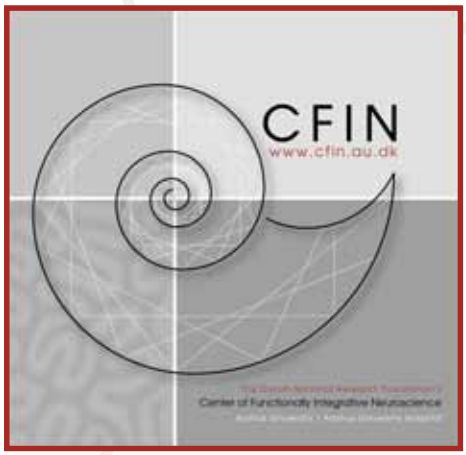

The Danish National Research Foundation's
Center of Functionally Integrative Neuroscience

ANNUAL REPORT 2011

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Social gathering in one of the elegant living rooms at Sandbjerg Manor during the annual CFIN & MIND*Lab* Retreat, August 2011
Photo: Alejandra Zaragoza Scherman

Introduction - 2011 in words

by Leif Østergaard

2011 marked CFINs tenth year as an interdisciplinary neuroscience research center, and the end of the two consecutive 5-year funding periods by which the Danish National Research Foundations (DNRF) founded CFIN under their Center-of-Excellence (CoE) program.

We wish to express our gratitude to the DNRF for their support, and in particular for the freedom, their CoE concept has offered us in terms of building a critical mass of scientists with complementary knowledge, and in terms of the opportunities to pursue ideas, which would have difficulty to develop under more traditional funding schemes. I take my own research area as an example of the potential of long-term investments: Puzzling observations made in MRI data from stroke patients in 1998 formed the basis for new ideas on oxygen availability in tissue, which were formulated in our DNRF grant applications in 2000. However, it is only now, after almost a decade of team-work among scientist from within statistical modeling, theoretical physics, NMR diffusion physics, biomedical engineering, vascular biology, basic neuroscience and clinical medicine that pieces of a puzzle, which could revolutionize our understanding of diseases in general, and of brain disorders in particular, start to fall into place (see also page 24-25). Throughout this annual report, similar examples show the strength of establishing interdisciplinary teams, which, given time and freedom, can develop new avenues in solving grand scientific challenges.

After extremely positive scientific evaluations of our work, commissioned in 2009 by the DNRF from leading international experts within our field (see Annual Report 2010), CFIN will continue as a productive, interdisciplinary neuroscience and cognition research environment in the years to come. Thanks to support from the Danish Agency for Science, Technology and Innovation's infrastructure grant scheme, CFIN has been able to establish MIND*Lab*, an experimental platform including 3.0 Tesla MRI, TMS and EEG at Aarhus University Hospital. In 2011, with the support of the VELUX foundation and the Institute of Clinical Medicine, we were able to add the first MEG system in Scandinavia, including a dedicated new building, to this instrument platform. Meanwhile, the majority of CFIN researchers, including instrument platform staff, are now funded by the Danish Agency for Science, Technology and Innovation's University Investment Capital (UNIK) grant to Aarhus University, also named MIND*Lab* (see www.mindlab.au.dk). With the help of our tireless coordinator of communications, Henriette Blæsild Vuust, we look forward to update you on the scientific progress of CFIN and MIND*Lab* in the years to come.

Integrative and interdisciplinary approaches to science have become central concepts in the criteria for strategic research funding, and to research and education strategies of modern universities. While CFIN strives to exemplify the potential of such approaches, we keep in mind that interdisciplinary research is all about the strongest *disciplinary* research - and about collaborations. It requires researchers to share their knowledge and ideas, to dedicate their precious time and resources to work outside their conceptual 'comfort zones'. Similarly, interdisciplinary research networks, by definition, requires group leaders to unselfishly engage in and support initiatives which benefit other research groups, in addition to promoting their own immediate research interests. Therefore, skills from various disciplines, as well as those of practicing generosity, reciprocity, respect and humility towards fellow researchers, are crucial to the success of interdisciplinary work at any level. With the dedicated group leaders who now jointly form the CFIN leadership, and the intellectual and social capital we have built over the years, I can think of no likelier place than our center for interdisciplinary potential to unfold!

On behalf of the CFIN group leaders I wish to thank our collaborators and benefactors for their continued support.

