve the understanding of BOLD-fMRI.

The primary aim is to find new and better methods to evaluate the cerebral plasticity of the brain in connection to rehabilitation after serious brain damage like stroke. Jakob Blicher is currently associated to CFIN while persuing his career as a clinical doctor.

Stroke MRI - Advanced neuroimaging in acute stroke therapy

by Niels Hjort

Magnetic resonance imaging (MRI) has expanded the understanding of acute ischemic stroke pathophysiology, especially by providing precise information on localization and extent of neuronal damage in the hyperacute phase following vascular occlusion. MRI is increasingly used in acute stroke, but the role of MRI in the selection of patients amenable for acute therapies has not been established into common guidelines.[1]

Our study focused on the use of MRI in the selection of acute stroke patients for intravenous thrombolytic therapy and monitoring of the response to therapy. During the 2-year study period, patients were transported directly to a specialized stroke admission at Aarhus University hospital with access to an MRI scanner. Patients were selected for treatment with intravenous thrombolysis. Multimodal MRI was performed prior to and repeatedly after intravenous thrombolysis.[2]

Monitoring the response to treatment

The ischemic lesion (infarct) can be visualized be diffusion-weighted MRI (DWI). In 85% of acute stroke patients, the infarct is surrounded by a zone characterized by tissue hypoperfusion, the so-called ischemic penumbra. The neuronal tissue in the penumbra is potentially salvageable. Hypoperfusion is demonstrated by perfusion-weighted MRI (PWI).[3] The temporal evolution and relation between the diffusion and perfusion lesion volumes and symptom severity was investigated in order to establish a measure of reperfusion to assess the success of recanalization therapies. Shrinkage of hypoperfusion volumes correlated strongly with significant neurological improvement. A hypoperfusion volume decrease of more than 30% was established as a clinically relevant definition of early reperfusion. Considerable volumes of potentially salvageable tissue were identified in the subacute phase following thrombolytic therapy. This suggests targets for future rescue perfusion studies.

Prediction of hemorrhagic transformation

Reperfusion is essential for survival of ischemic tissue. Reperfusion can, on the other hand, also contribute to tissue damage and cause secondary hemorrhage, so-called hemorrhagic transformation. The relation between reperfusion, blood-brain barrier (BBB) disruption, and subsequent hemorrhagic transformation was studied by use of repeated contrast-enhanced T1-weighted and fluid-attenuated inverse recovery (FLAIR) imaging. Major post-contrast parenchymal enhancement on T1-weighted imaging performed two hours after treatment was found to be highly predictive of subsequent hemorrhagic transformation. This method was superior to the FLAIR method in predicting hemorrhagic transformation. Blood-brain barrier disruption (demonstrated by either of the methods) was associated with reperfusion. The findings provide insight into the pathophysiology of reperfused ischemic tissues, most importantly by demonstrating the interdependence of reperfusion, BBB breakdown, and subsequent hemorrhagic transformation.[4]

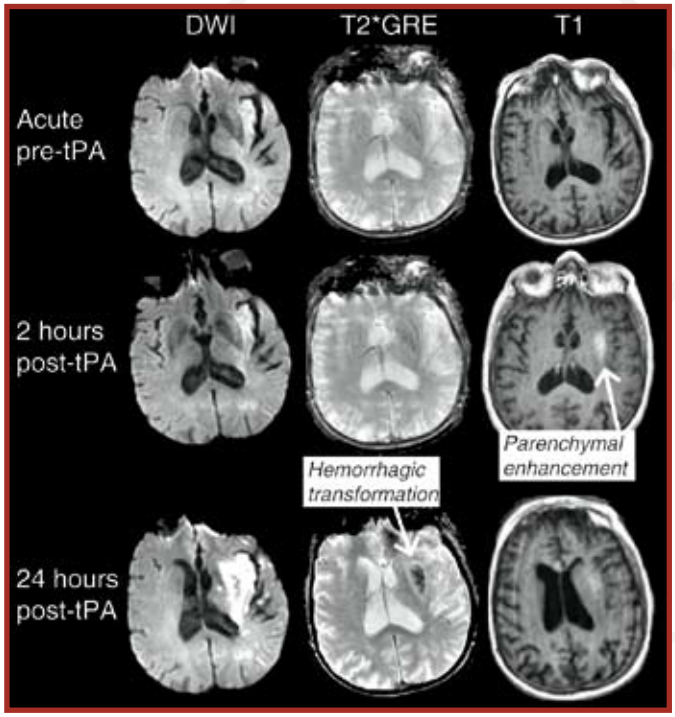
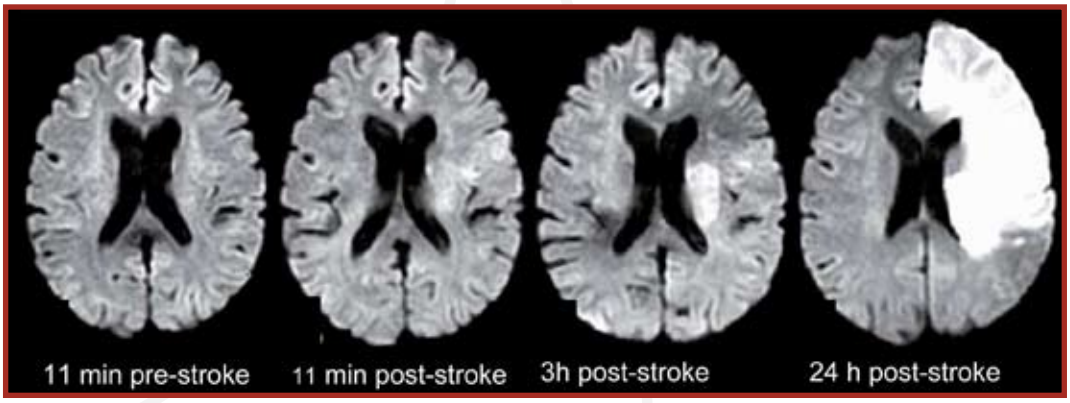


Figure
MRI scans from a patient admitted due to right-sided hemiparesis. Thrombolytic treatment was initiated 2 hours after onset of symptoms. Evidence of blood-brain barrier disruption is found 2 hours after treatment initiation in the basal ganglia region on the left side. The hyperintensity on the T1-weighted images is resulting from leakage of the gadolinium-containing contrast agent injected at the baseline perfusion-weighted examination 3 hours earlier. On the following day, a hemorrhagic transformation is found in the same location.

Since completion of the 2-year study period, MRI has been used as a routine to examine acute stroke patients admitted to Aarhus University Hospital, Nørrebrogade.

Earliest acute stroke ever imaged.
The image shows diffusion weighted images in a patient brought to Aarhus University Hospital after a brief episode of stroke-like symptoms (transitory ischemic attack). The symptoms had disappeared at arrival and images showed no lesion (left).
Eleven minutes into the scan, new symptoms ocurred - and despite rapid thrombolytic treatment, brain damage spread. This underlines the severity of the underlying atherosclerotic disease. Patients with transitory ischemic attack have extreme risk of developing a stroke in the weeks following their brief symptoms.[2]



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CFIN Retreat 2008 at Sandbjerg Manor
Photos: Henriette Blæsild Vuust

FUNCTIONAL HEMODYNAMICS

Carbogen Inhalation Increases Oxygen Transport to Brain Tissue

by Mahmoud Ashkanian

Background

Hyperoxic therapy has been hypothesized as a treatment in acute stroke. The therapy is suspected, however of reducing cerebral blood flow (CBF), because of a vasoconstrictive effect of oxygen on cerebral arterioles. We postulated that vasodilatation would predominate when 5% CO_2 is added to the inhaled oxygen, a gas known as carbogen. This could potentially improve future therapy using oxygen. This thesis presents a systematic test of that hypothesis in three different physiological states: Study I (normoxia), Study II (hypoperfusion) and Study III (hypoxia).

Methods

Using positron emission tomography (PET), we measured CBF during inhalation of test gases (O_2, CO_2, carbogen, and atmospheric air) in ten healthy volunteers (Study I), and six patients with occlusive carotid artery disease (Study II). In Study III five volunteer breath-hold divers were scanned in two different breath-holding conditions: breath-holding after breathing atmospheric air, and breath-holding after breathing carbogen (5% CO_2 + 95% O_2).
In these studies PET scans [^{15}O]-H_2O and [^{15}O]-O_2 were used to measure CBF and $CMRO_2$ respectively.

Results

In Study I, inhalation of either CO_2 or carbogen significantly increased global CBF, whereas pure oxygen inhalation decreased global CBF (figure 1).

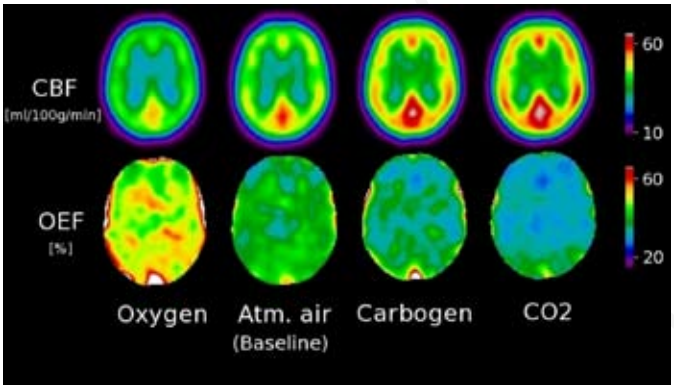

Figure 1
Average changes in CBF (upper row) and OEF (lower row) among test subjects. Mean CBF and OEF during inspiration of oxygen, atmospheric air, carbogen, and dioxide are depicted in columns one to four, respectively.

Accordingly OEF changed in opposite direction resulting in unchanged $CMRO_2$, except in white matter during oxygen inhalation relative to inhalation of atmospheric air. Subjects from Study I were used as control group for the patients in Study II.

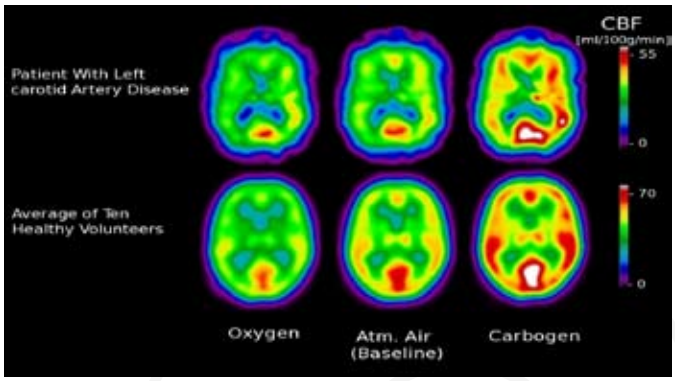

Figure 2
The upper row shows CBF changes in one patient with occluded carotid artery during inhalation of oxygen, atmospheric air and carbogen (from left to right). The lower row illustrates corresponding average CBF changes in the control group (healthy volunteers, *N*=10).

Figure 2 compares CBF changes following inhalation of oxygen, atmospheric air and carbogen in one patient and the control group. The results of Study II showed no significant interaction between group and condition (P=0.25), indicating similar effects of oxygen and carbogen in the two groups.

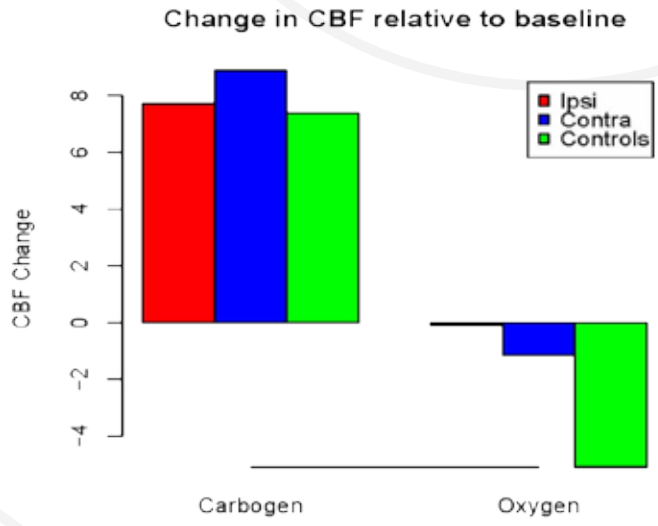

Figure 3
Quantitative changes of CBF during inhalation of carbogen and oxygen relative to atmospheric air (baseline) i patients (ipsilateral and contralateral hemisphere, n = 6) and controls (n = 10)

Contrasts in the additive ANOVA model showed that carbogen significantly increased CBF (P=0.0001), while oxygen insignificantly reduced it (P=0.06), (figure 3).

We found no significant differences between groups in effects of oxygen or carbogen on Sa_{O2} or PaO_2 values. Considering normal breath-holding as the baseline, PET measurements in Study III showed that inhalation of carbogen (relative to air) before breath-holding resulted, on average, in 18% higher ΔCBF, 3% lower $\Delta CMRO_2$ and 37% lower ΔOEF (figure 4).

Conclusion

The present study demonstrates that concomitant increases of CBF and Sa_{O2} happen more readily with inhalation of carbogen than with oxygen. Thus, inhalation of carbogen improves oxygen transport to brain tissue more readily than oxygen inhalation alone. We speculate that inhalation of carbogen would salvage ischemic brain tissue in stroke patients more effectively than inhalation of oxygen alone. Though the present results are promising, further studies are needed to rule out possible unwanted side effects of long-term use of carbogen in stroke patients.

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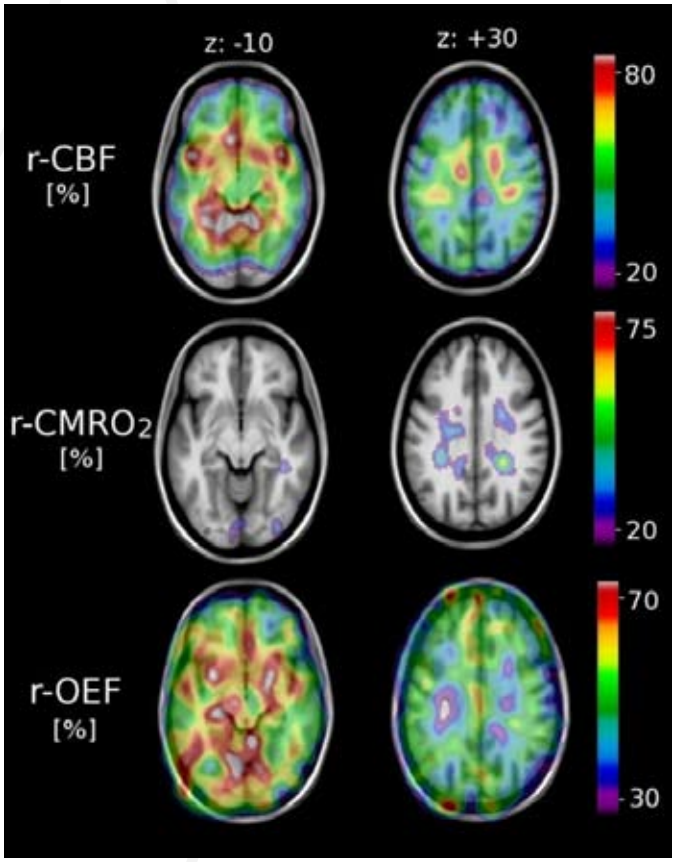
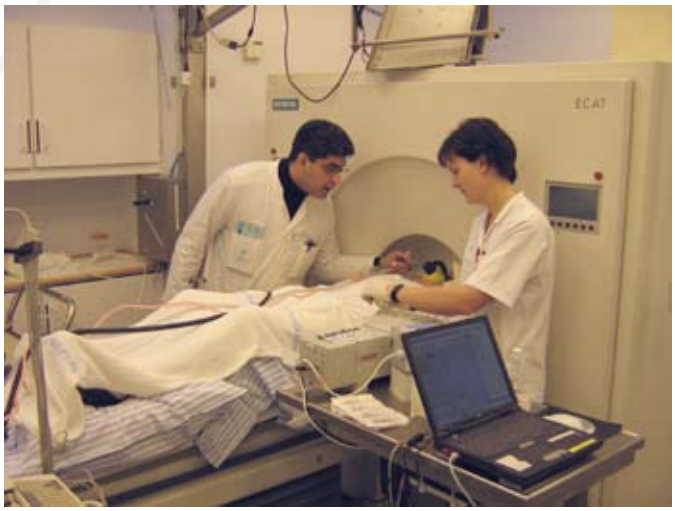


Figure 4
The relative changes in CBF, $CMRO_2$ and OEF (from top to down) in two different slices.


CFIN researchers Per Borghammer and Mahmoud Ashkanian at work in the PET Center.


CFIN researcher Mahmoud Ashkanian during his Carbogen Inhalation study in the PET Center.

Hedonia: TrygFonden Research Group

by Morten L. Kringelbach and Tipu Z. Aziz

The main purpose of the research in Hedonia: TrygFonden Research Group is to further our understanding of the functional neuroanatomy of pleasure – and in particular the lack of pleasure, anhedonia, which is found in depression and eating disorders, including obesity. The research is being carried out using a combination of neuroimaging methods in normal, neuropsychiatric and clinical populations. The hope is that this may help develop new clinical and psychiatric interventions. The research group is a transnational research group based at CFIN, Aarhus University and University of Oxford, UK.

In the following we have described how one of these techniques, deep brain stimulation, may be able to provide new insights. The research is carried out in collaboration with Professor Tipu Aziz, who has pioneered the use of DBS for treatment-resistant affective disorders including depression, Parkinson's Disease and chronic pain; an approach which has shown remarkable promise in alleviating the symptoms of these debilitating disorders and bettering the lives of the sufferers.

Deep brain stimulation

The video is brief, just a couple of minutes, but it is reality TV as riveting as anything you will ever see. A man in his mid-fifties, affable, articulate, faces the camera and talks a bit about a medical procedure he has had. He holds in his hand what looks like a remote control. "I will turn myself off now," he says mildly. The man presses a button on the controller, a beep sounds, and his right arm starts to shake, then flaps violently. It is as if a biological hurricane has engulfed him; or perhaps it is that his arm is made of straw and some evil sprite is waving it about. Whatever is going on, he seems to be possessed. With effort, the man grasps the malfunctioning right arm with his left hand, and slowly, firmly, subdues the commotion, as if he were calming a child in the throes of a temper tantrum. He is breathing hard and concentrating, and it is clear he cannot keep it up much longer. With an almost desperate gesture, he reaches out for the controller and manages to press the button again. There is a soft beep and suddenly, it is over. He is fine.

Composed, violently afflicted, then composed again. All with the flick of a switch. As before/after moments go, this one is potent, verging on the miraculous. It is the kind of thing you would expect to witness under a revival tent, not in the neurology ward of a British hospital. Once you have seen it, you will have an indelible image of Parkinson's disease. The word "tremor" does not convey what can happen to people, the way they are thrashed and harassed by their own bodies. But this scene, involving a patient of ours, informs viewers about more than a disease; it is a vivid window onto a powerful medical technology known as deep-brain stimulation (you can watch the video at www.kringelbach.dk/nrn).

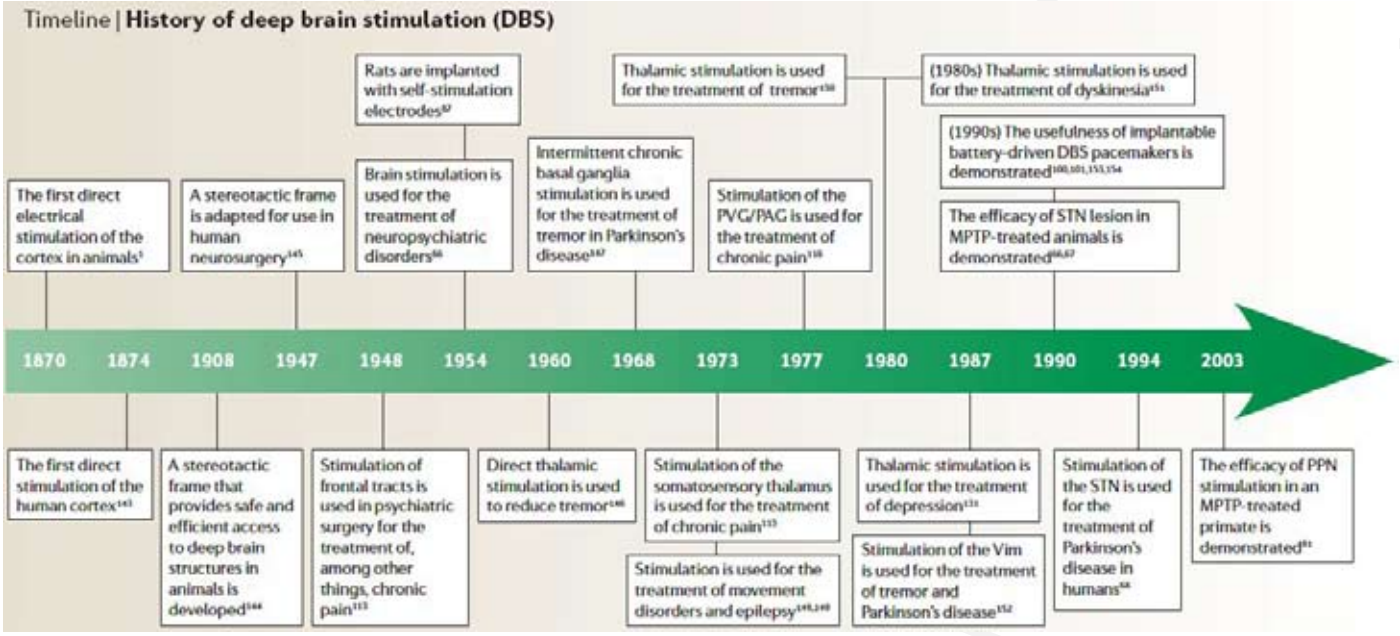


Figure 1
The history of Deep Brain Stimulation (DBS)

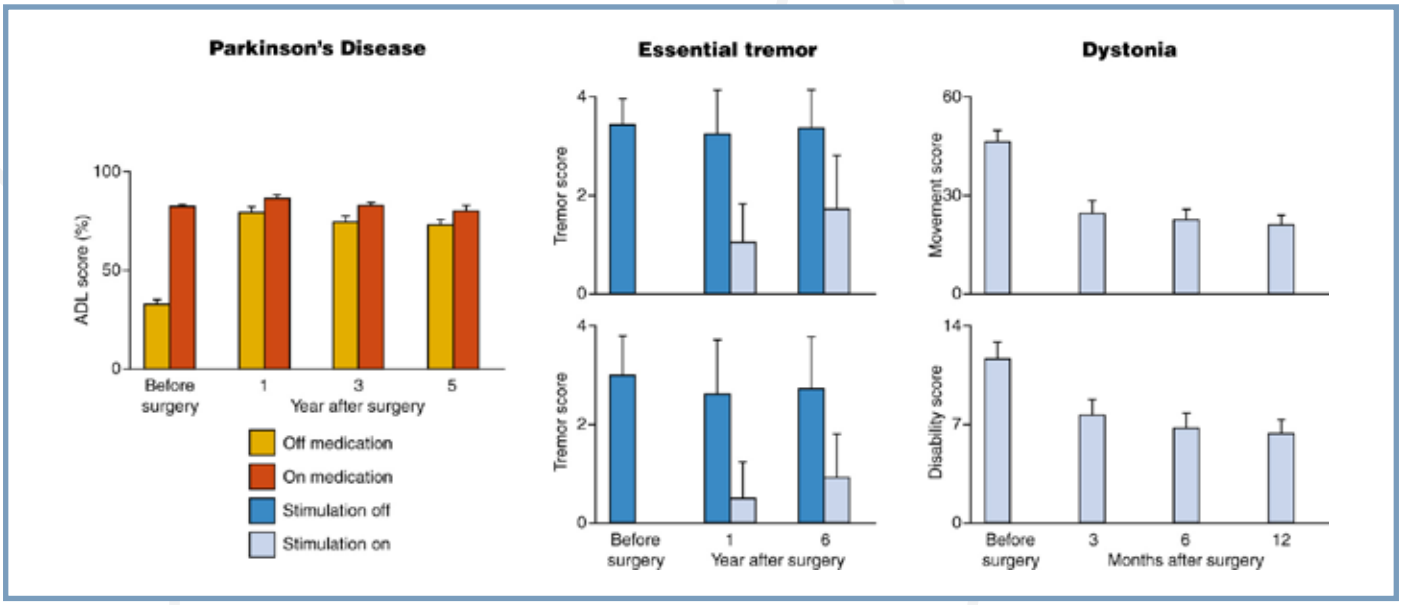


Figure 2
Long term outcomes of DBS for movement disorders
A) Scores on the Schwab and England scale for activities of daily living (ADL) at baseline and one, three, and five years after surgery with medication on (orange) and off (yellow) for 49 patients with Parkinson's disease. A score above 70 percent indicates complete independence and a score below this threshold indicate the need for a caregiver. Off-medication scores were significantly improved at one, three, and five years (P<0.001). B) Outcomes of DBS on (light blue) and off (dark blue) for essential tremor using rating scale subscores for upper limb action tremor (top) and upper limb postural tremor for the hemibody contralateral to surgery (lower) for 37 patients with essential tremor. Significant improvements were found when comparing stimulation on and off (P<0.00001). C) Long term outcome for dystonia using the mean scores for the movement (upper) and disability (lower) subscales of the Burke-Fahn-Marsden Dystonia scale before and 3, 6, and 12 months after surgery for 22 patients with dystonia. Significant long-term improvements were found on stimulation compared to scores before surgery (P<0.001).

Sudden, radical transformation is the hallmark of deep-brain stimulation. The treatment, essentially a pacemaker for the brain, consists of a deceptively simple, two-part device. A surgeon threads one or two thin wires into carefully selected locations deep within the brain, then inserts a small battery just beneath the skin near the collarbone. Pulses of electricity travel from the battery to a four-pronged electrode situated at the tip of each wire. The effects are instantaneous, usually appearing while the patient is still on the operating table - the quieting of a tremor, the ability to walk again, or, in some patients with otherwise treatment-resistant depression, a renewed pleasure in living.

Deep-brain stimulation came into its own in the 1990s, and since then surgeons have performed it on more than 30,000 people, mostly to quell Parkinson's disease and other movement-related disorders. It is not a cure, but it can keep symptoms at bay for years. Recently, though, as the electrodes have become safer and the batteries smaller and longer-lasting, and as advances in brain-imaging techniques like MRI have made it possible to place electrodes with still greater precision, neurosurgeons have begun investigating the technology as a way to ease a host of other health problems.

Deep-brain stimulation has made it possible for children with a disabling movement disorder called dystonia to leave their wheelchairs and lead near normal lives. It has brought immediate relief to people suffering from cluster headaches and other kinds of unremitting pain. It has shown tantalizing promise for some psychiatric disorders, including severe cases of depression, obsessive compulsive disorder, and Tourette's syndrome. It has been attempted as a cure for anorexia and obesity. Some neuroscientists speculate that it could help stem the memory loss of Alzheimer's. The brain is an electrical organ, so there is very little that goes wrong with it that could not, hypothetically, benefit from finely calibrated pulses of electricity. Clinical trials of deep-brain stimulation - preliminary testing on small groups of patients - are multiplying at hospitals around the world, from Cleveland and Toronto to Milan, Bristol, and Grenoble.

Despite the recent advances, technologically speaking, deep-brain stimulation is not yet fully mature. Today's devices are programmed to deliver steady, unchanging pulses of electricity. Over the next decade, we expect to see a much "smarter" device, one that would turn itself on and off as needed, tailoring its therapy to what is happening moment-to-moment in the patient's brain.

More than 250 hospitals in the United States alone perform deep-brain stimulation for movement disorders. Other applications are considered experimental, in part because they are not yet FDA-approved, but strong evidence is mounting in their favor. Take, for example, pain.

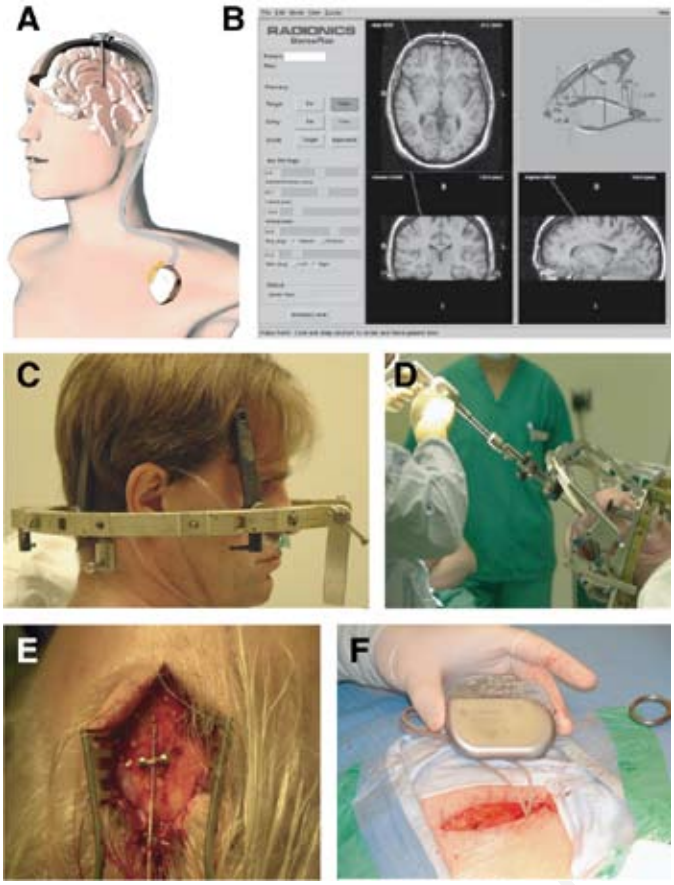


Figure 3
The neurosurgical procedures involved in DBS
A) Schematic of the principles of DBS. B) Illustration of the process of the neurosurgical pre-planning. C) Application of the Cosman-Roberts-Wells stereotactic head frame on the patient. Note that the base ring is parallel to the orbitomeatal line. D) The precise positioning of the electrode through perforating the calvarium with a twist drill. E) Securing the electrode to the skull with a titanium miniplate and screws. F) Placement of the implantable pulse generator in a subcutaneous pectoral pouch.

Pain surgery

In May 2001, a man named Robert Matthews fell and broke his left leg. The fracture did not heal properly, and the leg developed a stubborn antibiotic-resistant infection. Fearing that it would spread to the rest of his body, doctors amputated his leg above the knee. Matthews' problems did not end there. Although his leg was gone, he felt as if it were still there, and in excruciating pain. He tried medications, hypnosis, and spinal-cord-nerve stimulation, but nothing helped.

When Matthews was referred in 2005, he was 58 years old and had been suffering from phantom-limb pain for four years. He was taking large daily doses of opiates and, understandably, felt anxious and depressed. We had previously shown that stimulation of the brainstem, the perhaps most primitive part of the brain, can ease otherwise treatment-resistant pain; Matthews seemed an ideal candidate.

On the day of the surgery, our team clamped Matthews into a stereotactic frame - a metal rectangle that surrounds the head and provides three-dimensional coordinates for any point within the brain. We scanned his brain twice, with MRI before the frame was attached (metal objects are unsafe in an MRI machine) and with CT after, and merged the images using computer software. Every individual's brain is slightly different and any given structure will not always be found in the exact same location. Now Aziz had a personalized map he could use to plot his trajectory with millimeter precision.

Matthews received an injection of local anesthesia so that he would not feel Aziz drill a hole the size of 2.5 mm in his skull. There are no nerve endings in the brain, which meant Matthews could be fully awake - and we would need his participation to make the hour-long operation come off. Aziz gently guided a wire tipped with four platinum-iridium electrodes through the brain and into the area known as the periventricular gray/periaqueductal gray. Aziz carefully electrified first one, then another, of the four electrode prongs, asking Matthews to describe what he felt.

This is one of the trickiest moments in deep-brain stimulation - getting rid of the symptom without causing side effects by accidentally stimulating the wrong brain cells. The electrode is only about a millimeter and a half wide but it straddles up to a million neurons. And packed tightly within the periventricular

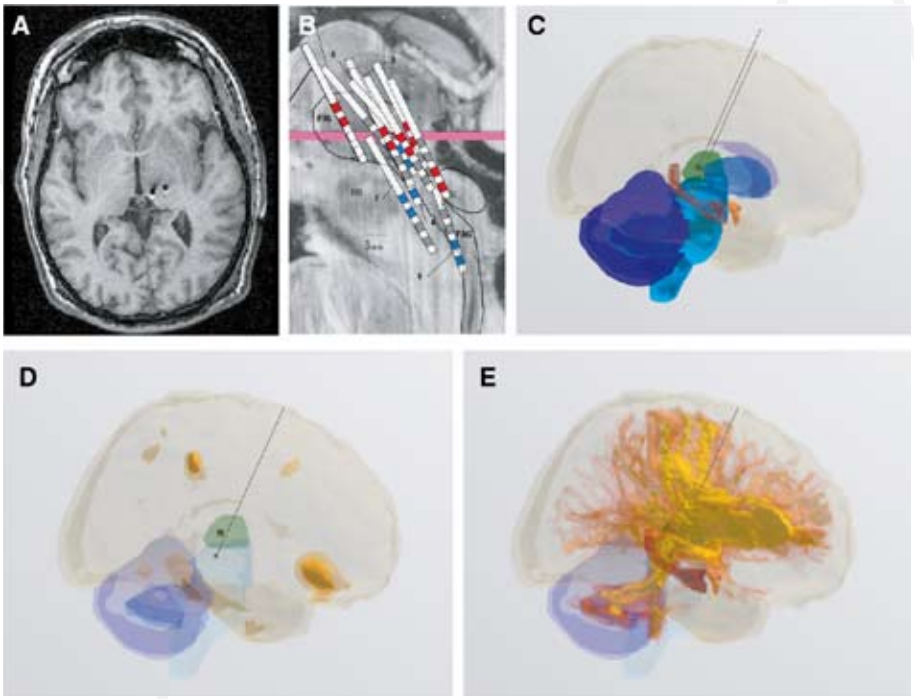


Figure 4
DBS for chronic pain
A) Axial MRI slice showing the implantation of electrodes in PVG/PAG and thalamus in a patient. B) Schematic illustration of the vertical placement of electrodes in the PVG/PAG in a series of chronic pain patients. C) Three-dimensional rendering of human brain showing the placement of the two electrodes in the PVG/PAG and thalamus, as well as some of the important subcortical structures. D) Three-dimensional rendering showing the whole-brain DBS induced activity from stimulation in the PVG/PAG. E) The connectivity of the PVG/PAG measured with diffusion tensor imaging.

gray/periaqueductal gray are cells that communicate with each part of the body; we wanted to affect only the ones related to Matthews' left leg. During the procedure, Aziz was alert to whether Matthews felt tingling or warmth in his hands, arms, face, or other leg, in which case he would either move the electrode, stimulate a different prong, or change the pulses. Moreover, this brain area is the seat of the so-called "fight or flight" response - once, when doing this procedure on a different patient, he had an anxiety attack on the table, which ended just as abruptly when Aziz repositioned the electrode. Rare but severe side effects that can result from imperfect electrode placement include eye bobbing, inappropriate laughter, unprovoked penile erections, and depression.

It has been demonstrated that fast pulses make pain worse while slower ones, i.e. low-frequency pulses ease it, so we started Matthews at about 10 per second, and methodically electrified each of the four electrode prongs in turn. When we got to the second and third prong, he felt a sudden calm descend--a comfortable feeling of warmth in his phantom leg. After four years, finally, relief. The pain returned almost immediately when we turned the stimulator off. After fine tuning the frequency, current, and length of the pulses, we ascertained that the best setting for Matthews was to stimulate at 1.5 volts - the strength of an AA battery - seven times per second, with a pulse duration of 300 microseconds.

Aziz affixed the electrode to Matthews's skull and implanted a battery the size of a slighter larger mobile phone battery over his right breast muscle. The battery is connected to the electrode by a wire that runs under the skin of Matthews' chest and neck and behind his ear to the top of his scalp. Matthews has a magnetic remote control he can use to turn the deep-brain stimulator on or off - but he rarely turns it off, because as soon as he does, the chronic pain returns in full force. His pain is 75 percent reduced since the operation, and he has been able to resume his life and take pleasure in it again.
Since 1999, Professor Aziz has treated more than 80 patients with chronic pain (the causes were various, including stroke); about half of them have improved enough to significantly reduce their medications. We have also seen remarkable in people suffering from cluster headache, a form of migraine.

Good as these outcomes are, in the future we should be able to do better, using technology similar to that of today's cardiac pacemakers. Computer software in these devices monitors the patient's heart, sending a jolt of electricity only when it recognizes that the heart is not beating properly. When brain pacemakers become this precise, they will not have to be on all the time, which means, among other things, that the batteries will not have to be replaced as often (they typically last between six months and five years, although rechargeable batteries are also starting to become available).

Before deep-brain stimulation can advance in sophistication, however, scientists must decode the language of neurons. We need to learn the details of how brain regions communicate, which electrical patterns might signify an oncoming tremor, headache, or epileptic seizure. Then we can program the device to recognize when one of these problems is coming on, and to deliver the specific pattern of pulses that will short-circuit it. Our team has made an intriguing advance toward discovering just such a "brain signature" for pain, and other studies are under way.

Figure 5
Professor Tipu Aziz showing his results to HM The Queen Elizabeth II.

The whole brain

All this excitement swirls around deep-brain stimulation not just because it is a promising therapy. It is also a powerful tool to help neuroscientists gain insights into the fundamental functioning of the human brain. Our best view of the brain until now has been through imaging studies such as MRI and PET scans, but what we get from them is rather vague: blood flows to these parts of the brain when a person does such-and-such or thinks such-and-such. With deep-brain stimulation, on the other hand, what you essentially have is an on/off switch located in a specific part of the brain. By observing what happens when that switch is activated, you can glean detailed information about how one brain structure acts on the brain as a whole. One particularly exciting avenue that we have pioneered is to combine deep-brain stimulation with an imaging technique called magnetoencephalography (MEG). MEG tracks neural activity on the scale of milliseconds (MRI, by contrast, gives average brain activity over six seconds, and PET over minutes), so it gives an exceedingly accurate, moment-to-moment report.

We used this technique on Robert Matthews, the phantom-limb patient. The electrode deep in his brainstem appeared to drive activity in many other brain regions. Among the most active when he felt pain relief was the mid-anterior orbitofrontal cortex. This structure, located just above the eyes, has been shown in other imaging studies to be a pivotal part of pleasures such as eating, orgasm, drugs and social interactions. What we learned from the scan of Matthews was that the cessation of pain is an intense form of pleasure - that pain and pleasure are intimately related. Together with our previous findings, this finding suggests that the orbitofrontal cortex might be an effective new stimulation target for people suffering from anhedonia, a lack of pleasure, which is common to depression and other mental illness. We expect many other revelations to emerge from studying people with brain implants. Thus in addition to its ability to help people in dire need, deep-brain stimulation promises to unlock some of the secrets of the normal brain.

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MIND*Lab*

by Leif Østergaard and Andreas Roepstorff

CFIN is an integral part of MIND*Lab*, a big cross disciplinary research project recently awarded 120 M DKK by the Danish Ministery of Science, Technology and Innovation.

Across religions, philosophies and scientific disciplines, man has sought to formulate theories of the human mind for millennia. Over the past century, technological and methodological innovations have driven the study of molecular, cellular, metabolic, haemodynamic and structural signatures of brain function at rest and during sensory and cognitive processing, as well as in disease. Meanwhile, powerful methods and influential theories of human cognition have been established within psychology, philosophy, language and sociology. These successful theories and methods can be broadly ascribed to 'top-down' cognition research or 'bottom-up' brain research. While translations among disciplines and complementary approaches are challenging, we believe that research pursuing such triangulations stands to benefit substantially in terms of convergence of ideas, synergies in research, and even cures for diseases of the human brain and disorders of the human mind.

At the University of Aarhus, anchored at CFIN, the research cluster CCC (Cognition, Communication, and Culture), the key research area RCC (Religion, Cognition and Culture), and the Music in the Brain research group (a collaboration between CFIN and The Royal Academy of Music) a unique collaboration has evolved across disciplines: Physicists, statisticians, philosophers, organizational theorists, anthropologists, psychologists, musicologists, linguists, scholars of religion, biologists and physicians work together in an effort to understand the brain, its disorder and its development through physical and social interactions – and vice versa. This work has created methodological and conceptual breakthroughs, as well as innovative approaches to the treatment of severe neurological and psychiatric disorders. This productive environment has attracted some of the most influential international cognitive neuroscientists to Aarhus. MIND*Lab* will allow researchers to address central scientific problems within culture, music, language and memory. Combining this knowledge with research on the most devastating neurological and psychiatric disorders, this effort seeks to preserve and recover function and quality-of-life in relation to diseases accounting for 35% of the disease burden in Denmark. MIND*Lab* will also develop new forms of teaching and sharing of knowledge, exploiting crucial synergies across traditional disciplines.

Among the research coordinators in the MIND*Lab* project are:

- Professor Leif Østergaard, Head of CFIN, Faculty of Health Sciences, University of Aarhus and Aarhus University Hospital
- Professor Eva B. Vedel Jensen, Dr.scient., Mathematical Institute, Faculty of Science, University of Aarhus
- Professor Armin W. Geertz, Dr.phil., Department of Religion, Faculty of Theology, University of Aarhus
- Professor Dorthe Berntsen, Psychological Institute, Faculty of Social Sciences, University of Aarhus
- Professor Sten Vikner, Dr.phil.habil., Department of English, Faculty of Humanities, University of Aarhus
- Associate Professor Andreas Roepstorff, CFIN and Department of Anthropology and Ethnography, Faculty of Humanities, University of Aarhus
- Dean Børge Obel, Aarhus School of Business, University of Aarhus
- Professor Troels Staehelin Jensen, Danish Pain Research Center, Faculty of Health Sciences, University of Aarhus
- Associate professor Peter Vuust, CFIN, Aarhus University Hospital and Professor at The Royal Academy of Music

Torben Lund and CFIN collegues looking at scanning equipment (and trying it on!) at RSNA Congress in Chicago, December 2008.
Photos: Søren Haack

COGNITION RESEARCH

by Andreas Roepstorff

Pinocchio on the cover of Trends in Cognitive Science[1], tales of objects and gifts in the brain hitting the headlines in an Indian newspaper, a CFIN researcher, wired up with measurement devices, carried on the shoulders of a young Spaniard who walk on burning coal amidst a crowd of screaming spectators in a small village in the middle of the Iberian peninsula. 2008 took CFIN cognitive research and researchers to quite unexpected places. Much of this reflects the "interacting minds" aspect central to the cognitive research at CFIN: it is ultimately about people doing things, with each other, to themselves and with things.