NEUROENERGETICS

by Albert Gjedde

The topic of neuroenergetics is important to the understanding of consciousness and the support of activation states of the brain. As such, it is worth repeating that a fundamental measure of brain energy metabolism, the rate of turnover of ATP, is unknown, because the degree of uncoupling of mitochondrial oxidative phosphorylation is undetermined. Other observations that have puzzled the neuroscientists in this respect and have stimulated large bodies of work raise the questions of how oxygen consumption manages to remain more or less constant in different physiological activation states and the extent to which neurons depend on astrocytes for a supply of lactate as fuel for oxidative metabolism. In 2011, workers in the Neuroenergetics theme focused on these issues as they strove to understand how the level of energy turnover affects the brain's maintenance of a conscious state, more as a cause of such a state than a consequence, during physiological stimulation, aging, and neurodegeneration.

ATP turnover

Among healthy humans, the distribution of brain oxidative metabolism values is astoundingly wide for a measure that reflects normal brain function and is known to change very little with most changes of brain function. Is it possible that the part of the oxygen consumption rate that is coupled to ATP turnover is the same in all healthy human brains, with different degrees of uncoupling explaining the variability of total oxygen consumption among people? To test the hypothesis that about 75% of the average total oxygen consumption of human brains is common to all individuals, Gjedde and co-workers determined the variability in a large group of normal healthy adults. To establish the degree of variability in different regions of the brain, we measured the regional cerebral metabolic rate for oxygen in 50 healthy volunteers aged 21-66 and projected the values to a common age of 25. Within each subject and region, we normalized the metabolic rate to the population average of that region. Coefficients of variation ranged from 10 to 15% in the different regions of the human brain and the normalized regional metabolic rates ranged from 70% to 140% of the population average for each region, equal to a two-fold variation. Thus the hypothetical threshold of oxygen metabolism coupled to ATP turnover in all subjects is no more than 70% of the average oxygen consumption of that population. It remains to be shown whether this percentage is the same for everyone, or whether the efficiency of mitochondrial function varies similarly among people, some individuals at one extreme having very efficient mitochondrial action, where 100% of the oxygen consumption is devoted to oxidative phosphorylation, while other individuals at the other extreme only devote 40% of the oxygen consumption to oxidative phosphorylation and the rest to heat. The question is whether regulation of energy turnover occurs by means of different degrees of uncoupling of otherwise constant oxygen consumption, or whether it is the rates of oxygen consumption that change. Current wisdom suggests that it is the latter but it is not impossible that the former makes a significant contribution.

Visual activation

The degree of oxygenation of hemoglobin in cerebral capillaries and veins is a function of the extraction of oxygen, which in turn reflects the relation of oxygen consumption to blood flow during different states of activation. Neuroimaging studies of functional magnetic resonance imaging and electrophysiology provide the linkage between the neural activity and this blood oxygenation-level-dependent (BOLD) signal. Fundamentally, changes of the BOLD signal are the indications of mismatched changes of blood flow and oxygen consumption in response to a stimulus. In a study of rats, Chris Bailey and his co-workers imaged BOLD responses to light flashes at the very high field strength of 11.7T. They compared the signals with neural recordings from superior colliculus and primary visual cortex in rat brain regions with different basal blood flow rates and energy demands. The goal was to assess the degree of neurovascular uncoupling in primary visual cortex and superior colliculus, as reflected by temporal and spatial variances of blood flow impulse response functions and assess, if any, the implications for general linear modeling of the BOLD signals as indicators of blood flow responses to stimuli. Light flashes induced large neural and BOLD responses reproducibly from both regions. However, the neural and BOLD signals from superior colliculus and primary visual cortex were markedly different. The colliculus signals followed the boxcar shape of the stimulation pattern at all flash rates, whereas the visual cortex signals had onset and offset transients that depended differently on the flash rate. The authors found that the collicular impuse response function generally is time invariant across wider flash rate ranges compared with visual cortex, whereas impulse response function were space invariant in both regions. The results serve as a warning that statistical analysis of BOLD responses may misinterpret neural activity in some cases, when neural signals are not determined simultaneously.