Chris and Uta Frith's extended stay at CFIN was a key event, structuring much of the year. The Friths effectively transformed The Yellow Villa at Peter Sabroesgade into a hotbed of visitors and ideas that during the year turned into projects, many of which are likely to pop up in the next annual report. A key methodological issue has been how to actually study interaction. Is it a matter of watching another person's action or of on-line joint action, is it a transfer of influence and ideas, or of one person setting the context for the other(s)? Can it be studied in the laboratory or in the scanner, on the internet or in the wild? Judging from the projects currently in the pipeline, the tentative answer appears to be "both-and".

Predictive coding is a central theoretical concept for the cognitive research at CFIN. The idea is that predictions about the input to a particular brain region is a major "currency" for the brain. If predictions are met, processes can be handled locally, but when predictions fail, an error term, which is propagated "upwards" in the system, is a sign that closer attention to the particular process is needed. This leads, the theory suggests, to momentary integration between higher and lower brain areas. Predictive coding is part of a larger move in neuroscience to see the brain as actively constructing percepts and anticipating events and outcomes of actions rather than just reflecting passively the environment.

2008 became the year, where predictive coding made it from internal discussions at CFIN to concrete research outputs. Jakob Hohwy, who moved from University of Aarhus to Monash University in Melbourne 2007 proposed with Andreas Roepstorff (CFIN) and Karl Friston (UCL) that predictive coding could explain binocular rivalry, a central and much debated visual illusion[2]. Binocular rivalry occurs when one eye receives one stimulus e.g. a face and the other a very different stimulus e.g. a house. Counterintuitively, the resulting experience is not that of a face/house, rather, one sees in most conditions an automatic shift between a face and a house. The predictive coding account proposes that binocular rivalry is the result of an unresolved competition between two very different interpretations of the complex stimuli: this is a house, and this is a face. Once the input to one eye wins, it fails to predict the input to the other eye, this strengthens the other percept, but once that wins it fails to explain…. The key argument is that the "correct" interpretation, that the two eyes see radically different things, is so unlikely to the visual system that it is refuted right away. The model generates a number of predictions that we are currently testing further. With the "Music in the Brain" group, we have also used predictive coding to explain key elements of musical perception, as an interplay of anticipation and surprise[3]. The key experiment here was a study of rhythmic anomalies that generates characteristic synchronized patterns in brain activity, the socalled mismatch negativity (MMN)[4].

Risto Näätänen, who discovered MMN in the 1970's, has over the last decades used MMN studies to identify fundamental neuronal processes first involved in processing expectations. This impressive body of work is one of the most consistent and important EEG findings. It is one of the best characterised instances of an neuronal error terms as suggested by predictive coding approaches. It has also lead Risto to formulate a theory of 'primitive intelligence' in the auditive cortex. We are very proud that Risto joined CFIN in 2008 as a regular visiting professor. His competences will be key in implementing EEG and MEG at CFIN, both as basic research paradigms and in clinical investigations[5].

See it from my side is one of those dead linguistic metaphors, which is so well-known that it is not even noticed as a metaphor. However, a study by Mikkel Wallentin and colleagues show that this may be more than just a metaphor. In an fMRI experiment, Mikkel found that an area known as Frontal Eye Field (or FEF) was involved when subjects were told to change spatial reference frame in a picture they remembered. This is very exciting, as the FEF machinery is also involved in actually directing eye movements[6]. Mikkel thereby, again, demonstrate that understanding sentences taps in with relevant perceptual and memory processes[7].

These appetizers have only introduced a few of the ongoing cognitive projects at CFIN, the following pages discuss a few in more detail. Enjoy!

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PhD student Else Marie Jegindø participating in the traditional 'Firewalking Ceremony' in San Pedro Manrique in Spain, 24 June 2008.

SELECTED RESEARCH PROJECTS:

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.

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

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

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

Joshua Skewes: Predictive coding binocular rivalry and brain function.

Joshua Skewes: Contextual moduations of coordination dynamics in joint action.

Joshua Skewes: Bioagency and behavioural science.

Joshua Skewes: As hard as it looks: consequences of perceived difficulty for the two visual systems hypothesis.

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

Randi Abrahamsen, Sanne Lodahl, Andreas Roepstorff, Leif Østergaard, Bobby Zachariae, Peter Svensson: Imaging pain.

Sanne Lodahl: The selforganising brain: context and interaction.

Kristian Tylén: Interacting sense making in the brain

Vibeke Bliksted: Social cognition in schizophrenia.

Ethan Weed: Language disturbances in right hemisphere lesioned patients.

Ivana Konvalinka: Joint tapping as a model of minimal social interaction.

Ivana Konvalinka: Synchronization of heart-rates during fire-walking.

Else Marie Jegindø: Modulation of pain by cognitive stance.

Sita Kotnis: Dual use of neurotechnologies.

Daniel Campbell-Meiklejohn: Interacting games, interacting brains.

COGNITION RESEARCH

Written in flowers, hoovers and chairs: material signals in the brain

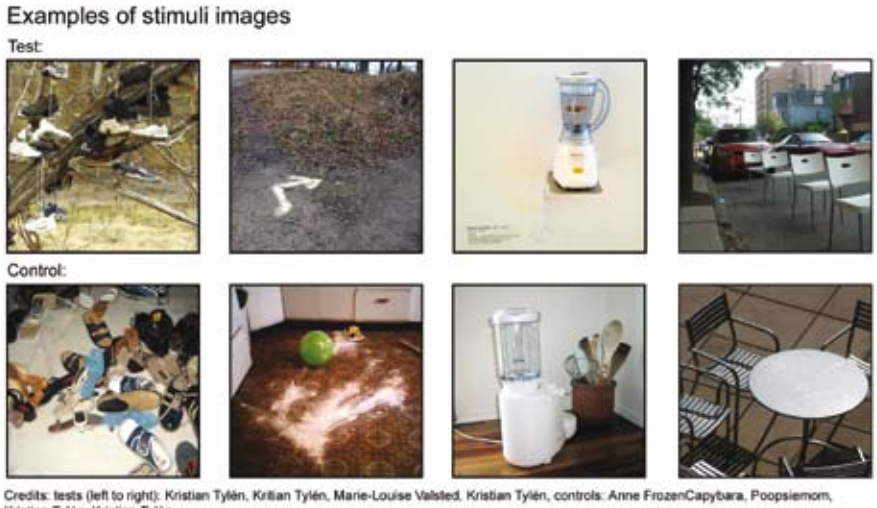
by Kristian Tylén

Sometimes a chair is just a chair. Something that you sit on. But at other times a chair is not just a chair. When we encounter chairs put out in the street we might infer that they are placed there to reserve a parking lot. Or when we see chairs put up on a wall we might recognize the intention that these should be explored for their artistic aesthetic effects. In both cases we do not think of the chairs as primarily there to sit on. In these particular contextualizations, the chairs become perceived as communicative symbols purposefully left behind by someone to convey a message, and the otherwise static, mute, material objects are suddenly perceptually explored as dynamic sources of human social meaning. This curious fact points to the way that human language and communication is not just a matter of specific conventional words, grammars and gestures. Rather, language is primarily an activity by which we socially coordinate acts and share ideas and experiences. And in many everyday situations even material objects and artifacts are employed as symbolic mediators of such social intents.

We used fMRI to address the neurocognitive foundations of our understanding of everyday material objects when these are used as communicative symbols (Tylén et al, in press). We predicted that subjects' inclination to do symbolic interpretations of objects would elicit activation in brain areas associated with other types of communicative mediation such as language, gesture and the recognition of social intentionality.

In a behavioral classification study 63 informants rated 150 photographs depicting naturally occurring scenes with material object configurations. The images were arranged in pairs where one depicted a scenario containing everyday objects manipulated in a striking and deliberate way for purposes of interpersonal communication while the other depicted the same objects in natural, utilitarian or accidental situations without any conspicuous intentional communicative relevance. Based on the informants' ratings we picked the 50 stimulus image pairs that scored best in the test as stimulus for an event-related fMRI paradigm (see fig. 1 for examples of stimulus image pairs). The images were presented in a randomized order to 22 subjects in a 3Tesla MR scanner. After scanning, subjects were asked to rate each stimulus image on various parameters including communicative intent and degree of conventionality of the communicative use of (some of) the objects. Their responses were subsequently used to statistically model the brain data.

Interestingly, we found that the perception of symbolic object configurations when contrasted with non-symbolic objects elicited activation in a network of brain areas traditionally associated with verbal language. The activations peaks resided for instance in the left fusiform gyrus (BA 19) – an area sometimes referred to as the Visual Word Form Area (Cohen et al, 2000) – as well as the Broca's region of inferior frontal cortex (BA 45) bilaterally (see fig. 2). These areas consistently show up in studies on reading and verbal language semantics, but have also been shown to be involved in other modes of non-verbal communication such as hand gestures (e.g. Lotze et al, 2006), facial expressions and body postures (Lawrence et al, 2006), and music (e.g. Vuust et al, 2006). In addition, we used subjects' ratings of the relative conventionality of each symbolic object configuration in a regression analysis to establish the impact of conventionality on the activation patterns. In accordance with a series of studies on figurative language and novel metaphors, we found activation in the right hemisphere homologue to Broca's region as a function of increasingly unconventional symbol use (see fig. 3). It has been suggested that this area is responsible for the integration of extra contextual information when this is needed to resolve semantic ambiguity (e.g. Grindrod & Baum, 2005).



Credits: tests (left to right): Kristian Tylén, Kritian Tylén, Marie-Louise Valsted, Kristian Tylén, controls: Anne FrozenCapybara, Poopsiemom, Kristian Tylén, Kristian Tylén

Figure 1
Examples of stimuli image-pairs. Test images include static objects and artifacts perceived as means for intentional communication. Control images include objects without any conspicuous communicational significance.

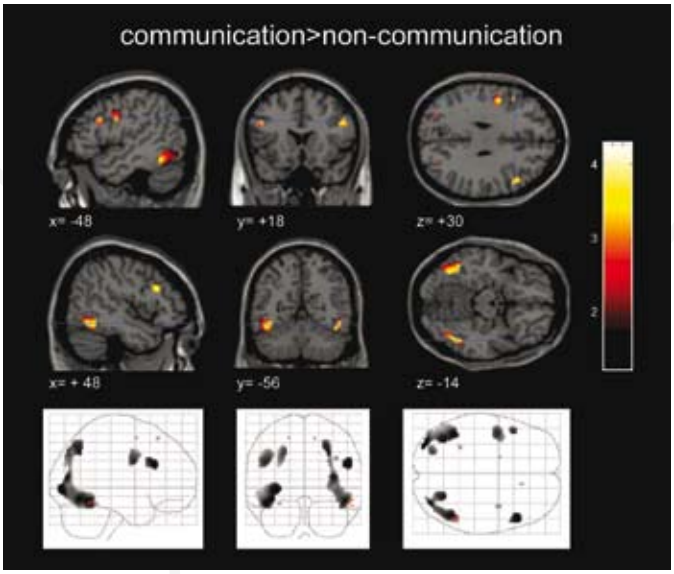


Figure 2
Functional brain activations associated with subjects' comprehension of static, material objects and artifacts used as symbols for purposes of communication ($p < 0.05$, FDR-corrected).

Together our findings suggest that when everyday objects like chairs, hoovers, or flowers are experienced as symbolic mediators of social communicative meaning this understanding is subserved by brain areas traditionally associated with verbal language and reading. The finding can be interpreted in support of contemporary approaches to language and communication that, rather than approaching language as an object with certain structural characteristics (grammars and lexica), focuses on language as an activity – a way of getting things done in a social world. In the latter perspective verbal language is not treated in isolation but is studied in functional continuation with a large distributed set

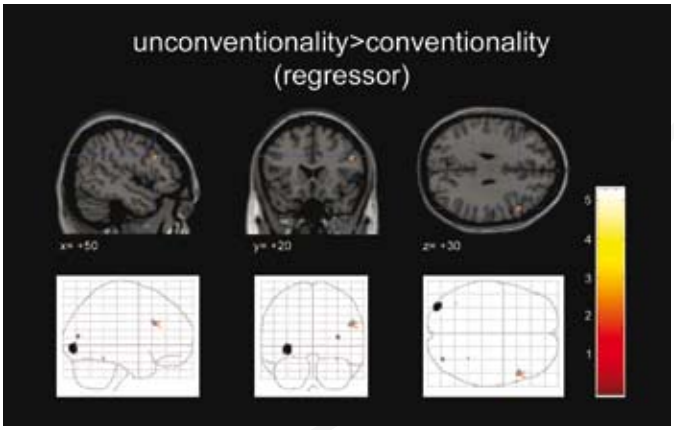


Figure 3
Functional brain activations as a function of increasing unconventionality of the symbolic objects ($p < 0.05$, FDR-corrected).

of multimodal resources that we employ in social coordination, meaning construction and thought processes. As a-kind-of-language emergent material symbols (like e.g. the chairs considered above) are thus examples of how our mental, social and material worlds are intertwined in complex and complementary ways in perception, cognition and social interaction.

The study was published in Brain and Language under the appealing title "Say it with flowers!" and turned out to be very popular story: it was picked up by The New Scientist Magazine and subsequently cited in a broad range of international news and science sites including Iranian, Polish and even several Indian papers, sometimes under quite unrecognizable headlines such as "Why a gift is the universal language of love" (see links to some of the publicity below).

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COGNITION RESEARCH

Highly religious participants activate social cognition in personal prayer

by Uffe Schjødt

Christian doctrine on God's nature includes abstract concepts like omnipresence, omniscience, and omnipotence. Recent cognitive studies, however, have demonstrated that religious subjects are generally incapable of keeping an abstract representation of God in online cognitive processing (Barrett & Keil, 1996).

We used functional magnetic resonance imaging (fMRI) to investigate how performing formalized and improvised forms of praying to God changed the evoked BOLD response in a group of highly religious Danish Christians (Table 1). Because the practice of praying comprises multiple subgenres and varies tremendously in form and content (mantra, petition, worship, thanksgiving etc.), we expected that praying, like other forms of mental practice, differ widely in both cognitive content and corresponding neural correlates. Specifically, we hypothesized that personal praying would reflect the subjects' belief in a personal god by activating areas of social cognition.

Factorial design		Domain	
		Religious	**Secular**
Speech Act	**Formalized**	The Lord's Prayer	Nursery Rhyme
	Improvised	Personal Praying	Making wishes to Santa Claus

Table 1
We used four conditions in a two-by-two factorial design. Factor 1: Religious or Secular Domain. Factor 2: Formalized or Improvised Speech Act.

The individual contrast of Personal Praying relative to making wishes to Santa Claus revealed a specific pattern of neural activity consisting of the temporoparietal junction, the temporopolar region, the anterior medial prefrontal cortex (MPFC) and the precuneus (Figure).

The temporoparietal junction, the temporopolar region and the anterior MPFC have all been extensively reported in studies of social cognition, and together they have been referred to as the three classic 'theory of mind' areas (Gallager & Frith, 2003). Previous imaging studies have shown that subjects playing reciprocity games against computers and humans

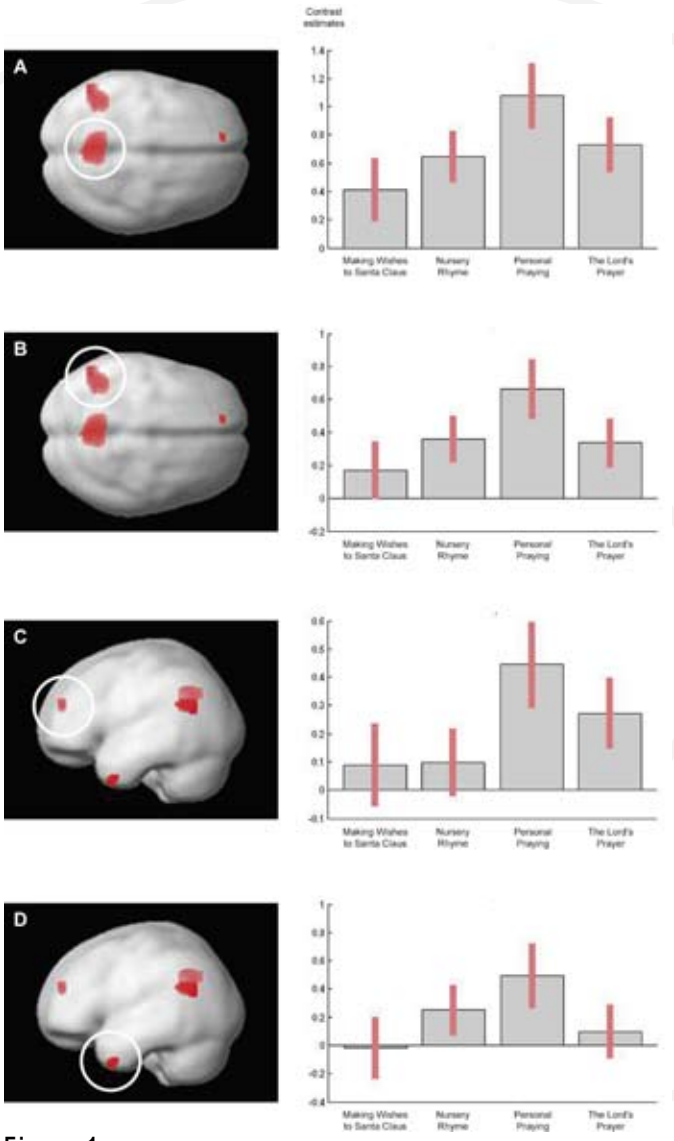

Figure 1
To the left: Personal Praying relative to Making Wishes to Santa Claus. Results are thresholded at p<0.05 corrected for multiple comparisons (FDR) with an extended threshold of 15 voxels. To the right: Effect size analysis of the regions of interest in the four conditions relative to baseline (90% C.I). A) Precuneus B) Temporoparietal junction C) Medial prefrontal cortex D) Temporopolar region.

recruit the anterior MPFC and the temporoparietal junction specifically for 'human' interaction (Rilling et al., 2004). We argue that this pattern of activation in Personal Praying supports our hypothesis that talking to God, who is considered 'real' rather than 'fictitious' like Santa Claus, is comparable to normal interpersonal interaction. Thus, in terms of brain function, the Christian participants mainly seem to think of God as a concrete person, rather than as an abstract entity.

We found the same pattern of activation in Personal Praying relative to The Lord's Prayer. This indicates that, compared with formalized prayers, improvised forms of praying are better capable of activating 'theory of mind' processing. We expected this because highly formalized prayers usually consist of frequently rehearsed, abstracted and non-personal content. Contrary to reciting The Lord's Prayer, personal praying consists of improvised and direct conversations with God about personal problems and requests. In this form of praying mentalizing, social reciprocity, autobiographical memory and updating of social narratives are much more relevant features.

Although The Lord's Prayer did show major activations in a number of regions in the opposite contrast, e.g. in the dorsolateral prefrontal cortex, the parietal cortex, a main effect analysis of 'formalized speech acts' (The Lord's Prayer and Nursery Rhyme relative to Personal Praying and Making Wishes to Santa Claus) revealed that these activations may be attributed to a general effect of rehearsal and retrieval in formalized speech.

The fact that personal praying and the Lord's Prayer activate different neural regions adds force to the general assumption in the comparative study of religion that religious practices and experiences are diverse phenomena rather than a uniform phenomenon as suggested by recent neurotheologians (d'Aquili & Newberg, 1999).

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NEW FACE AT CFIN

Daniel Campbell-Meiklejohn, is a postdoctoral research fellow on the Interacting Minds project. He joined CFIN from the University of Oxford in the United Kingdom. He is also linked to the Ludomani (Pathological Gambling) group.

Daniel is a behavioral and cognitive neuroscientist. Originally from Vancouver, Canada, he began psychological research at the University of British Columbia. In his early years, he worked on projects at many levels of neuroscience (genetic, behaviour, and cognition) on diverse topics ranging from serotonin function, stress, dyslexia, preconscious attention, decision-making and stereotype formation. Daniel completed his Masters in Neuroscience and DPhil in Experimental Psychology at the University of Oxford. His DPhil project consisted of a variety fMRI and pharmacology experiments of decision-making and reward-processing, including the intriguing decision-making behaviour of 'loss-chasing' - when we take even more risks to recover our old losses, or more accurately, how we know when to stop[1]. This behaviour is not only because we do it every day, but a central role in pathological gambling diagnosis.

Daniel could not resist the offer to work on the Interacting Minds project at CFIN, headed by the outstanding leadership of Professors Chris Frith, Uta Frith, and Andreas Roepstorff. Daniel proudly joins a diverse team of researchers from philosophy, psychology, anthropology, statistics, linguistics and engineering. The collective aim is to effectively study the biological basis of social interaction. Daniel also joins a talented group of researchers in the Ludomania group to continue productive work on pathological gambling. His current projects study decisions and learning processes involving other people, application of neuroscience to economic problems, the biological basis of shared representations and ongoing studies of gambling behviour. His tools are pharmacological manipulations, fMRI, game theory, behavioural studies, and whatever new and exciting equipment he can get his hands on.

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MUSIC IN THE BRAIN

Anticipation is the key to understanding the effects of music on emotion

by Peter Vuust

Music is an integral part of life's highly pleasurable activities such as having good dinners, dancing, going to the movies and hanging out with friends [1,2]. Music can evoke a range of different emotions including everyday emotions such as happiness, sadness [3], surprise and nostalgia, as well as emotions that are unique to music such as for instance the sensation of swing [4].

Recently, Juslin and Västfjäll tried to establish a framework for understanding how music translates into human emotion[5]. There is certainly a need for a framework to guide the study of the physiological mechanisms underlying the experience of music and the emotions that music evokes. However, this framework should be organised hierarchically, with musical anticipation as its fundamental mechanism as we have recently argued in a number of papers [1,6,7].

Juslin and Västfjäll claim that the study of musical emotions has suffered from a neglect of the underlying psychological mechanisms evoking these emotions and propose that these mechanisms could be summarized as (a) Brain stem reflexes, (b) Evaluative conditioning, (c) Emotional contagion, (d) Visual imagery, (e) Episodic memory, and (f) Musical expectancy. A problem with these categories is that they are not ordered hierarchically, are not mutually exclusive and only category (f), musical expectancy, directly links musical and psychological mechanisms as such. This limits the scope of the proposed framework especially if its purpose is to act as a guideline for experiments trying to identify the brain systems involved in processing musical emotions. We believe that such a framework would be more useful if the mechanisms for evoking musical emotions were organized hierarchically, with musical expectancy as the most fundamental mechanism.

It is hard to imagine that musical emotions are evoked without some sort of musical meaning assigned to what is heard, unless we think of emotions, such as fear, evoked by the mere occurrence of a loud sound. However, in this case it is questionable whether one would define this as music. Most music theoreticians consider musical anticipation as one of the principal means by which music conveys meaning and emotion. According to this point of view, understanding music is related to the anticipatory interplay between local auditory events and a deeper structural layer partly inherent in the music itself, and partly provided by mental structures in the listener induced by the music [4]. In short, the musical

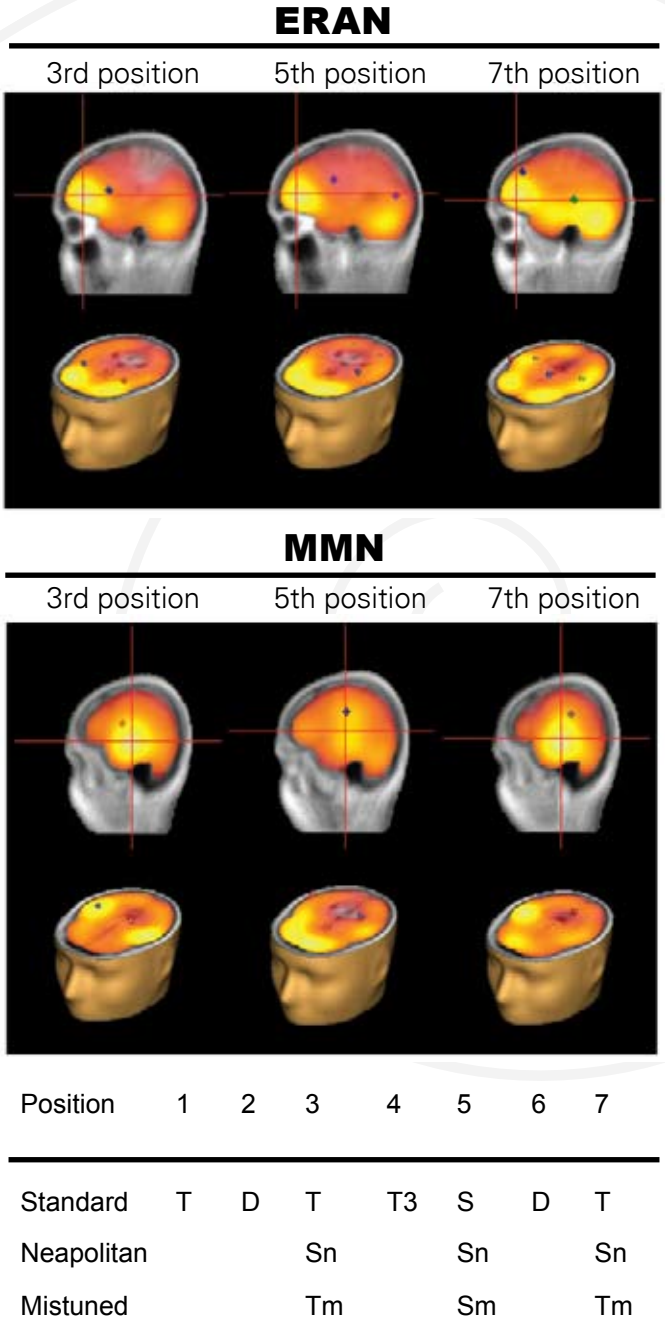


Figure 1
Localization of the early right anterior negativity (ERAN) to Neapolitan subdominants (Sn) and mistuned tonic and subdominant chords (Tm/Sm). The ERAN is a marker of harmonic expectation with primary generators located in the frontal cortex, Brodmann area 44. It relies on anticipatory structures that tracks the hierarchical organization of music. The MMN is elicited by any discriminable change in repetitive auditory input and its primary generators are located in the auditory cortices. Thus, the MMN indexes expectation of a more primitive kind than the ERAN.

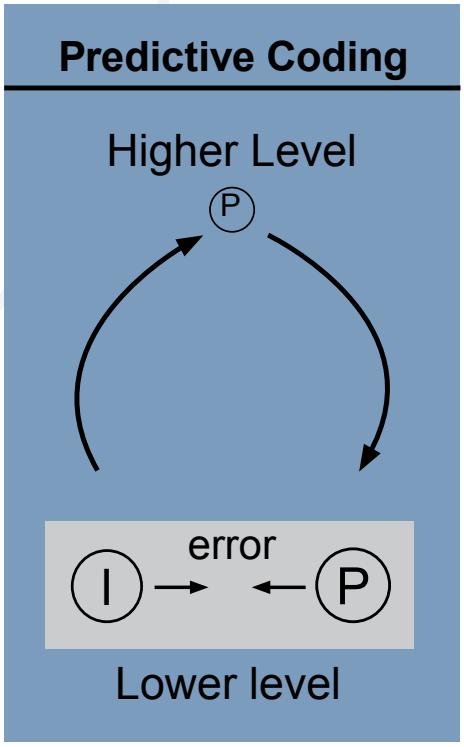
experience is dependent on the structures of the actual music as well as on the expectations of the interpreting brain. These expectations are dependent on long term learning of musical structures (culture dependent statistical learning), familiarity with a particular piece of music, short term memory for the immediate musical history while listening to a musical piece, as well as deliberate listening strategies [8]. Brain structures underlying musical expectation are thus shaped by culture as well as personal listening history and musical training [7,9]. Moreover, as soon as one hears the first sound of a musical piece, structures enabling anticipation such as meter, tonality and memory for particular musical pieces seem to be in place already and unavoidable. Thus, it is difficult to imagine any of the proposed mechanisms acting without the involvement of musical expectation.

Juslin and Västfjäll believe that musical expectation is something that develops slowly over time during listening experience and is not fully developed until the age of 5-11. This may well be correct if musical expectation is restricted to anticipation of complex musical structures such as the hierarchy of harmony (Figure 1) dependent on long term learning see e.g.[10]. However, expectation of the simple repetitive sound patterns, such as pitch deviants in successive pitch trains, has been detected even before birth, as indicated by the mismatch negativity (MMN) measured by EEG/MEG. Moreover, in an elegant study, Winkler et al. showed [11] that the auditory predictive model is updated for each new acoustic event in the sound environment, indicating that the anticipatory structures of music are in constant flux during the listening experience. These results demonstrate that anticipation has a role at many levels in the hierarchy of musical structure.

Juslin and Västfjäll also claim that the degree of volitional influence on musical anticipation is low. However, we recently conducted a study in which musicians were asked to maintain either the main meter or a counter meter while listening to Stings “The Lazarus Heart” [8]. In this experiment the subjects could volitionally imposed two very different anticipatory frameworks onto the music. Deliberately listening to a melody from the perspective of two different tonalities would be another example of volitional control of the anticipatory framework.

The relationship between musical expectancy and emotion was originally explored by Meyer and has recently been elaborated by Huron in his book “Sweet anticipation”. If we consider music expectation/anticipation as the fundamental mechanism for musical experience, then this maps nicely onto recent theories of how the brain works. Karl Friston has provided a promising model of brain function, in which predictive coding, as a central principle of brain function, provides an account of how the brain identifies and categorizes the causes of its sensory inputs. The model posits a hierarchical organization whereby lower level brain regions estimate predictions of their expected input based on contextual information through backwards connections from higher level regions. A comparison between prediction and actual input produces an error term that, if sufficiently large, will be fed back to call for an update of the model. This generates a recursive process, which aims at minimizing the difference between input and prediction. As the representational capacity of any neuronal assembly in this model is dynamic and context sensitive, this, among other issues, addresses the problem of top-down control. Lately, we have argued that processing violations of musical anticipation in different aspects of the music (e.g. rhythm/harmony) evokes different error messages (MMN/early anterior negativity (EAN)) and networks [6,12] (Figure 2). These effects are training dependent and can be explained by the predictive coding theory. Thus, in our opinion, musical expectation is

Figure 2
The predictive coding model: lower level brain regions estimate predictions of their expected input based on contextual information through backwards connections from higher level regions. A comparison between prediction and actual input produces an error term that calls for an update of the model, generating a recursive process, aiming at minimizing the difference between input and prediction, resulting in an updated model with a better chance at predicting future events. This predictive coding theory is a model of perception as well as learning.



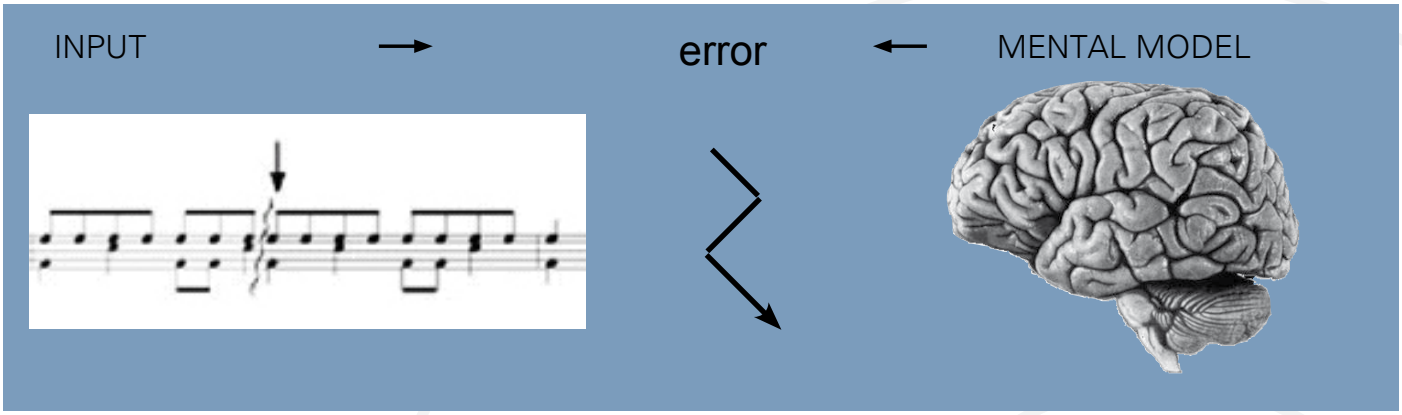


Figure 3
Music creates anticipatory structures that induce an expectational model in the mind of the listener. When these expectations are violated this gives rise to event-related responses such as the MMN, the ERAN and the P3 that can be measured e.g. with EEG or MEG. We suggest that these brain responses is a sign of the predictive coding process, i.e. that the MMN and the ERAN reflect an error term: a mismatch between the brain model and the incoming input and that later responses reflect updating of the model.

a good candidate for the fundamental mechanism guiding the experience of musical meaning as well as emotion. Anticipation in itself may evoke a wealth of emotions such as awe, surprise, discomfort, the sensation of swing etc. According to Huron this is due to a variety of different survival-related responses to anticipation in particular the "prediction response" that rewards fulfilled expectations. However, anticipatory structures such as meter and tonality act indirectly on the other proposed mechanisms in that they form the basis for musical memory as well as for musical meaning.

If we consider the large amount of neuroscientific research on music that has been published in recent years, it is certainly true that studies of musical emotions seem to be pointing in different directions. Consider for instance the somewhat different activation patterns reported in studies of major and minor mode music [3,13] supposedly evoking very simple emotions (happy/sad). Even though these results may be due to many different factors contributing to the emotional state of the subjects under different experimental conditions, we agree with the Justlin and Västfjäll that one of the reasons for these somewhat inconsistent results may be found in the lack of a theoretical framework. However, this framework needs to be organized hierarchically with music anticipation as the guiding mechanism.

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NEW FACE AT CFIN

Eduardo Adrian Garza Villarreal, was born and educated in Monterrey in Mexico. He had an informal education in Arts and Music and took his Medical Doctor degree from the Faculty of Medicine, Autonomous University of Nuevo Leon (Universidad Autonoma de Nuevo Leon), Monterrey, Mexico in 2006. After this he was research assistant in Pediatric Rheumatology at the University Hospital UANL, Monterrey, Mexico in 2007.

Eduardo came to Denmark in 2007 and was employed as a Research Assitant at the Center of Functionally Integrative Neuroscience / University of Aarhus as part of a formal international collaboration between the University of Aarhus and Universidad Autonoma de Nuevo Leon in Mexico.

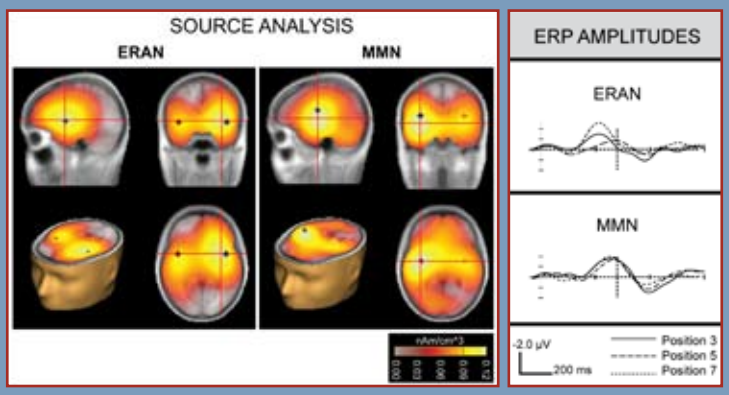
Currently Eduardo is a PhD Student at University of Aarhus / Center of Functionally Integrative Neuroscience & The Royal Academy of Music in the *Music in the Brain* group. His latest research has been about music processing in the brain cortex, in collaboration with the Cognitive Brain Research Unit, University of Helsinki, Finland. Read more about this project below.

Eduardo's interest in research is to investigate how music is processed in the brain, how it evokes memories and emotions, and the possible clinical implications of these findings.

The frontal lobe ERAN and temporal lobe MMN:
two different brain responses to violations in chord progressions.

This project aimed to study the localization of harmony processing of music in the brain cortex as opposed to sound tuning processing. 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. From recent studies we know that the early right anterior negativity (ERAN: a brain response elicited when a harmonically incongruous chord is inserted within or at the end of a musical sequence) reflects the processing of harmony rather than the building of a tonal context, and that the MMN is elicited by violations of the tuning of the sounds upon which harmony is based (Leino et al., 2007). Electroencephalography (EEG) was recorded, and brain electric source analysis (BESA) was performed to localize the sources of cortical processing of MMN and ERAN.

We found that the dominant transcerebral sources for the ERAN were localized in Broca's area and its right homologue, with a left lateralization.The MMN signal was instead localized on the bilateral auditory cortex. These findings demonstrate the predominant role of the auditory cortices in detecting local auditory regularities and of the prefrontal cortex in parsing hierarchical regularities in music.



Knowledge about the neural processing of music is important to a range of different issues including the ongoing debate about the potential transfer effect of music training to other cognitive domains. Clinically, this research may have far reaching consequences for rehabilitation in relation to language disorders, neurosurgery, and cochlear implantees.

MUSIC IN THE BRAIN

Processing of musical chords in the human brain

by Karen Johanne Pallesen

Behavioural observations and functional MRI were used to investigate emotional and cognitive processes during stimulation with major, minor and dissonant musical chords. Musical chords were employed as stimuli to study their experienced emotional salience and the correlated brain activity. The chords were also used as a tool to study the interaction of cognition and emotion in the auditory modality. Moreover, by comparing two subject groups of musicians and non-musicians, the brain activity pattern during both passive perception and cognition as a function of individual differences in competence was studied.

"Happy major" and "Sad minor"

The ability to rate a major chord as more happy than a minor chord appears to be general.

An emotional rating task showed that individuals with a minimum of musical training judged very brief (500 ms) major chords as more happy than minor chords. This shows both that the sound parameters that contain the emotional cues are present in isolated musical sound units, and that these cues are coded also by listeners that do not possess explicit musical knowledge. While passive exposure to the western music culture may also play a role in mediating the non-musicians' judgments, this role may be smaller than assumed in learning-based theories.

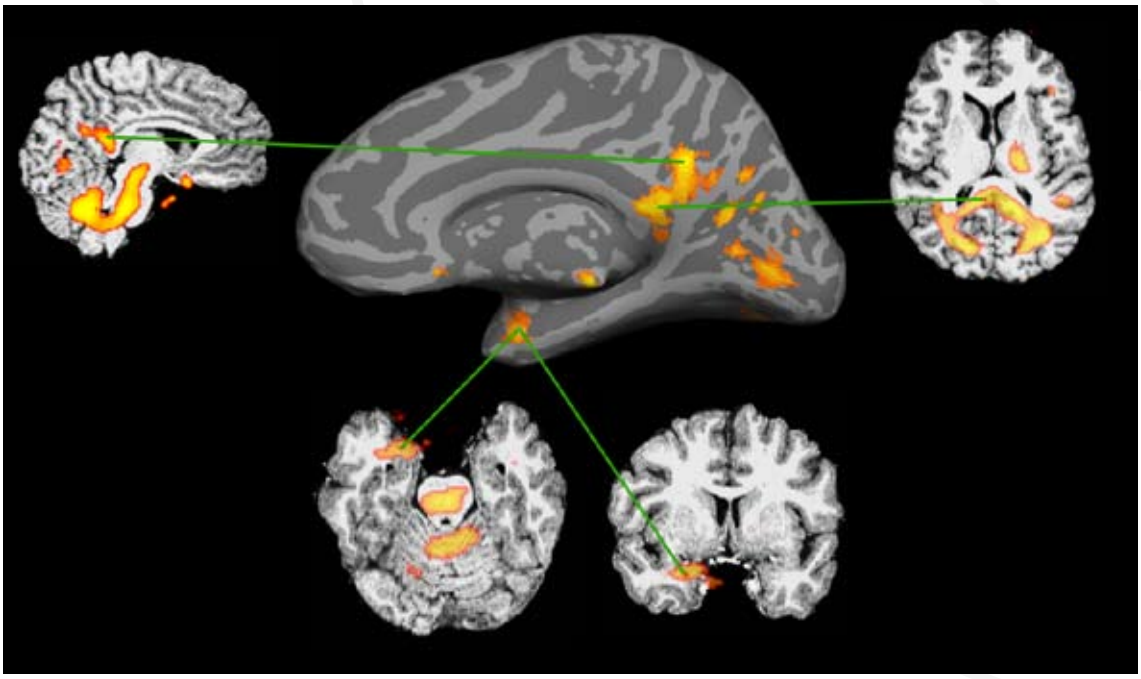
Emotional responses to musical chords are enhanced in the passive listener's brain

Interaction between emotion and cognition demonstrated with musical chords.

Previous studies of visual processing have indicated that cognition down-regulates the processing of emotional stimulus qualities. The current fMRI results showed that the differential emotional connotations of major, minor and dissonant chords were visible in the measured BOLD brain responses only during passive listening, and not when an easy or a difficult cognitive task were imposed on the listener. This finding indicates a strong down-regulating effect of emotional processing during cognition, which may reflect the brain's need to focus its processing resources.

The magnitude of the emotional brain responses to the musical chords during passive listening appeared to be independent of musical training, a finding which may relate to the minimal musical properties contained in a single chord.