Motor activation

In humans as well as in rats, rates of cerebral blood flow (CBF) and glucose consumption (CMR_{glc}) rise in visual and motor cortices during continuous stimulation, while the oxygen-glucose index (OGI) declines as evidence of mismatched oxygen consumption ($CMRO_2$), CBF, and CMR_{glc}. It is a puzzle how blood flow and glucose consumption remain coupled in brain, while oxygen use stays largely constant. To test whether the mismatch reflects a specific role of aerobic glycolysis during functional brain activation, Vafaee and co-workers determined CBF and $CMRO_2$ with positron emission tomography when 12 healthy volunteers executed finger-to-thumb apposition of the right hand. Movements began 1, 10, or 20 minutes before administration of the relevant radiotracers. In primary and supplementary motor cortices, as well as in cerebellum, CBF had increased at 1 minute of exercise and remained elevated for the duration of the 20-minute session. In contrast, the $CMRO_2$ numerically had increased insignificantly in left primary and supplementary cortices at 1 minute, but had declined significantly at 10 minutes, returning to baseline at 20 minutes. As measures of CMR_{glc} are impossible during short-term activations, we used measurements of CBF as surrogate indices of CMR_{glc}. The decline of $CMRO_2$ at 10 minutes paralleled a substantial decrease of OGI at this time. The commensurate generation of additional lactate in the tissue implied an important role of this metabolite as regulator of CBF during activation. Thus, it is possible that blood flow is coupled to glucose consumption by the action of lactate, rather than the opposite.

Novel roles of lactate during activation

The deliberations caused Bergersen and Gjedde to present the novel perspective that lactate is a so-called volume transmitter of cellular signals in brain that acutely and chronically regulate the energy metabolism of large neuronal ensembles. From this perspective, they interpreted recent evidence to mean that lactate transmission serves the maintenance of network metabolism by two different mechanisms, one by regulating the formation of cAMP via the lactate receptor GPR81, the other by adjusting the NADH/NAD+ redox ratios, both linked to the maintenance of brain energy turnover and possibly cerebral blood flow. The role of lactate as mediator of metabolic information rather than metabolic substrate answers a number of questions raised by the controversial oxidativeness of astrocytic metabolism and its contribution to neuronal function, including the effect of

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.

Michael Gejl Jensen, Birgitte Brock, Albert Gjedde et al: 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.

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.

Yoshitaka Kumakura, Arne Møller, Albert Gjedde et al.: Dopamine synthesis capacity in relation to sensation-seeking in healthy volunteers.

Suzan Dyve, Anne M Landau, Doris Doudet, Albert Gjedde et al: Noradrenaline release by vagus nerve stimulation in minipigs.

Adjmal Nahimi, Karen Østergaard, Albert Gjedde et al.: A Common Noradrenergic Mechanism of Depression and LDopa Induced Dyskinesia in Parkinson´s Disease *in vivo.*

Jenny-Ann Phan, Marina Romero-Ramos, Albert Gjedde et al: The neuroprotective role of noradrenalin on dopaminergic neurotransmission in Parkinson´s disease.

Anders B. Rodell , Joel F. Aanerud , Hans Brændgaard , Albert Gjedde: Flow independent analysis of 11C-PIB binding in Alzheimer's disease and healthy controls.

Anders B. Rodell, Joel F. Aanerud, Hans Brændgaard, Albert Gjedde: Low residual CBF variability in Alzheimer's disease after correction for CO_2 effect.

lactate-pyruvate ratios in the circulation on the magnitude of cerebral blood flow.

Healthy aging

These findings raise the question of how blood flow and energy turnover in brain are coupled during aging. In this respect, it is clear that the cerebral metabolic rate of oxygen consumption ($CMRO_2$), cerebral blood flow (CBF), and oxygen extraction fraction (OEF) are important to the evaluation of healthy aging of the brain. Although a frequent topic of study, changes of CBF and $CMRO_2$ during normal aging are still controversial, as some authors find decreases of both CBF and $CMRO_2$ but increased OEF, while others find no change, and yet others again find divergent changes. In a reanalysis of previously published results from positron emission tomography of healthy volunteers, we followed $CMRO_2$ and CBF measures of 66 healthy volunteers aged 21 to 81 years. The magnitudes of $CMRO_2$ and CBF had declined with age in large parts of the cerebral cortex, including association areas, but the primary motor and sensory areas were relatively spared. We found significant increases of OEF in frontal and parietal cortices, excluding primary motor and somatosensory regions, and in the temporal cortex. Because of the inverse relation between OEF and capillary oxygen tension, increased OEF can compromise oxygen delivery to neurons, with possible perturbation of energy turnover. The results establish a potential mechanism of progression from healthy to unhealthy brain aging, as the regions most affected by age are the areas that are most vulnerable to neurodegeneration.