Figure 1
BOLD responses which were larger during passive listening to minor chords than during passive listening to major chords, including the amygdala, retrosplenial cortex, brainstem and cerebellum. The areas activated in this contrast were not present during working memory processing. Group results are overlaid on planar sections and inflated cortex of a single individual (corrected for multiple comparisons: $Z > 3.0$, $p < .05$).



From: Karen Johanne Pallesen, Elvira Brattico, Christopher J. Bailey, Antti Korvenoja, Juha Koivisto, Albert Gjedde, Synnöve Carlson (2005). Emotion processing of major, minor and dissonant chords: An fMRI study.
In: Ann N Y Acad Sci, The Neurosciences and Music II: From Perception to Performance 1060, 450-453.

Dissonance counteracts cognitive down-regulation

Processing of unpleasant cues may be upheld in the face of cognitive demands.

By introducing a controlled manipulation of both the cognitive load and the emotional stimulus connotation, the current results confirmed previous findings that the magnitude of the observed task-related decreases depends on the cognitive load. Furthermore, the results indicated that a strong emotional cue may be processed in the brain in spite of a demanding cognitive task. Hence, the task-related decreases commonly observed in structures associated with emotion processing may conversely be counteracted by partly upheld emotional processes.

Do musicians have a general cognitive advantage?

Brain activity during memorization of musical chords indicates a better focus.

A comparison of the BOLD responses measured with fMRI during memorization of the major, minor and dissonant musical chords in groups of non-musicians and musicians showed that musical competence lead to both enhanced behavioural performance and greater brain activity in lateral prefrontal and parietal cortical areas. Rather than enhanced processing and encoding of the musical stimuli, this suggests that musicians possess superior cognitive control skills, possibly achieved via musical training.

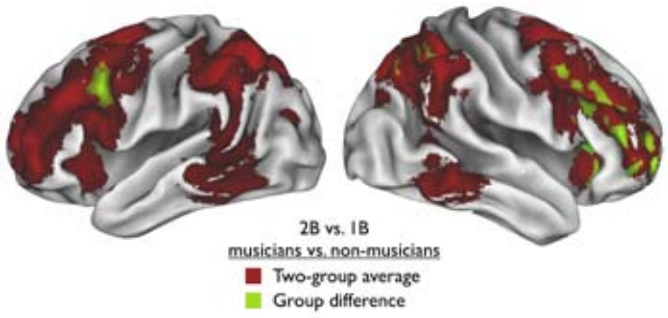


Figure 2
Working memory load-dependent brain responses (2B vs. 1B) differ between musicians and nonmusicians. The group difference image (musicians vs. nonmusicians; green) is overlaid on the across-groups mean response (red), and rendered on the inflated cortical surface of the template brain used for labeling. Both average (red) and difference (green) contrast images were thresholded at Z=3.0 and corrected for multiple comparisons at the cluster level (p<0.05). All colored regions exceed this criterion of significance.
From: Karen Johanne Pallesen, Elvira Brattico, Christopher J. Bailey, Antti Korvenoja, Juha Koivisto, Albert Gjedde, Synnöve Carlson (2007). Auditory working memory is enhanced in musicians: An fMRI study. Submitted.

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MUSIC IN THE BRAIN

Explaining music preferences and -emotions

by Anders Christian Green

Music listening is an everyday activity for virtually everyone in every human culture, past or present, and it is therefore of great interest to explore its psychological and biological roots.

The project investigated key aspects of music listening, such as what happens when we like a piece of music, why we like that particular piece, and what the underlying neural mechanisms of emotional responses in music are. These questions were examined using behavioural experiments as well as fMRI (Green et al., 2008; Green et al., under review).

In the experiments, participants were scanned while listening to short melodies. The melodies were composed especially for the studies, which ensured a large degree of experimental control, and ruled out any previous familiarity with the melodies. (See Figure 1 for two examples).

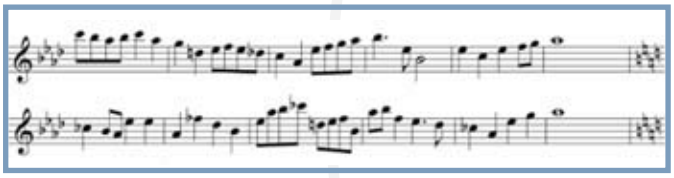

Figure 1
Two examples of melodic stimuli used in the experiments, one melody in Ab major (top), and one in Ab minor (bottom).

The results indicated that musical melodies were able to tap into very fundamental parts of the human brain: A positive subjective evaluation of melodies was found to cause differential brain activation of areas related to the neural reward processing system, including the insula and the dorsal striatum.

The study further asked the question: What causes this differential liking in music listening? In the attempt to answer this question, it was chosen to focus on the effect of systematically varying the degree of prior exposure. Would participants prefer novel or familiar melodies, or perhaps something in between? The results showed that melodies heard the most often were liked best. This is in accordance with the so-called mere exposure effect, which is a well-known psychological phenomenon, but whose neural background remains largely undiscovered until now. The present study is thus the first to elucidate the neural background of the mere exposure effect in music: Previous exposure was shown to cause differential activation mainly of the dorsolateral prefrontal cortex – most likely reflecting the implicit memory and working memory-related processes that subserve the mere exposure effect.

Concerning emotional responses in music listening, it was studied how musical modes – major and minor – caused different neural activation patterns in listeners. Musical mode is known to be a factor in determining emotional responses to music. It was found that minor mode melodies were evaluated as sadder than major melodies, and in comparison they caused increased activity in limbic structures, namely left parahippocampal gyrus, and bilateral ventral anterior cingulate, as well as in left medial prefrontal cortex (Figure 2). Different explanations of the sadness quality linked to the minor mode have been proposed, one of which hinges on the fact, that the minor mode contains more dissonance than major. This possible explanation was addressed in the study,

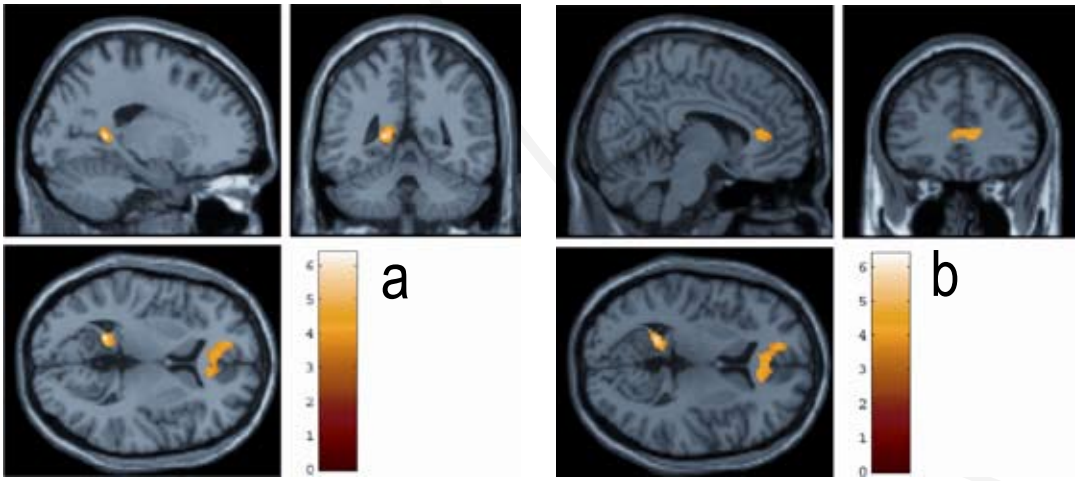

Figure 2
Statistical activation maps of the minor versus major contrast, revealing involvement of the left parahippocampal gyrus (a), and bilateral ventral anterior cingulate, and left medial frontal gyrus (b).
Green et al. Neuroreport 2008.

where it was indicated that the higher degree of dissonance of the minor mode may explain some, but not all, of the activity increase in brain areas engaged specifically by minor mode melodies.

In the future, neuroscience and functional imaging will hopefully continue to uncover the links between music and the brain.

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Green, AC, Bærentsen, KB, Stødkilde-Jørgensen, H, Wallentin, M, Roepstorff, A, Vuust, P. (2008) *Music in minor activates limbic structures: A relationship with dissonance?* Neuroreport, 19, 711-715

Green, AC, Bærentsen, KB, Stødkilde-Jørgensen, H, Roepstorff, A, Vuust, P. *Listen, learn, and like! Dorsolateral prefrontal cortex activation supports an implicit memory-related mere exposure effect in music.* Under review.

NEW FACE AT CFIN

Risto Näätänen, Professor Emeritus at the Academy of Finland, accosiated to Cognitive Brain Research Unit at University of Helsinki, and Professor of Cognitive Neuroscience, University of Tartu, Tartu, Estonia was in June 2008 officially appointed Guest Professor at CFIN / The Clinical Institute, University of Aarhus. Risto Näätänen has a doctorate in Psychology from University of Helsinki in Finland and has been working in the field of cognitive electro physiology – examining the mechanisms of the human brain during auditory stimulation.

Risto Näätänen and his research group discovered the Mismatch Negativity (MMN) in 1978 – an event-related brain response to deviations in repetitive auditory stimulation measured with EEG (electroencephalography) and MEG (magneto encephalography). MMN measurements have far-reaching clinical applications within a wide range of clinical areas of specialisation like audiology, neurology, psychiatry, physiology, psychology and learning. Read more below.

Risto Näätänen has published more than 300 scientific articles and is one of the most cited researchers in brain science worldwide.

The Mismatch Negativity (MMN) in clinical research

The mismatch negativity (MMN) is elicited by any discriminable change in repetitive auditory stimulation even in the absence or attention or behavioural task. Therefore, it can be used to study different patient groups including even comatose patients, and small infants who cannot give reliable bahavioural responses. One of the most important uses of the MMN is in the prediction of coma outcome, where it currently is the best single-measure predictor of the outcome of anoxic coma. Also, in case of vegetative patients, it permits one to monitor the gradual recovery of consciousness and to predict the recovery of cognitive abilities occurring in the next 2 years.

There are approximately 40 studies showing MMN-amplitude attenuation in patients with schizophrenia. Besides abnormal auditory-cortex function, these studies also show the dampening of the frontal-cortex attention-switching mechanism. In addition, the MMN also enables one to monitor the gradual progress of the disease, in particular the decline of cognitive abilities leading to hospitalization.

A further important clinical use of the MMN involves stroke causing aphasia where the MMN can be used to map the loss of auditory function and to monitor latent healing of the brain even during the first days from stroke onset, when reliable behavioural responses cannot yet be obtained.

In addition, the MMN can index the auditory-processing abnormalities in individuals with dyslexia in whom it can also provide an index for the effectiveness of different rehabilitation programs.

In addition to auditory discrimination, the MMN can also index the duration of auditory sensory-memory traces, which might provide a general index of brain plasticity. This duration gradually decreases with aging, which age-related decrease can be expedited by chronic alcoholism, and these traces are especially short in neurodegenerative diseases such as Alzheimer's disease.

Awards and Honours in 2008

Festschrift in Honour of Professor Chris Frith, FRS: "Mind in the Brain".

17 - 18 September 2008 the UCL institute of Cognitive Neuroscience celebrated Chris Frith's unique contribution to psychology and brain imaging with a fantastic event at Royal Society, London. The large lecture hall was packed full, and colleagues and former students came flying in from three continents to pay tribute. The diversity of presentations testifies to the range of ideas, Chris has developed and disseminated. There were examples of computer simulated scizophrenic bird songs, Austrian puppet theatre, bayesian machines in top-top interaction, and a rare video account of the man himself on ketamine: halucinating, yet sensible as ever.

As always, Chris turned the event into a joy- and playful investigation of ideas, probing each speaker with tough questions while wearing new and matching ties for each session: electronic diagrams for the engineers, psychedelic colours for the psychiatrists.

At the two pictures on the right Chris Frith is shown in a couple of these specially selected shirt-and-tie outfits. The pink shirt and red/blue tie with BLAM on it was for the session on schizophrenia, and the blue shirt with the tie with coloured disks was for the session on consciousness.

Photos: Sanne Lodahl

Andreas Roepstorff receives the Rigmor & Carl Holst-Knudsen prize.

Coordinator of cognition research at CFIN, Associate Professor Andreas Roepstorff was awarded with the prestigious Rigmor & Carl Holst-Knudsen Videnskabspris 2008. The Rigmor & Carl Holst-Knudsen Science Prize celebrated its 50th anniversary in 2008 and this year not one but three scientists with connection to University of Aarhus was awarded 75.000 DKK each. Apart from Andreas Roepstorff, Professor Lene Hau (Mallinckrodt Professor of Physics and Applied Physics at Harvard University), and Professor Tim Bollerslev (Professor of Economics at Duke University) received the honour.

Photos: Lars Kruse/AU-foto

The prizes were presented at a reception in the Aula at University of Aarhus on 28 May 2008.

The picture on the left shows:
Rector at University of Aarhus, Lauritz B. Holm-Nielsen, Associate Professor, Andreas Roepstorff, Dean of Faculty of Humanities, Bodil Due, Dean of Faculty of Natural Sciences, Erik Meineche Schmidt, Professor Lene Hau, Professor Tim Bollerslev, and Dean of Faculty of Social Sciences, Svend Hylleberg.

Photo: Robert Taylor

Uta Frith honoured as Women of Outstanding Achievements in science, engineering and technology (SET).

In March 2008 CFIN Guest Professor Uta Frith was honoured by the British organisation UK Resource Centre for Women in Science, Engineering and Technology (UKRC) at UKRC's annual photo exhibition in London.

Professor Uta Frith was chosen as one of six women from 125 nominees by a judging panel from the British world of science, engineering and technology (SET), government and industry for discovery, innovation and entrepreneurship. The aim of the photo exhibition is to create a growing collection of portraits that will act as inspirational images to encourage other women to take part and progress in a career within science, engineering and technology.

University of Aarhus' 80th Anniversary and Annual Celebration

University of Aarhus opened on 11 September 1928, and each year there is a celebration to mark the anniversary of this date. In 2008 the University had its 80th anniversary, and this event was marked with a festive scientific and social program in the University Aula.

HM The Queen Margrethe II, HRH The Crown Prince Frederik, and Professor Uta Frith
Photos: Lars Kruse / AU-foto

Professor Uta Frith from CFIN was asked to be special guest speaker and gave a talk entitled *Autism and the Enigma of Human Communication.* The audience - as always - listened enthusiastically to Professor Friths' talk.

Other awards and honours in 2008

Apart from the awards and honours mentioned above, 2008 was also the year that:

- Chris Frith was elected a fellow of the British Academy.
- Chris Frith received an Award for Outstanding Contribution to British Neuroscience from the British Neuroscience Association.
- Uta Frith was elected Member Deutsche Akademie der Naturforscher Leopoldina.
- Uta Frith was made Honorary Fellow at Newnham College, Cambridge.
- Uta Frith was elected Foreign Member of the Royal Society of Arts and Sciences in Göteborg, Sweden.

Leif Østergaard elected to Det Kgl. Danske Videnskabernes Selskab.

Head of CFIN, Professor Leif Østergaard was elected member of the prestigious Royal Danish Academy of Sciences and Letters early 2008.

The Academy was founded in 1742 to strengthen the position of basic science in Society and foster understanding and interactions across scientific disciplines.

See www.royalacademy.net

CFIN staff

Head of CFIN - Professor Leif Østergaard

Professors:
Doris Doudet
Chris Frith
Uta Frith
Albert Gjedde
Morten L. Kringelbach
Hans C. Lou
Risto Näätänen
Leif Østergaard

Associate professors:
Sune Nørhøj Jespersen
Jakob Linnet
Arne Møller
Andreas Roepstorff
Peter Vestergaard-Poulsen
Peter Vuust
Ona Wu

Senior scientists / Post.docs:
Bhador Bahrami
Daniel Campbell-Meiklejohn
Mallar Chakravarty
Ken Ramshøj Christensen
Brian Hansen
Niels Hjort
Kristjana Yr Jonsdottir
Anne M. Landau
Torben Ellegaard Lund
Irene Klærke Mikkelsen
Malene Vejby Mortensen
Kim Mouridsen
Mette Møller
Thomas Nielsen
Yoshiyuki Nomura
Anders Bertil Rodell
Donald F. Smith
Manouchehr Seyedi Vafaee
Mikkel Wallentin

PhD students:
Joel Fredrik Astrup Aanerud
Mahmoud Ashkanian (PhD degree 05.09.08.)
Christopher Bailey
Per Borghammer (PhD degree 27.03.08.)
Niels Buhl
Mette Buhl Callesen
Søren Christensen (Melbourne)
Anders Dohn
Jesper Frandsen
Jacob Geday
Anders Christian Green (PhD degree 12.12.08.)
Louise Gyldensted
Yi Ching Lynn Ho (Singapore)

CFIN Retreat at Sandbjerg Manor, 15 - 17 September 2008.
Photos: Henriette Blæsild Vuust

Birgitte Fuglsang Kjølby
Sita Ramchandra Kotnis
Sanne Lodahl
Kartheeban Nagenthiraja
Karen Johanne Pallesen (PhD degree 24.11.08.)
Esben Thade Pedersen (Singapore)
Bjørn Petersen
Ericka Peterson
Uffe Schjødt
Kamila Ewa Sip
Joshua Charles Skewes
Astrid Frøhlich Staanum (PhD degree 11.08.08.)
Christine Sølling (PhD degree 29.04.08.)
Kristine Rømer Thomsen
Louise Munk Rydtoft
Kristian Tylén, Guest Researcher
Eduardo Adrián Garza Villarreal
Mads Sloth Vinding
Ethan Weed

Research year students:
Adjhmal Nahimi (Research Year defense in December 2008)
Erik Søndergaard Poulsen

Thesis students:
Morten Friis-Olivarius
Rune Vingborg

Research Assistants:
Martin Carlsen
Martin Dietz
Mette Frøslev
Line Gebauer Josefsen
Ivana Konvalinka
Anders Bay Neumann
Elisabeth Pedersen
Victoria Wohlert

Technical Staff:
Michael Geneser, Radiographer
Kim Vang Hansen, Imaging Analyst
Jørgen Kold, Imaging Analyst
Poul Erik Nielsen, System Administrator
Lars Riisgaard Ribe, Software Engineer
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

Following a strong sense of synergy and wish to extend collaborations during the grant-writing proces early 2008, this years CFIN retreat was extended to include researchers involved in the MIND*Lab* application. With the subsequent funding, we look forward to future, inspiring late-summer interactions during the intense scientific and social program at Sandbjerg Manor.
Photo: Sanne Lodahl

Facts about CFIN

Invited lectures

Leif Østergaard:

- *Diffusion and Perfusion Weighted MRI.* SMRT Regional Seminar in Denmark, Society for Magnetic Resonance Technologist, 29 February 2008.
- *Perfusion ved Stroke: Teknik og Fysik.* Vejle, Danish Society for Magnetic Resonance, 26 March 2008.
- *Novel Approaches to Acute Stroke Imaging - and Stroke Therapy Development.* Keynote speaker. Singapore, National Neuroscience Institute, 11 April 2008.
- *Stroke Imaging: The need for standardization.* Keynote speaker. Advanced Neuroimaging Workshop., Japan, 14 April 2008.
- *Stroke MRI: New Approaches. The European I-Know Project.* Keynote speaker. Tokyo, 14 April 2008.
- *Brain Imaging in Acute Stroke.* Keynote speaker. Stroke: From Molecule to Rehabilitation, Norway, The Research Council of Norway, NevroNor, 17 April 2008.
- *New Developments in Stroke MRI.* Keynote speaker. Neuroradiologie Aktuell, Germany, Verein zur förderung der neuroradiologischen Wissenshaft und Fortbildung, 25 April 2008.
- *Perfusion Imaging.* ESMRMB School of MRI, European Society for Magnetic Resonance in Medicine and Biology, Bern, 30 May 2008.
- *Perfusions- og diffusions-MR ved akut stroke: De seneste udviklinger.* Keynote speaker. Annual Meeting, Sweden, Nordic Society for Neuroradiology, 12 June 2008.
- *Om hjerneforskning og forskningsstøtte i et tværdisciplinært og tværinstitutionelt forskningsmiljø.* Administrativ Efteruddannelse af Universitetsansatte: Administration af EU-projekter, Universitetsdirektørudvalgets Efteruddannelsesudvalg, 1 September 2008.
- *Musik i hjernen.* Seminar, Institute of Microbiology and Immunology, 2 September 2008.
- *Can Neuroimaging Help Us Discriminate between Diseases of the Ageing Brain?* 5th Congress of European Union Geriatric Medicine Society, European Union Geriatric Medicine Society, Copenhagen, 4 September 2008.
- *Tværdisciplinær Forskning.* Aarhus, IT-Vest, 11 September 2008.
- *Hjerneforskning: Fra Fysik og Musik til Patientbehandling.* University of Aarhus, 80th Anniversary, Faculty of Health Sciences, 12 September 2008.
- *Hvordan bliver vi klogere? Og gør det os gladere?* Herlev, Hjortespring Søndagsskole, 21 September 2008.
- *Imaging of Brain and Spine: The Stroke.* Visions for the Future of MRI, Berlin, Bayer Schering Pharma, 26 September 2008.
- *Få styr på din Hjerne: Hjernen og Musik.* Aarhus, Folkeuniversitetet i Aarhus, 29 October 2008.

Albert Gjedde:

- *Neuroimaging: On the past, present and future of neurons.* Meeting in Danish Society for Neurorehabilitation, University of Southern Denmark. February 2008.
- *Am I my Brain?*, Brain Week 2008, Copenhagen. March 2008.
- *The Brain and Sexuality*, Tarup Ungdomsskole. April 2008.
- Lecture on *Schizophrenia*, European Medical Research Council, London. April 2008.
- *PET study of cerebrometabolic effects of non-ionising radiation from mobile telephones*. Eigtveds Pakhus, Copenhagen. May 2008.
- Lecture on *Brain Imaging*. Vejlefjord. May 2008.
- *Imaging the Curse of Monoamines*. Vancouver General Hospital. June 2008.
- *What we know and don´t know about the brain*. Aabenraa Højskole. July 2008.
- *From receptor availability to receptor reactivity*. Neuroreceptor Mapping 2008, Pittsburgh. 17 - 19 July 2008.
- *The Brain can predict - especially the Future*, University of Aarhus. September 2008.
- *The Brain can predict - especially the Future.* Youth Organisation for Natural Science, Aarhus. October 2008.
- *Power, Sex and Suicide.* NeuroCluster, Værløse. October 2008.
- *Hepatic Encephalopathy*. Staff Meeting, Aarhus Hospital. October 2008.
- *Walk together, talk together; Evidence from Brain Research*. Aarhus. October 2008.
- *Consciousness in the Brain.* Folkeuniversitet, Aarhus. November 2008.
- *How Mumbo Jumbo Conquered the (Western) World.* Education day for the Human Resource Department at Aarhus Hospital. November 2008.
- *What we know and don´t know about the brain.* Annual General Meeting, Rungsted Society, Christiansborg Slotskirke. November 2008.
- *Mitochondria; power, sex and suicide.* Department of Nuclear Medicine, Rigshospitalet, Copenhagen. December 2008.

Andreas Roepstorff:

- *Interacting Minds*, CCC Seminar, University of Aarhus, Aarhus, Denmark, 4 April 2008.
- *Scanning identities*, ENSN, Our Brains Our Selves. Historical and Ethnographic Approaches to the new Brain Sciences, USA, 2 May 2008.
- *Netværksviden*. Takketale ved Rigmor og Carl Holst Knudsen's videnskabspris, University of Aarhus, Denmark, 28 May 2008.
- *To lie or not to lie: deception as contextual decision making* (with Kamila Sip), Social and Affective Neuroscience, Boston, USA, 7 June 2008.
- *Cultural Influences on the Development of Embodied Attention*, The Enculturated Body: Scales of Embodied Meaning in Communication, 26 June 2008.

- *The brain and nothing but the brain. How should anthropology relate to the new neurosciences?*, Ton Otto & Nils Bubandt, Holism, 4 July 2008.
- *Theory of Mind in the Brain (not theory of "mind in the brain)*, CNCC, Social Cognition and Social Narrative, San Marino, SM, 7 July 2008.
- *Relating Brain Scans and Experience. Conceptual tool boxes*, CFIN, CFIN-MIND*Lab* retreat, Sandbjerg Manor, Denmark, 16 September 2008.
- *Bayesian Machines in top-top interaction, Mind in the Brain.* Festschrift in Honour of Chris Frith, London, UK. 17 September 2008.
- *Presentation of the thematic report/programme proposal "Understanding and Misunderstanding: Cognition, Mind and Culture"* , Vetenskapsrådet, Sverige, 'Understanding and Misunderstanding: Cognition, Mind and Culture' – A scoping workshop by HERA, ESF and VR , Uppsala, Sweden, 24 September 2008.
- *Challenges and the ideal world*, Vetenskabsrådet, Sverige, 'Understanding and Misunderstanding: Cognition, Mind and Culture' – A scoping workshop by HERA, ESF and VR , Uppsala, Sweden, 25 September 2008.
- *An Anthropologist's View on Consciousness*, Marc Raichle, Brain, Agency, Self, Intersubjectivity and Consciousness (BASIC) Initiative Workshop, St. Louis, USA, 24 October 2008.
- *Can we find ourselves in the scanner? Cognitive Neuroscience and its Impact on Self and Other*, J. Scott Jordan, Institute for Prospective Cognition, Virtually Human: Science, Arts and the 21st Century Self, USA, 27 October 2008.
- *Evolution, Udvikling og Materialitet*, Research Day, Denmark, 5 November 2008.
- *Hjernens Betydning (The meaning of the Brain)*, Folkeuniversitetet i Aarhus, Denmark, 5 November 2008.

Arne Møller:
- *PET-centret, Aarhus University Hospital & CFIN, Aarhus University.* Cambridge, The Division on Addictions, Health Alliance, 16 January 2008.
- *De små grå*. Hinnerup Kulturhus, Aarhus, Gigtforeningen, 8 March 2008.
- *De små grå.* Marselisborg Center, Aarhus, Gigtforeningen, 26 April 2008.
- *Hjerneforskning i ludomani: Kampagne om ludomani - unge og spil.* DR-byen, Copenhagen, Støttegruppen i København og Center for Ludomani i Kbh., 21 October 2008.

Peter Vuust:
- *Polyrhythmic structures in Music.* Oxford University, Psychiatric Department, 11 February 2008.
- *Functional Magnetic Resonance Imaging in new music research.* Skejby, MR-centret, 29 February 2008.
- *Musikalsk udvikling.* 5 March 2008.
- *Research at the Academy of Music.* Finland, Sibelius Akademiet, 13 March 2008.
- *It Don't Mean a Thing,...? - Musik og hjerne.* CVU Nordjylland, 27 March 2008.
- *Musik og hjerne.* 27 March 2008.
- *Hold hjernen i form med musik.* Gigtskolen i Århus, Gigtforeningens oplysningskreds, 29 April 2008.
- *Music in the Brain.* Copenhagen, Det Kgl. Danske Musikkonservatorium, 7 May 2008.
- *Professor tiltrædelsesforelæsning: Hjerneforskning på Det Jyske Musikkonservatorium: nu og i fremtiden.* Det Jyske Musikkonservatorium, 15 May 2008.
- *Musik som bevæger.* Copenhagen, Fitness.dk, 30 May 2008.
- *Musikkens påvirkning af følelser, motorik og sprog.* Vingsted-centret, 9 June 2008.
- *Hjerne, kreativitet og læring.* Gråsten, Dansk Oplysningsforbund, 17 June 2008.
- *Kunsten at blive god til at skabe - om hjerne og musik.* Testrup Højskole, 18 August 2008.
- *Perceiving music where there is none.* Aarhus Universitets Kursuscenter, Sandbjerg, CFIN, 16 September 2008.
- *Things, that make you go . . . hmm.* Sensecamp, Senselab, Delta, 24 September 2008.
- *It Don't Mean a Thing.* Studenterhuset, Aarhus, FOF, 21 October 2008.
- *Musikkultur og kommunikation: Musik, øvelsespraksis og hjernen.* Det Jydske Musikkonservatorium, 23 October 2008.
- *Musik som bevæger.* Herning Messecenter, DGI, 25 October 2008.
- *Minisymfonikerne: Musikkens betydning for de 0-6 årige.* Keynote speaker. Fora, Odense Symfoniorkester, 27 October 2008.
- *Things that make you go... hmm.* Lydens magt - et kommunikativt potentiale, Tekne, 29 October 2008.
- *Musik som udvikler og kommunikerer.* Keynote speaker. Trivsel i ledelse, Aarhus skolelederforening/Børn og Unge i Aarhus, 30 October 2008.
- *Developing a Strategy for Research in Teaching and Learning in a Music Academy.* AEC Congress, Association Européenne des Conservatoires, Académies de Musique et Musikhochschulen, 7 November 2008
- *Musik og hjerneforskning.* Forskningskursus, 12 November 2008.
- *It Don't Mean a Thing . . ., or Does it?* Mozart & Science Congress 2008, Austria, 17 November 2008.
- *Neural Processing of Polyrhythmic Structures in Music.* Keynote speaker. Montreal, BRAMS - Université de Montreal, 19 November 2008.
- *Musik og hjerneforskning, om børns musikalske udvikling fra 0-12 år.* Keynote speaker. Børnekulturtopmøde, Køge Kommune, 4 December 2008.

Chris Frith:

- *Making up the mind: How the brain creates out mental world.* Brighton Science Festival, Brighton, UK, 1 March 2008.
- *Social cognition: The group versus the individual*. Keynote speaker, Social and affective Neuroscience Meeting, Boston, 6 June 2008.
- *False perceptions or false beliefs? A Bayesian resolution*. Institute of Psychiatry, London, 19 June 2008.
- *Hallucinations and Delusions: The price we pay for our creative brains*. University of Bergen, 21 June 2008.
- *Problems with the awareness and control of action*. Physiological Society, Cambridge, 15 July 2008.
- *Is there evidence of free will in Passingham's research?* Festschrift for Dick Passingham, Wadham College, Oxford, September 2008.
- *Social Interactions: Why do we Cooperate?* Exciting Biologies 2008: Biology of Cognition, Chantilly, France, MGH - Fondation IPSEN - Cell, 17 October 2008.
- *Interacting minds: Why do we cooperate and how?* Department of Experimental Psychology, University of Bristol, 12 November 2008.

Uta Frith:

- *Causal modelling: A framework for understanding dyslexia*. Bergen University, Logopedisk avdeling, Statped Vest, Seminar: Ut med språket!, 19 May 2008.
- *Dyslexia: comparing different theories. A contest between the currently favoured theories dyslexia. One comes out as the clear winner.* Bergen University, Logopedisk avdeling, Statped Vest, Seminar: Ut med språket!, 19 May 2008.
- *Progress from a historical point of view.* Inaugural Conference in the Dame Stephanie Shirley Lecture Series, Prior's Court, Berkshire, 12 June 2008.
- *Confessions of a cognitive psychologist.* Memory & Language Development Across the Lifespan: A festschrift for Philip T. Smith. Experimental Psychology Society and European Society for Cognitive Psychology, University of Reading, Holland House, 2 - 3 July 2008.
- *Autism and the Enigma of Human Communication.* Special guest speaker at University of Aarhus 80th Anniversary Meeting, 12 September 2008.
- *What autism teaches us about social cognition*. John Damien Lecture Stirling University, 9 October 2008.
- *Lettura magistrale: Problematiche dell'autismo, i disturbi pervasivi e la sindrome di Asperger. La teoria della mente.* Evento "L'AUTISMO OGGI: Lavoro con Famiglia, Scuola, in Rete. Esperienze e gruppi di lavoro", Genova, 23 - 24 October 2008

Uta & Chris Frith:

- *Autism and the Social Brain*. Convegno Internazionale Autismo dall'età evolutiva ai giovani adulti. Centro Congressi di VILLA MARIGOLA della Cassa di Risparmio della Spezia LERICI. 25 October 2008.
- *Salience of social stimuli in autism spectrum disorders*. Robert Sommer Award Symposium: The Neurobiology of Salience, Giessen University, 7 - 8 November 2008.
- *Social Cognitive Neuroscience: Where is it heading?* Psychology Department, Nottingham Uiniversity,14 May 2008.

Morten Kringelbach:

- *Sensory and social pleasures*, Research day, Department of Psychiatry, University of Oxford, 9 January 2008.
- *Brain pleasures*, Department of Psychiatry, University of Oxford 9 January 2008.
- *Phantom brains*, St Barnabas Primary School, 9 January 2008.
- *Social reward*, Academic Forum, John Radcliffe Hospital, 13 February 2008.
- *Deep brain stimulation and pleasure*, PhD course, Copenhagen, Denmark, 22 May 2008.
- *Deep brain stimulation for pain*, NIH workshop 'Pain and the elderly', USA, 1 July 2008.
- *Looking for pleasure in the human brain*, EOS, Spain, 18 July 2008.
- *Nydelse i hjernen*, DPU, Denmark, 28 August 2008.
- *Nydelse i den følelsesfulde hjerne*, Silkeborg Seminarium, Denmark, 3 September 2008.
- *A life without pleasure: mechanisms of a depressed brain*, BA Festival, Liverpool, UK, 10 September 2008.
- *Pleasures of the brain: sensory processing related to food intake*, ZEM meeting, Stuttgart, Germany, 11 September 2008.
- *The pleasure of music*, CFIN retreat, Denmark, 16 September, 2008.
- *A sense of space*, Dana Centre, London, 9 October, 2008.
- *Nydelse og begær*, Femina Livsstilsmesse, Denmark, 25 October 2008.
- *Den nydelsesfulde hjerne*, Brædstrup, Denmark, 4 November 2008.
- *Direct recordings of social reward in the human anterior cingulate cortex*, SFN Washington, USA, 17 November 2008.
- *The pleasure center*, MBA, Oxford, 29 November 2008.

Risto Näätänen

- *The Mismatch Negativity (MMN) as an index of auditory memory.* I.O.P. 2008, St. Petersburg, Russia. 8 -13 September 2008.
- *Welcoming Address of the Vice-President (Academic Affairs) at the Opening Ceremonies of the 14th World Congress of Psychophysiology*, I.O.P., 2008, St.Petersburg, Russia, 8 September 2008.
- *The Mismatch Negativity (MMN) in clinical research.* ASPR (Australasian Society for Psychiatric Research) Conference, Newcastle, Australia, 2 - 5 December 2008.

Doris Doudet

- *In vivo Imaging in Animal Models of Neurodegenerative Diseases: Where Are We Now?* World Molecular Imaging Congress 2008, Nice, France. 10 – 13 September 2008.
- *Clinical effects and PET imaging of human retinal pigment epithelial cells on gelatin microcarriers (hRPE-GM) (Spheramine®) versus gelatin microcarriers alone (GM) implanted in MPTP-treated primates.* American Academy of Neurology 60th Annual Meeting, Chicago, USA. 12 - 19 April 2008.

Kim Mouridsen:

- *DSC-MRI: Nuts and bolts about deconvolution.* Keynote speaker. ISMRM, 2008, Toronto, Canada, 3 May 2008.
- *Multispectral Imaging Used as Voxel-Based Predictor for Disease Outcome.* Keynote speaker. Trondheim, Medical Imaging Laboratory, Norwegian University of Science and Technology, 20 November 2008.

Jakob Linnet:

- *Pathological Gambling: Dopaminergic neurotransmission and cognitive biases.* University of British Columbia (UBC), Department of Neurology, 19 February 2008.

Mikkel Wallentin:

- *ENHED?- hjerneforskning, kunst og ny teknologi- Videnskabscafé.* ARoS - Aarhus Kunstmuseum, Videnskabscaféen (www.vcaf.dk), 23 January 2008.
- *Putative sex differences in verbal abilities and language cortex - a critical review.* David B Pillemer workshop, Aarhus, Anvendelsesorienteret Grundforskning i Hukommelse og Kognition (AGHOK), 6 August 2008.
- *What is it to you? Spatial perspectives in language and brain.* Colloque international la pluralité interpretative. Fondements historiques et cognitifs de la notion de point de vue, 12 June 2008.

Other CFIN researchers:

- Callesen, Mette Buhl. *Pathological Gambling in Parkinson's Disease*. Seventh Annual OAK Meeting for Danish Brain Research Laboratories, Odense, Denmark, 14 June 2008.
- Hansen, Brian. *NMR, MR skanning og hjerneforskning.* University of Aarhus / Aarhus University Hospital, 13 December 2008.
- Ho, YC. *Dissociation of CBF responses corresponding to negative BOLD activity.* ISMRM Scientific Meeting, Toronto, Canada, 3 May 2008.
- Josefsen, Line Gebauer. *Gambling in Denmark: Cognitive bias and neurobiological correlates.* 7th European conference on gambling studies and policy issues, Nova Gorica, Slovenien, The European Association for the Study of Gambling, 3 July 2008.
- Josefsen, Line Gebauer. *Towards DSM V: Classification of Pathological Gamblers.* The Division on Addictions, Cambridge Health Alliance & Harvard Medical School, 22 January 2008.
- Petersen, Bjørn. *Musical eartraining with cochlear implants.* Hotel Ebeltoft Strand, Danaflex, 23 September 2008.

Conferences

Leif Østergaard:

- International Stroke Conference 2008., San Francisco, 20 - 22 February 2008.
- International Society for Magnetic Resonance in Medicine 16th Scientific Meeting, Toronto, 4 - 9 May 2008.
- European Stroke Conference, Vienna, 12 - 16 May 2008.
- Forskningsledernetværket FL1. 3 - 4 June 2008.
- Virtual Physiological Human Concertation Day. Brussels. 22 October 2008.
- ICT-BIO. Brussels, 23 - 24 October 2008.

Albert Gjedde:

- White Paper Briefing Conference, European Medical Research Council, Frankfurt, Germany. 29 - 30 January 2008.
- European Commission, 7th Research Framework Programme, Brussels. February 2008.
- Nordic Research Council, Oslo, Norway. March 2008.
- European Medical Research Council, London. April 2008.
- Human Brain Mapping, Melbourne, Australia. 20 - 24 June 2008.
- Vice Chair – Gordon Conference, New Hampshire, USA. 17 - 22 August 2008.
- Neuroinformatics Meeting , Stockholm, Sweden. 7 - 9 September 2008.
- Nordic Medical Research Council, Riga. September 2008.
- European Medical Research Council, Strasbourg. October 2008.
- American College of Neuropsychopharmacology General Meeting, USA. December 2008.

Arne Møller:

- 7th European Conference on Gambling Studies and Policy Issues. 1 - 4 July 2008.
- Health risks from non-ionising radiation due to mobile telephony. 1 January - 27 May 2008.
- Ledelse - nærvær og fravær. 27 February 2008.
- Seventh Annual OAK Meeting: Danish Brain Research Laboratories Meeting Odense, 13 - 14 June 2008.
- The pedunculopontine nucleus implications for surgical pratice & Parkinson's patients. 18 April 2008.

Peter Vestergaard-Poulsen:
- International Society for Magnetic Resonance in Medicine annual meeting, May 2008, Toronto, Canada.
- Cardiff University Brain Research Imaging Centre (CUBRIC), School of Psychology, Cardiff University. ESMRMB course in DWI.
- Institute for Clinical and Experimental Medicine (IKEM), Prague, Czech Republic. ESMRMB course in MRS.

Andreas Roepstorff:
- European Neuroscience and Society Network: Our Brains, Our Selves workshop, 30 November - 1 December 2008, Aarhus, Denmark.
- Global Minds, 28 - 29 November 2008, University of Aarhus, Denmark.
- From Change to Innovation. Workshop at Megaseminar 2008: Problems of change and continuity, 14 - 16 January 2008, Sandbjerg, Denmark.

Peter Vuust:
- Research Course at The Royal Academy of Music. 3 September - 19 November 2008.
- International Conference on Music Perception and Cognition X, Hokkaido Univeristy, Sapporo, Japan. 23 - 29 August 2008.
- Neuromusic III, Montreal, Canada. 24 June - 1 July 2008.

Other CFIN researchers:
- Jespersen, Sune Nørhøj. Advanced MR Imaging Symposium & Workshop. 12 August 2008. Organizer.
- Jespersen, Sune Nørhøj. International Society for Magnetic Resonance in Medicine (ISMRM) annual meeting, May 2008, Toronto, Canada.
- Linnet, Jakob. Introduction to the SCID-I: CFIN/PETC SCID training program 10 - 12 December 2008.
- Lund, Torben E. *Filtering Resting State fMRI*, Morning Workshop at the 14th Anual Meeting of the Organization for Mapping of the Human Brain, Melbourne, Australia. June 2008.
- Näätänen, Risto. 10th International Conference on Cognitive Neuroscience (ICON) 1 - 5 September 2008, Bodrum, Turkey.
- Wallentin, Mikkel. International Workshop on Social and spatial perspective taking. 26 - 28 February 2008.

Radio / TV / newspress

CFIN researchers have participated in the following in 2008:

Leif Østergaard
- *Eliteforsker 2008: Leif Østergaard.* dk4, 19 March 2008.
- *Patenter og virksomheder vælter ud af dansk grundforskning.* Kasper Frandsen. Altinget | Forskning & Innovation, 27 May 2008.

Albert Gjedde
- *The Brain and Sexuality*. By Birgitte Dalgaard, P1 Apropros, DR Østjylland. January 2008.
- *Addiction.* TV 2 Østjylland. February 2008.
- *Fra Berkeley til Berlin* (*From Berkeley to Berlin*), Morgenavisen Jyllands-Posten, Feature article, 23 April 2008.