Alzheimer's disease

It is still debated whether Alzheimer's disease is a vascular disorder, a disorder of neurovascular coupling, or an intracellular degeneration originating in mitochondria or tau-proteins. Rodell and co-workers tested the claim that the well-known decline of inter-individual CBF variability in Alzheimer's disease (AD) is particularly evident when the variability from changes of arterial CO_2 tension (P_aCO_2) is eliminated. Specifically, we tested whether the variability of CBF in brain of patients with AD differed significantly from brain of age-matched healthy control subjects (HC). To eliminate the CO_2-induced variability, we developed a novel and generally applicable approach to the correction of CBF for changes of P_aCO_2 and applied the method to positron emission tomographic (PET) measures of CBF in AD and HC groups of subjects. After correction for the differences of CO_2 tension, the patients with AD lost the inter-individual CBF variability that continued to characterize the HC subjects. The difference (ΔK_1) between the blood-brain clearances (K_1) of water (the current measure of CBF) and oxygen (the current measure of oxygen clearance) was reduced globally in AD and particularly in the parietal, occipital, and temporal lobes. Rodell and co-workers then showed that oxygen gradients calculated for brain tissue were similar in AD and HC, indicating that the low residual variability of CBF in AD may be due to low functional demands for oxidative metabolism of brain tissue rather than impaired delivery of oxygen. Thus, Alzheimer's disease most likely involves mitochondrial dysfunction as a cause or consequence of taupathy.

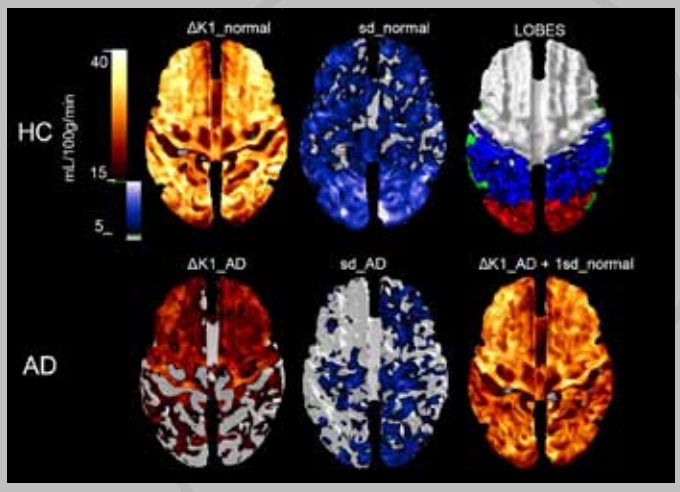

Figure 1
Loss of functional flow variability in patients with Alzheimer's disease: The left column shows the group mean flow reserve in healthy control subjects and patients with Alzheimer's disease in hot metal color scale (values below 15 mL/100g/min in gray). The middle column shows the standard deviation (sd) in black, blue and white color scale (values below 5 mL/100g/min in gray). The right column, top row, shows the position of temporal lobe in green, occipital lobe in red, and parietal lobe in blue. For comparison, the bottom row of right column shows the calculated image of adding 1 SD of the flow reserve of healthy aged control subjects to the flow reserve of the patients with Alzheimer's disease. It is evident that the standard deviations for the AD patients are much lower than for the control subjects, and that the difference of flow reserve can be explained by the loss of functional flow variability in the patients (from Rodell et al., in preparation).

Oxygen metabolism in Parkinson's disease

Decreased activity of the mitochondrial electron transport chain has also been implicated in the pathogenesis of Parkinson's disease (PD) and most likely would predict a decrease in the rate of cerebral oxygen consumption ($CMRO_2$). To test the prediction, Borghammer and co-workers compared PET measures of $CMRO_2$ and CBF in PD patients and healthy control subjects. Nine early-stage PD patients and 15 healthy age-matched controls underwent PET for