Arne Møller
- *Ludomani.* (by Ib Schou). DR Radio - P4, 9 January 2008.
- *Medicin kan hjælpe ludomaner: Lovende resultater fra århusianske forskere kan blive første skridt til medicin mod ludomani. Det vil forbedre og forkorte behandlingen af nogle ludomaner.* Ekstra Bladet.dk, 4 February 2008.
- *Århus-forskere er klar med pillen mod spilletrang: Spilleforskere i Århus er førende i verden. Hjerneforskere har fokus på ludomani. Parkinson-medicin kan udløse ludomani. Dopamin er hjernens kokain.* Morten Svith & Birgitte Krøyer. Århus Stiftstidende, 4 February 2008.
- *Ludoman.* Ritzaus Bureau, 4 February 2008.
- *Ludomani.* Aarhus Stiftstidende, 4 February 2008.
- *Medicin kan hjælpe ludomaner: Lovende resultater fra århusianske forskere kan blive første skridt til medicin mod ludomani..* Ritzau. Urban, 5 February 2008.
- *Ludoman.* TV 2 News, 5 February 2008.
- *Ludoman.* Ekstra Bladet, 5 February 2008.
- *5 millioner kroner til forskning i ludomani: Når spilleautomaten tager magten.* Parkinson Nyt, 3 March 2008.
- *11.687 risikerer spilletrang.* (by Christine Brasch Andersen & Thomas Gösta Svensson). Ekstra Bladet, 5 March 2008.
- *Medicin gør dig spilleglad: Medicin mod Parkinsons sygdom kan gøre dig afhængig af spil.* I dag får mere end 11.500 danskere medicinen, der kan blive en rigtig dyr fornøjelse. Ekstra Bladet, 5 March 2008.
- *Pokerhjerner: Poker minder os om livet.* Kim Lykke Vester. Pokermagasinet ace, 32-35, 12 May 2008.
- *Pille mod ludomani: Forskningsresultater kan være første skridt mod ludomani-medicin.* Ritzau. MetroXpress, 27 May 2008.
- *Parkinson og Ludomani.* TV2, TV Syd, 14 December 2008.
- *Parkinson og Ludomani.* DR Radioavisen, 14 December 2008.
- *Parkinson og Ludomani.* DR, Regionalradio P4, 14 December 2008.
- *Parkinson og Ludomani.* Jyllandsposten, 15 December 2008.

Andreas Roepstorff
- *Hurtigere, højere, stærkere - og klogere med smart drugs (Faster, taller, stronger - and wiser with smart drugs)*, Information, 30 May 2008.
- *Formiddag på 4'eren*, DR P4, 22 October 2008.
- *Praxis*, TV2, 27 October 2008.

Chris Frith

- Scientific Adviser, BBC 2 series on alternative medicine, 2008. *Hypnotherapy*, 17 March; *Reflexology*, 24 March; *Meditation*, 31 March.
- Main Stage Talk, *Making up the Mind*. Brighton Science Festival, 1 March 2008.
- *Zum Irren Geboren*. Interview with Steve Ayan in Gehirn & Geist, April, 2008, pp 42-44.
- Café Scientifique in Bishops Stortford, *Making up the mind*. 12 May 2008.
- Institute for Cultural Research, *Making up the Mind: How the brain creates our mental and social worlds*. 15 November 2008.
- *Don't think about it*. New Scientist 199, 77-77.

Peter Vuust

- *Se det i ørerne*. Troels Donnerborg. Fyens Stiftstidende, 13 January 2008.
- *Dung dung dung*. Troels Donnerborg. Fyens Stiftstidende, 13 January 2008.
- *Enetime: Pust liv i sangstemmen.* Julie Elver. Politiken, 26 January 2008.
- *Musikalsk hviletid.* Danni Travn. Nordjyske Stiftstidende, 27 January 2008.
- *Hav det godt. DR*, 13 February 2008.
- *Nordjysk Debat.* Jesper Knox Sørensen. DR P4, 28 February 2008.
- *Hjerne swingninger.* JP Aarhus, 31 May 2008.
- *Forskere finder kreativiteten.* Politiken, 6 June 2008.
- *Hjerneforskning: Jazzmusikere lukker for selvkontrollen*, 6 June 2008.
- *P1-morgen.* P1 - DR, 4 July 2008.
- *Stemme: 'Sprog og musik er som en cykel og en motorcykel'*. Dagbladet Information, 15 September 2008.
- *Levende lørdag: Levende korsang.* DR P4, 15 November 2008.

Morten Kringelbach

- Newstalk Ireland (Sean Moncrieff), 28 February 2008. Interview on pleasure in the brain (5 min).
- Canada AM, 3 March 2008. Live Canadian morning TV on baby faces (5 min).
- DR P3 Mondo, 6 March 2008. Interview on baby faces.
- Canada Discovery Channel (Kim Jagtiani), 17 March 2008. Interview on baby faces.
- Deutsche Welle Radio (Kateri Jochum), 11 April 2008. Interview om Flocka and baby faces.
- TV DR2 Tema aften (Jens Birkholm), 3 August 2008. Interview on adrenalin hunters and addiction in the brain.
- TV Avisen, DR, (Jakob Illeborg), 2 october 2008. Headline news on Deep Brain Stimulation.
- Go'Morgen Danmark, TV2, (Jakob Illeborg), 3 october 2008. Pleasure in the brain.
- Deadline 22.30, DR, (Jakob Rosenkrandtz), 3 October 2008. Pleasure in the brain.
- DR P1 Sex (Susanna Sommer), 25 october - 21 November 2008. Five radio programs on sex.
- JP-radio, (Hanne Bærentzen), 10 November 2008. Interview on pleasure.
- DR P1 Agenda, (Louise Witt-Hansen), 22 November 2008. Interview on beautiful and ugly faces

- Betty Nansens Teater, *Lystens Hjerne*, (Morten Kringelbach), 1 January 2008.
- Reuters, *Study sheds light on parental instinct* (Michael Kahn), 27 February 2008.
- Discovery Channel, *Adult Brains Wired to Go Ga-Ga Over Babies* (Jennifer Viegas), 27 February 2008.
- Canadian Press, *You've got the cutest little baby face* (Sheryl Ubelacker), 27 February 2008.
- The Daily Telegraph, *Babies faces make us want to care for them* (Nic Fleming), 27 February 2008
- Washington Post, Daily Telegraph, The Mirror, and many others worldwide, 28 February 2008.
- Politiken, *Babyer får vores hjerner til at smelte* (Jeanette Ringkøbing), 28 February 2008.
- Jyllands Posten, *Hjernen har et blødt punkt for babyer* (Louise Andreasen), 3 March 2008.
- Io e il mio bambino, *Che cosa stimola l'istinto genitoriale?* (Francesca Capelli), 4 March 2008.
- Jyllands Posten, *Klæbehjerne på kommando* (Louise Andreasen), 6 March 2008.
- Le Monde de l'enfance, *L'attirance pour des visages de bébé : un instinct universel plus que maternel* (Valerie Buron), 1 April 2008.
- Wall Street Journal, *At the Sight of a Baby* (Robert Lee Hotz), 4 April 2008.
- The Psychologist Magazine, *Identifying the cuteness response* (Christian Jarrett), 1 May 2008.
- Scientific American Mind, *Study sheds light on parental instinct* (Aimee Cunningham), 1 May 2008.
- Fyens Stiftstidende, *Kærligheden får os til at knokle* (Malene Birkelund), 5 May 2008.
- Readers' Digest, *Questions about pleasure* (Cynthia Dermody), 11 July 2008.
- videnskab.dk, *Måtte slås for at blive hjerneforsker* (Sybille Hildebrandt), 14 August 2008.
- videnskab.dk, *Jagten på nydelse styrer alt hvad vi laver* (Sybille Hildebrandt), 14 August 2008.
- Berlingske, *Professor i nydelse* (Lone Theils), 27 September 2008.
- Aarhus Stiftstidende, *Professor i nydelse* (Lone Theils), 28 September 2008.
- Information, *Vore basale behov er mad, sex og andre mennesker* (Mads Qvortrup), 10 October 2008.
- Femina, *Nydelse er hjernens drivkraft* (Margrethe Vadmand), 16 October 2008.

- Grazia Magazine, *La cioccolata? Fa bene al cervello* (Deborah Ameri), 28 November 2008.
- Politiken, *Nu er det nu* (Nils Thorsen), 31 December 2008.

Other CFIN researchers
- Frith, Uta. BBC Radio programme Case Study on The Wild Boy of Aveyron. Producer: Marya Burgess
- Frith, Uta. *En gåde langt fra afklaring.* (by Jeanette Ringkøbing). Politiken, 13 January 2008.
- Wallentin, Mikkel. *DR/P1 Apropos: Lykken som eufori.* (by Connie Aagaard & Mikkel Krause). DR P1, 5 February 2008.

Boards / Committees

CFIN researchers are involved in the following:

Leif Østergaard
- Expert reviewer, A. I. Virtanen Institute for Molecular Sciences. 1 October - 31 December 2008.
- External Expert, Academy of Finland. 1 February - 30 April 2008.
- Member, Royal Danish Academy for Sciences and Letters (Det Kongelige Danske Videnskabernes Selskab). From September 2008.
- Member, Forskningsledernetværket FL1. From December 2007.
- Member, Nomination Committee, International Society for Magnetic Resonance in Medicine. 1 June 2008 - 1 May 2009.
- Scientific Evaluator, Swiss National Science Foundation. 28 March - 28 April 2008.

Albert Gjedde
- Chairman, Kongelige Biblioteks vejledende forskningsråd, 1 August 2006 - 31 July 2011.
- Member, Forskningsrådet for Sundhed og Sygdom, 1 August 2005 - 30 July 2011.
- Executive council member, European Dana Alliance for the Brain, From 1 January 2001.
- Deputy member – Udvalget vedrørende videnskabelig uredelighed.

Andreas Roepstorff
- Member, Steering Committee, A Topological Approach to Cultural Dynamics, From 1 July 2008.
- Member, Programstyret: ELSA program for bioteknologi, nanoteknologi og kognitive videnskaber, From 1 August 2007.
- Member, Bedømmelsesudvalg, ELSA-Fuge projekter, Norwegian Research Counsil, 1 August - 1 November 2008, Norway.
- Member, Steering Committee, Neuroscience an Society Network (ENSN), 24 April 2007 - 31 December 2011.
- 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.

Uta Frith
- Member, Advisory Panel for an ESRC/MRC funded Large Grant on *Social Interaction: A Cognitive Neurosciences Approach* Glasgow University (26 November 2008 Committee meeting)

Risto Näätänen
- Director of PENS Spring School “Models in neuroscience: turning experiments into knowledge”, St. Petersburg, Russia, 2008.
- First Vice President 2004 - present of International Organization of Psychophysiology (IOP).
- Member of Editorial boards:
  - International Journal of Psychophysiology
  - Audiology and Neuro-Otology
  - Clinical Neurophysiology
- Editor of International Journal of Psychophysiology.

Hans C. Lou
- Member, Editorial board, Acta Paediatrica
- Member, Prize Committee Philis Foundation, Stockholm, Sweden
- Member of board, Elsass Foundation, Copenhagen, Denmark
- Meritorious member, Child Neurology Society, USA.
- Associate Fellow, Queens College, Oxford.

Peter Vestergaard-Poulsen
- Staff-student committee for Biomedical Engineering, Clinical Institute, University of Aarhus.

Peter Vuust
- Chairman, Forskningsudvalget ved Det Jyske Musikkonservatorium. From 1 August 2005.
- Member, Kulturministeriets forskningsudvalg. From 1 January 2008.

Teaching

- Gjedde, Albert. *Tissue autoradiography of blood flow and glucose metabolism*. Brain Energy Metabolism and Blood Flow course, Panum Institute, Copenhagen. April 2008.
- Gjedde, Albert. *The Imperial GSK PET Course*, Imperial College, London. April 2008.
- Gjedde, Albert. Course in imaging techniques. Vejle Fjord. May 2008.

- Gjedde, Albert. *PET in clinical pharmacological research*. PhD course, Research in pharmacotherapy, University of Aarhus. September 2008.
- Gjedde, Albert. *Imaging the Curse of the Monoamines*. LUNDBECK, Copenhagen. October 2008.

- Jespersen, Sune Nørhøj. Lectures for visiting physics classes in high school. From 1 December 2007.
- Jespersen, Sune Nørhøj. Organizer of course in biophysics under the education in Biomedical Engineering.
- Jespersen, Sune Nørhøj. Teaching biophysics, a PhD course on MRI, MR1, MR2 and MR3.

- Lund, Torben E. Teaching fMRI at MR3 course under the education in Biomedical Engineering.
- Lund, Torben E. Organizor of course Statistical Parametric Mapping of NeuroImaging data.

- Roepstorff, Andreas. Kognitiv hjerneforskning. PhD course in cognition research, 9 December 2008, Odense, Denmark.

- Vestergaard-Poulsen, Peter. Organizing a course in Biophysics/ Neurophysics under Biomedical Engineering.
- Vestergaard-Poulsen, Peter. Teaching in: Biophysics / Neurophysics; PhD course in Magnetic Resonance Imaging, MR1, MR2 and MR3. Lecturer for visiting high school students.

- Vuust, Peter. Coordinator, Music in the Brain. From 1 August 2007.

- Østergaard, Leif. External Referee. 1 November - 15 December 2008. Medical Research Council, Great Britain.

Research stays abroad

- Hansen, Brian. Six month postdoc studies at The McKnight Brain Institute, University of Florida, USA. 1 October 2007 - 1 April 2008.
- Josefsen, Line Gebauer. Research stay at the Division on Addictions, Cambridge Health Alliance & Medical School. 1 August 2007 - 1 February 2008.

Scholarships & awards (see also page 53)

- Jespersen, Sune Nørhøj. Kornings Foundation, 12.000 Dkr.
- Josefsen, Line Gebauer. Traveling Scholarship from The Oticon Foundation. 1 August 2007 - 1 February 2008.
- Josefsen, Line Gebauer. Traveling Scholarship from The Vilhelm Kiers Foundation. 1 August 2007 - 1 February 2008.
- Poulsen, Erik Søndergaard, Research Year Student. First prize for best poster and best oral presentation at Kongres for Medicinsk Studenterforskning, Sandbjerg Manor, 12-14 September 2008.
- Østergaard, Leif. The Minister of Science, Technology and Innovation's EliteForsk-prize 2007. Copenhagen, Denmark. 24 January 2008.

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, G. Sorensen)
- 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
- Lauren Steward, Psychology Department, Goldsmiths, University of London
- 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, Denmark
- Nordic Neurolab, Bergen, Norway
- GlaxoSmithKline, Cambridge, England
- Schering AG, Berlin, Germany
- GE Medical Systems, Milwaukee, U.S.A.

Completed PhD theses, 2008

- Per Borghammer, M.D. *Perfusion and Metabolism PET Studies in Parkinson's Disease.* 27 March 2008.
- Christine Sølling, M.D. *Organization and Impact of MRI-based Selection Criteria before Thrombolytic Treatment in Acute Stroke.* 29 April 2008.
- Astrid Frøhlich Staanum, M.Sc. *Diffusion in Biological Tissue: A Theoretical Approach.* 11 August 2008.
- Mahmoud Ashkanian, M.D., B.Sc.(Eng). *Carbogen Inhalation Increases Oxygen Transport to Brain Tissue.* 5 September 2008.
- Karen Johanne Pallesen, M.Sc. *Processing of musical chords in the human brain studied with fMRI.* 24 November 2008.
- Anders Christian Green. *Cognitive Neuroscience of Music: Brain activity related to liking, the mere exposure effect, and emotional responses in music perception.* 12 December 2008.

Completed Master theses, 2008

- Morten Friis-Olivarius. *Improvisation - A Neural Foundation in Creativeness.*
- Mads Sloth Vinding. *Optimal Control Theory in MRI on 2D Spatial-Selective Excitation Pulses - a feasibility study*.
- Louise Munk Rydtoft. *High-field MR Studies of Alzheimer's Disease in Transgenic Mice*.

CFIN Friday Seminars 2008

CFIN seminar coordinators:
Associate Professor Arne Møller,
Communications Coordinator Henriette Blæsild Vuust.
Read more at: http://www.cfin.au.dk//cfinseminars

Spring seminars:
- Rikke Fast: *The Forgetful Dog - an update on PhD project*
- Leif Østergaard & Albert Gjedde: *CFIN and DNC*
- Pernille Bruhn: *Anticipation: a neurocognitive investigation of its basic principles*
- Risto Näätänen: *The mismatch negativity (MMN) in clinical research*
- Yi Ching Lynn Ho: *Differentiating the subtle nature of CBF responses to diverse physiological challenges*
- Anette Chemnitz Hansen and Thomas Schmidt: *Commercialisation of reserach results through patenting and technology transfer*
- Lars Ribe and Leif Østergaard: *News on web mail and presentation of Researcher ID*
- Lauren Stewart: *When all the Songs Sound the Same: Insights into the Musical Brain*
- Anne Birgitte Lindgren & Inge Andresen: *Research Support Office*
- Mette Buhl Callesen: *Pathological Gambling in Parkinson's Disease*
- Jesper Schmidt: *Hearing and Hearing related disorders in Professional Musicians*

Fall seminars:
- Donald F. Smith: *Mysteries and Fallacies of Functional Brain Mapping*
- Anne Sabers: *Treatment with antiepileptic drugs in pregnancy: a therapeutic dilemma*

- Tae-Hee Cho & Marc Hermier: *I-Know / Stroke Imaging*
- Hanna Järnum: *Advanced cerebral 3T MRI*
- Suzan Dyve: *Pre-operative functional mapping of neurosurgical patients: a discussion of patient-benefit*
- Christopher Bailey: *High-field fMRI and electrophysiological studies in rodents*
- Niels Tommerup: *Genome Research*

CFIN Retreat 2008

The annual CFIN Retreat was held at Sandbjerg Manor 15-17 September 2008. This year's program was:

MIND*Lab* presentations
- Sten Vikner: *Cognition, Language and Music*
- Armin Geertz: *Cognition and Religion*
- Dorthe Berntsen: *Memory and cognition*
- Raben Rosenberg: *Cognition: A Psychiatrists Perspective*

Tool-Box I
- Torben E. Lund: fMRI: *Blobs, Synchronicity and beyond.*
- Ocke-Schwen Bohn: *Experimental paradigms in perception research.*
- Armin W. Geertz / Andreas Roepstorff: *Looking at Language. Cognition and religion: An anthropological view.*

PhD students – session 1
Coordinator: Andreas Roepstorff
- Ethan Weed: *Getting the message right: the role of the right cerebral cortex in pragmatic inference.*
- Sita Kotnis: *The brain as battlefield. An ethnographic study of the military use of neuroscience.*
- Joshua Skewes: *Agency and intersubjectivity in a neurophenomenological context.*

PhD students – session 2
Coordinators: Sten Vikner, Dorthe Berntsen, Armin Geertz, Andreas Roepstorff
- Anne Mette Nyvad: *Sætningsknuder i teoretisk og neurolingvistisk perspektiv.*
- Sanne Lodahl: *The Self-Organising Brain; Context & Interaction.*
- Uffe Schjødt: *BOLD Response to receiving prayers is modulated by performer's social status.*
- Osman Kingo: *Object individuation and concept formation in infancy.*

Tool-Box II
- Albert Gjedde: *PET and Neurotransmitter detection.*
- Dorthe Berntsen: *Measuring phenomenal qualities of memory and imagination.*

PhD students – session 3
Coordinators: Arne Møller, Albert Gjedde
- Mette Buhl Callesen: *Parkinson's Disease and Pathological. Gambling.*
- Ericka Peterson: *Mastering your PhD.*

Tool-Box III
- Kim Mouridsen: *Neuroinformatic tools.*
- Brian Hansen: *High Field MR Microscopy.*

PhD students – session 4
Coordinators: Leif Østergaard, Peter Vestergaard-Poulsen, Kim Mouridsen, Sune Jespersen
- Mads S. Vinding: *Optimal Control Theory and MR Imaging.*
- Louise Rydtoft: *Ultra-High-Field MR Studies of Neurite Density and Plaque Deposition in an Alzheimer's Disease Mouse Model.*
- Niels Buhl: *Simulating and modeling the diffusion signal in a single neuron.*
- Kartheeban Nagenthiraja: *Prediction models in acute stroke.*
- Jesper Frandsen: *Fiber Tracking.*

Tool-Box IV
- Morten Kringelbach: *MEG*
- Peter Vuust: *Perceiving music where there is none*

PhD students – session 5
Coordinator: Peter Vuust
- Eduardo Garza: *The frontal ERAN and temporal MMN.*
- Bjørn Petersen: *Reestablishing speech understanding through musical ear training after CI.*
- Anders Dohn: *Absolute Pitch.*

CFIN researchers Kristine Rømer Thomsen and Peter Vuust participating in the Berlin Marathon 2008
Photo: Henriette Blæsild Vuust

2008 Publications

Peer reviewed articles:

Ashkanian, M; Borghammer, P; Gjedde, A; Østergaard, L; Vafaee, M. (2008) *Improvement of brain tissue oxygenation by inhalation of carbogen.* Neuroscience, 156, 932-8

Berridge, KC; Kringelbach, ML. (2008) *Affective neuroscience of pleasure: reward in humans and animals.* Psychopharmacology (Berl);199: 457-80.

Borghammer, P; Jonsdottir, KY; Cumming, P; Østergaard, K; Vang, K; Ashkanian, M; Vafaee, M. S.; Iversen, P; Gjedde, (2008) A. *Normalization in PET group comparison studies - the importance of a valid reference region.* NeuroImage; 40, 529-40

Borghammer, P; Vafaee, MS; Østergaard, K; Rodell, A; Bailey, C; Cumming, P. (2008) *Effect of memantine on CBF and CMRO2 in patients with early Parkinson's disease.* Acta Neurologica Scandinavica; 117, 317-23

Christensen, S; Calamante, F; Hjort, N; Wu, O; Blankholm, AD; Desmond, P; Davis, S; Østergaard, L. (2008) *Inferring origin of vascular supply from tracer arrival timing patterns using bolus tracking MRI.* J Magn Reson Imaging; 27, 1371-81

Frith, C; Frith, U. (2008). *Implicit and explicit processes in social cognition.* Neuron, 60, 503-510

Frith, C; Singer, T. (2008) *The role of social cognition in decision making.* Philosophical Transactions of the Royal Society of London. Biological Sciences; 363(1511), 3875-3886

Frith, C. (2008) *In praise of cognitive neuropsychiatry.* Cognitive Neuropsychiatry; 13, 1-7 (Commentary/Editorial)

Frith, C. (2008) *Social cognition*. Philos Trans R Soc Lond B Biol Sci, 363(1499), 2033-2039

Frith, C; Frith, U. (2008) *The self and its reputation in autism*. Neuron; 57, 331-2 (Commentary/Editorial)

Frith, C. (2008) *Social cognition: hi there! here's something interesting*. Curr Biol, 18, R524-525 (Commentary/Editorial)

Frith, U. (2008) *Neuropsychological studies of Autism Spectrum Disorders.* Japanese Journals of Neuropsychology; 24

Frith, U. (2008) *Q & A. Uta Frith.* Curr Biol, 18, R451-453 (Commentary/Editorial)

Frith, U. (2008) *... with Uta Frith.* Psychologist, 21, 88-88. (Commentary/Editorial)

Frith, U. (2008) *Foundations of sand?* Psychologist, 21, 900-900 (Commentary/Editorial)

Gilbert, SJ; Bird, G; Brindley, R; Frith, CD; Burgess, PW. (2008) *Atypical recruitment of medial prefrontal cortex in autism spectrum disorders: an fMRI study of two executive function tasks.* Neuropsychologia, 46, 2281-2291

Gjedde, A. (2008) *Functional brain imaging celebrates 30th anniversary*. Acta neurologica Scandinavica, 117, 219-23. (Editorial)

Green, AC; Bærentsen, KB; Stødkilde-Jørgensen, H; Wallentin, M; Roepstorff, A; Vuust, P. (2008) *Music in minor activates limbic structures: a relationship with dissonance?* NeuroReport; 19, 711-715

Hall, N; Gjedde, A; Kupers, R. (2008) *Neural mechanisms of voluntary and involuntary recall: A PET study.* Behavioural Brain Research; 186, 261-72

Hjort, N; Wu, O; Ashkanian, M; Sølling, C; Mouridsen, K; Christensen, S; Gyldensted, C; Andersen, G; Østergaard, L. (2008) *MRI detection of early blood-brain barrier disruption: Parenchymal Enhancement predicts focal hemorrhagic transformation after thrombolysis.* Stroke; 39, 1025-8

Ho, YC; Vidyasagar, R; Shen, Y; Balanos, GM; Golay, X; Kauppinen, RA. (2008) *The BOLD response and vascular reactivity during visual stimulation in the presence of hypoxic hypoxia.* Neuroimage; 41, 179-88

Hohwy, J; Roepstorff, A; Friston, K. (2008) *Predictive coding explains binocular rivalry: an epistemological review*, Cognition, 108, 687-701

Kienast, T; Siessmeier, T; Wrase, J; Braus, DF; Smolka, MN; Buchholz, HG; Rapp, M; Schreckenberger, M; Rösch, F; Cumming, P; Gruender, G; Mann, K; Bartenstein, P; Heinz, A. (2008) *Ratio of dopamine synthesis capacity to D2 receptor availability in ventral striatum correlates with central processing of affective stimuli.* Eur J Nucl Med Mol Imaging; 35, 1147-58

Kilner, JM; Frith, CD. (2008) *Action observation: inferring intentions without mirror neurons.* Curr Biol. 18, R32-3 (Commentary/Editorial)

Korsholm, K; Madsen, KH; Frederiksen, JL; Rowe, JB; Lund, TE. (2008) *Cortical neuroplasticity in patients recovering from acute optic neuritis.* NeuroImage; 42, 836-44

Kringelbach, ML; Lehtonen, A; Squire, S; Harvey, AG; Craske, MG; Holliday, IE; Green, AL; Aziz, TZ; Hansen, PC; Cornelissen, PL; Stein, A. (2008) *A specific and rapid neural signature for parental instinct.* PLoS ONE; 3, 1664

Kringelbach, ML; Aziz, TZ. (2008) *Sparking recovery with brain "pacemakers"*. Scientific American Mind, 6, 36-43

Kringelbach, ML; Vuust, P; Geake, J. (2008) *The pleasure of reading.* Interdisciplinary Science Reviews 33, 321-335

Lerche, S; Brock, B; Rungby, J; Bøtker, HE; Møller, N; Rodell, A; Bibby, BM; Holst, JJ; Schmitz, O; Gjedde, A. (2008) *Glucagon-like-peptide-1 inhibits blood-brain glucose transfer in humans.* Diabetes; 57, 325-31

Näätänen, R. (2008) *Mismatch negativity (MMN) as an index of central auditory system plasticity.* International Journal of Audiology, 47 (Suppl. 2): S16-S20

Nielsen, T; Mouridsen, K; Maxwell, RJ; Stødkilde-Jørgensen, H; Østergaard, L; Horsman, MR. (2008) *Segmentation of dynamic contrast enhanced magnetic resonance imaging data.* Acta. Oncol; 47, 1265-70

Nielsen, T; Murata, R; Maxwell, RJ; Stødkilde-Jørgensen, H; Østergaard, L; Horsman, MR. (2008) *Preclinical Studies to Predict Efficacy of Vascular Changes Induced by Combretastatin A-4 Disodium Phosphate in Patients.* Int. J. Radiat. Oncol. Biol. Phys; 70, 859-66

Overgaard, M; Fehl, K; Mouridsen, K; Bergholt, B; Cleeremans, A. (2008) *Seeing without seeing? Degraded consciousness in a blindsight patient.* PLoS ONE; 3(8):e3028

Renfrew, C; Frith, C; Malafouris, L. (2008) *Introduction. The sapient mind: archaeology meets neuroscience.* Philos Trans R Soc Lond B Biol Sci; 363(1499), 1935-8 (Commentary/Editorial)

Roepstorff, A. (2008) *Things to think with: words and objects as material symbols,* Philosophical Transactions of the Royal Society B, 363, 2049.

Roepstorff, A; Kotnis, S. (2008) *Neurosecurity, a question of technology or cosmology?*, Bulletin of the Atomic Scientist, August 2008 (http://www.thebulletin.org)

Schjødt, U; Stødkilde-Jørgensen, H; Geertz, AW; Roepstorff, A. (2008) *Rewarding Prayers*, Neuroscience Letters, 443, 165-168

Silani, G; Bird, G; Brindley, R; Singer, T; Frith, C; Frith, U. (2008). *Levels of emotional awareness and autism: an fMRI study.* Soc Neurosci, 3(2), 97-112

Sip, KE; Roepstorff, A; McGregor, W; Frith, C. (2008) *Detecting deception: the scope and limits.* Trends in Cognitive Sciences; 12, 48-53

Sip, KE; Roepstorff, A; McGregor, W; Frith, C. (20089 *Response to John-Dylan Haynes: There's more to deception than brain activity.* Trends in Cognitive Sciences; 12, 127-128 (Commentary/Editorial)

Smith, D; Hansen, S; Jakobsen, S; Bender, D; Audrain, H; Ashkanian, M; Stork, B; Minuzzi, L; Hall, H; Rosenberg, R. (2008) *Neuroimaging of mirtazapine enantiomers in humans.* Psychopharmacology; 200(2), 273-9

Spinks, JA; Näätänen, R; Lyytinen, H. (2008) *In Memoriam: Evgeny Nikolaevich Sokolov (1920-2008).* Psychophysiology, 45, 883-885

Staanum, AF; Jespersen, SN; Østergaard, L; Kiselev, VG (2008) *The effect of impermeable boundaries of arbitrary geometry on the apparent diffusion coefficient.* J. Magn. Reson; 194, 128-35

Sterzer, P; Frith, C; Petrovic, P. (2008) *Believing is seeing: expectations alter visual awareness.* Current Biology; 18, R697-R698

Sørensen, LC; Maroun, LL; Borch, K; Lou, HC; Greisen, G. (2008) *Neonatal cerebral oxygenation is not linked to foetal vasculitis and predicts intraventricular haemorrhage in preterm infants.* Acta Paediatr. 97, 1529-34

Takasawa, M; Jones, PS; Guadagno, JV; Christensen, S; Fryer, TD; Harding, S; Gillard, JH; Williams, GB; Aigbirhio, FI; Warburton, EA; Østergaard, L; Baron, JC. (2008) *How reliable is perfusion MR in acute stroke? Validation and determination of the penumbra threshold against quantitative PET.* Stroke; 39, 870-7

Vuust, P; Frith, C. (2008) *Anticipation is the key to understanding music and the effects of music on emotion.* Behavioral and Brain Sciences; 31, 599-600 (Commentary/Editorial)

Vuust, P; Roepstorff, A. (2008) *Listen up! Polyrhythms in brain and music.* Cognitive Semiotics; 3, 134-58

Vuust, P. (2008) *Den musikalske hjerne : Al menneskelig aktivitet sætter sig spor i hjernen, og musikalsk læring kan også spores i visse dele af hjernen.* KOGNITION & PÆDAGOGIK, nr. 70

Wallentin, M; Frith, C. (2008) *Language is shaped for social interactions, as well as by the brain : Commentary on Christiansen & Chater: Language as shaped by the brain.* Behavioral and Brain Sciences; 31, 536-537 (Commentary/Editorial)

Wallentin, M; Østergaard, L; Weed, E; Mouridsen, K; Roepstorff, A. (2008) *Accessing the mental space - Spatial working memory processes for language and vision overlap in precuneus.* Human Brain Mapping; 29, 524-532

Wallentin, M; Roepstorff, A; Burgess, N. (2008) *Frontal eye fields involved in shifting frame of reference within working memory for scenes.* Neuropsychologia; 46, 399-408

Weed, E. (2008) *Looking for Beauty in the Brain.* Estetika: The Central European Journal of Aesthetics; 1, 5-23

Weed, E. (2008) *Theory of Mind Impairment in Right Hemisphere Damage: A Review of the Evidence.* International Journal of Speech-Language Pathology; 10, 414-424

Wintermark, M; Albers, GW; Alexandrov, AV; Alger, JR; Bammer, R; Baron, JC; Davis, S; Damaerschack, B; Derdeyn, CP; Donnan, GA; Eastwood, JD; Fiebach, JB; Fisher, M; Furie, KL; Goldmakher, GW; Hacke, W; Kidwell, CC; Kloska, SP; Köhrman, M; Koroshetz, W; Lee, TY; Lees, KR; Lev, MH; Liebeskind, DS; Østergaard, L; Powers, WJ; Provenzale, J; Schellinger, P; Silbergleit, R; Sorensen, AG ; Wardlaw, J; Wu, O; Warach, S. (2008) *Acute stroke imaging research roadmap.* Am. J. Neuroradiol; 29, 23-30

Wintermark, M; Albers, GW; Alexandrov, AV; Alger, JW; Bammer, R; Baron, JC; Davis, S; Demaerschalk, B; Derdeyn, CP; Donnan, GA; Eastwood, JD; Fiebach, JB; Fisher, M; Furie, KL; Goldmakher, GV; Hacke, W; Kidwell, CC; Kloska, SP; Köhrmann, M; Koroshetz, W; Lee, TY; Lees, KR; Lev, MH; Liebeskind, DS; Østergaard, L; Powers, WJ; Provenzale, J; Schellinger, P; Silbergleit, R; Sorensen, AG; Wardlaw, J; Wu, O; Warach, S. (2008) *Acute stroke imaging research roadmap.* Stroke; 39, 1621-8

Books and book chapters:

Kringelbach, ML. *Den nydelsesfulde hjerne. Nydelsens og begærets mange ansigter.* Gyldendal, 2008.

Kringelbach, ML. *The Pleasure Center. Trusting your animal instincts.* Oxford University Press, 2008.

PhD Theses:

Ashkanian, M. *Carbogen Inhalation Increases Oxygen Transport to Brain Tissue.* University of Aarhus, 2008.

Blicher, J. *Excitability changes in the central nervous system in relation to motor trainng and recovery after stroke.* 2008.

Borghammer, P. *Perfusion and Metabolism PET Studies in Parkinson's Disease.* 2008.

Green, AC. *Cognitive Neuroscience of Music: Brain activity related to liking, the mere expossure effect, and emotional responses in music perception.* 2008.

Pallesen, KJ. *Processing of musical chords in the human brain studied with fMRI.* 2008.

Staanum, AF. *Diffusion in Biological Tissue: A Theoretical Approach.* 2008.

Sølling, C. *Organization and Impact of MRI-based Selection Criteria before Thrombolytic Treatment in Acute Stroke.* 2008.

Posters:

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CFIN researcher Irene Klærke Mikkelsen is flying high during the ISMRM conference in Toronto, Canada. May 2008.

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CFIN Funding & Bibliometry

by Leif Østergaard

CFIN maintained a large degree of external funding in 2008, amounting to over DDK 25 million, with the Danish National Research Foundation as its largest, single funding source. The Central Denmark Region and the University of Aarhus supports CFIN research and running costs, although general reductions in the Central Denmark Regions budget resulted in reductions in CFIN staff. With less than five permanently funded positions from the Central Denmark Region and the University of Aarhus (out of over 80 employees), employment of young central research leader talents in tenure track positions remain a central strategy in the in the consolidation of CFIN in MIND*Lab*.

Funding Source	DKK 2008	Total 2001-2014
Danish National Research Foundation	9.576.500	83.865.000
Public Grants	12.518.412	133.746.765
Private grants	4.991.475	54.576.414
Major Equipment (MR, PET, MEG)		73.500.000
Central Denmark Region	4.931.235	
University of Aarhus	5.967.727	
Total	**37.985.349**	**345.688.179**

Figure 1
Funding Source 2001-2014 (DKK)

Measurable outcomes of public and private support to our research come in several forms: Education of young, aspiring researchers and PhD students, new high-level courses within Aarhus University, publications in prestigious journals, and new knowledge and research-driven innovation that currently change the diagnosis and treatment of major neurological and psychiatric diseases. We hope this annual report has demonstrated CFINs efforts and success within these areas of dissemination.

Table 2 below shows the impressive growth in publications by CFIN researchers in international journals, with an increasing proportion in influential, high-impact journals. While external funding and the number of scientific employees (PhD students, post. docs. and academic staff) has grown linearly since CFIN was founded in 2001, several factors contribute to the increase observed in 2008: The prestigious Niels Bohr professorship awarded to the Interacting Minds project in 2006 has brought Chris Frith and Uta Frith, both extremely productive scientists, to CFIN. The project, coordinated by Andreas Roepstorff and funded by the Danish National Research Foundation, has already resulted in numerous new collaborations and publications in prestigious, high-impact neuroscience journals such as Neuron, Current Biology, Trends in Cognitive Sciences and Behavioral and Brain Sciences. The Tryg Foundation Research group and Professor Risto Näätänen, with the collaborations they bring to strong functional neurosurgery and MEG research environments in Oxford and Helsinki, have further contributed to the increased scientific publications. Importantly, interdisciplinary researchers and research themes developed during the first CFIN funding circle have now matured to increase future publication quality: The time interval from recruitment of a thesis or PhD student to final, scientific result generally takes 3-4 four years of training, experimental work and data analysis – followed by another year until publications appear in print. While this explains the modest publication increases 2001-2006, we expect to see increases in publication rate and quality as a result of increased graduate and postdoctoral student numbers in recent years.

Acknowledging the challenges of measuring and benchmarking scientific quality (especially with research that bridge scientific disciplines) attention to metrics of excellence is crucial to attract and maintain public and private funding: Future funding of University activities will be distributed according to quality indicators in an attempt to increase Danish competitiveness in a global knowledge economy. See:
http://fi.dk/site/forside/forskning/den-bibliometriske-forskningsindikator.

CFIN and the MIND*Lab* collaboration continuously monitor publication rate and quality relative to internal performance goals.

Impact Factor	2001	2002	2003	2004	2005	2006	2007	2008
Impact Factor 0-1	6	4	12	8	8	3	13	8
Impact Factor 1-3	8	10	8	9	13	15	12	16
Impact Factor 3-5	7	6	6	5	8	13	8	16
Impact Factor 5-7	5	5	7	3	5	7	9	6
Impact Factor 7-	0	2	2	0	3	2	6	11
Total	26	27	35	25	37	40	48	57

Table 2
Publication Impact Factor

Journal Impact Factor

The Journal impact factor, used above, is a measure of the citations to science and social science journals. It is frequently used as a proxy for the importance of a journal to its field. Impact factors are calculated each year by for over 6000 science and social science journals.

The impact factor of a journal is calculated based on a two-year period. It can be viewed as the average number of citations in a year given to those papers in a journal that were published during the two preceding years. For example, the 2008 impact factor of a journal would be calculated as follows:

> A = the number of times articles published in 2006-7 were cited in indexed journals during 2008
>
> B = the number of "citable items" (usually articles, reviews, proceedings or notes; not editorials and letters-to-the-Editor) published in 2006-7
>
> 2008 impact factor = A/B
> (note that the 2008 impact factor is published in 2009, because it can not be calculated until all of the 2008 publications had been received.)

A convenient way of thinking about it is that a journal that is cited once, on average, for each article published has an IF of 1 in the expression above.

Measuring long-term impact of research – and researchers

The long term impact of scientific work published as articles is assessed by carefully monitoring the number of citations the articles receives by other scientist who acknowledge the importance of important, earlier work in the field by citing specific articles in their own publications.

The citation elite: ISI Highly Cited

The number of citations is also to some extent a measure of scientific influence of a researcher: The total number of citations to the articles written by a subject is hence taken as a strong indicator of scientific contribution, since it is derived from pattern of interaction among millions of published articles.

ISI HighlyCited.com identifies researchers whose collected publications have received the highest number of citations world-wide across the past two decades. Highly Cited Researcher are hence among the 250 most cited researchers for their published articles within a specific time-period.

We are proud to have two ISI Highly Cited researchers within neuroscience as part of the CFIN group: Chris D. Frith and Risto Näätanen. Every day, 4 articles citing their work are published – 61.714 citations in total.

Denmark is home to only three other Highly Cited neuroscientists: Arne Schousboe from the Royal Danish School of Pharmacology, Niels Henrik Diemer, Copehagen University and Jørgen Drejer, NeuroSearch A/S.

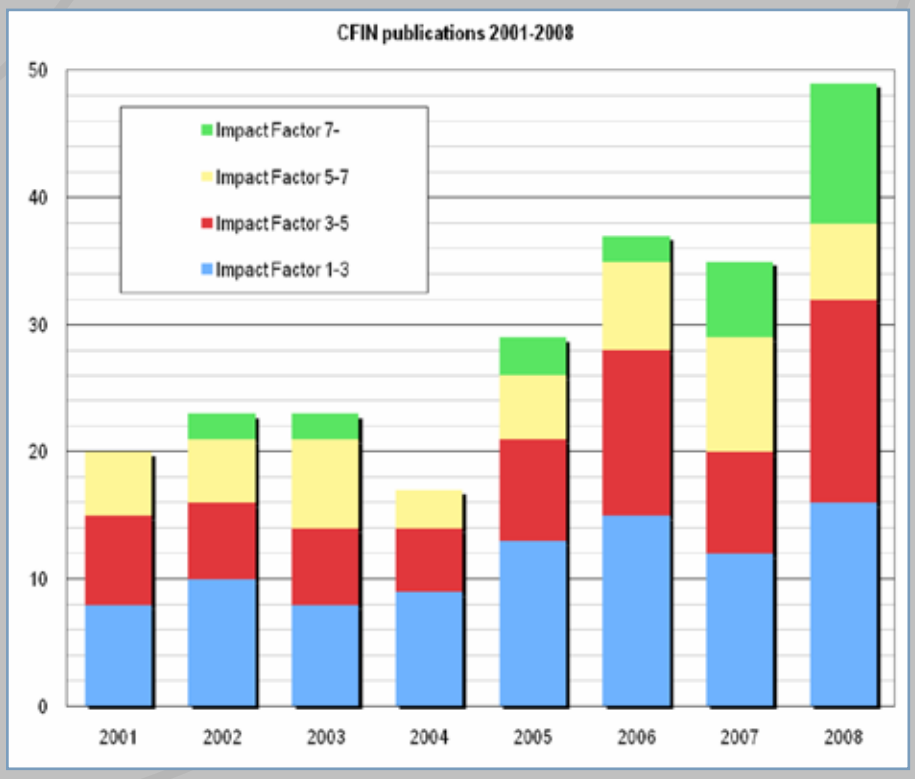

Figure 3
CFIN Publications 2001 - 2008

neuroinformatics
emotion
functional hemodynamics
neurotransmission
brain
MEG
neuroconnectivity
fMRI
neuroenergetics
subject
stroke

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