quantitative mapping of $CMRO_2$ and CBF. Between-group differences were evaluated for absolute data and intensity-normalized values, but no group differences were detected in regional magnitudes of $CMRO_2$ or CBF. Upon normalization with the reference cluster method, significant relative $CMRO_2$ decreases were evident in widespread prefrontal, parieto-occipital, and lateral temporal regions. Sensory-motor and subcortical regions, brainstem, and the cerebellum were spared. A similar pattern was evident in normalized CBF data, as described previously. While the data did not reveal substantially altered absolute magnitudes of $CMRO_2$ in the brain of PD patients, the data-driven intensity normalization revealed widespread relative $CMRO_2$ decreases in cerebral cortex. The pattern was very similar to that reported for CBF and CMR_{glc} studies of PD, and in the CBF images from the same subjects. Thus, the present results are consistent with parallel declines in $CMRO_2$, CBF, and CMR_{glc} in spatially contiguous cortical regions in early PD, and they support the hypothesis that mitochondrial electron chain dysfunction is a primary pathogenic mechanism in early PD, as it may be in Alzheimer's disease.

Glucose metabolism in Parkinson's disease

Models of Parkinson's disease (PD) in animals suggest a characteristic pattern of metabolic perturbation in discrete, very small basal ganglia structures. These structures generally are too small to allow valid detection by conventional positron emission tomography. However, the high-resolution research tomograph (HRRT) has a resolution of 2 mm, sufficient for the investigation of important structures such as the pallidum and thalamic subnuclei. Using this HRRT, Borghammer and co-workers used fluorine-18-labeled fluorodeoxyglucose (FDG) to measure cerebral glucose consumption in 21 patients with PD and in 11 age-matched control subjects. The authors used three types of normalization, white matter, global mean, and data-driven normalization and did volume-of-interest analyses of small subcortical gray matter structures, and voxel-based comparisons tested the extent of cortical hypometabolism. The most significant subcortical relative hypermetabolism was detected in the external pallidum (GPe), irrespective of normalization strategy. Hypermetabolism was suggested also in the internal pallidum, thalamic subnuclei, and the putamen. The authors saw widespread cortical hypometabolism in a pattern that was very similar to patterns reported previously in patients with PD. Therefore, the presence and extent of subcortical hypermetabolism in PD depends on the type of normalization. However, in addition to widespread cortical hypometabolism, the findings suggested that PD probably is characterized by true hypermetabolism in the GPe, as previously by 2-deoxyglucose autoradiography in animals with hypermetabolism most robustly in the GPe.

Conclusions

The studies confirmed a general mechanism of flow-metabolism coupling in brain in which a resting steady-state is supported by commensurate rates of glucose and oxygen consumption. Departures from steady-state then occur during activations in which transient generations of lactate follow increases of glycolysis, which in turn stimulate increases of cerebral blood flow. It is not clear if uncoupling and recoupling of oxidative phosphorylation contribute to the general invariance of oxygen consumption rates during these departures from steady-state. However, both healthy aging and the neurodegenerative disorders of Alzheimer and Parkinson tend to resemble more extreme versions of the changes of mitochondrial function that occur during physiological stimulation, and hence may be the results of failures of return to steady-state related to the appearance of reactive oxygen and nitrogen species, perhaps because of insufficient blood flow stimulation by lactate.

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Vafaee MS, Vang K, Bergersen LH, Gjedde A. Oxygen Consumption and Blood Flow Coupling in Human Motor Cortex during Intense Finger Tapping: Implication for a Role of Lactate. In review.

NEUROTRANSMISSION

by Arne Møller & Anne M. Landau

The 10th annual OAK-meeting (http://www.cfin.au.dk/OAK2011) took place in Aahus in June 2011. The goal of these meetings is for younger neuroscientists from **O**dense, **A**arhus and **K**openhagen to meet and present their projects to each other and to more experienced scientists. This unique opportunity gives young researchers practice in performing oral presentations and allows them to find out what their colleagues are working on in other neurolaboratories in Denmark. This environment gives the young researchers a place to network both at professional and social levels.

The impact of the scientific content is increasing each year, and there was a close race between the speakers to win the prize for the best presentation (won by Sanne Simone Kaalund from Copenhagen).

Professor Mark West gave the keynote lecture titled *Structural Changes in the Brain Related to Alzheimer's disease*. OAK 2012 will take place in Odense in mid-June.

The "Neurotransmission, Psychiatry, and Neuropharmacology" course will be expanded to also include neuropsychology. This course will become a part of the new Sino-Danish Center master's degree in neuroscience in Beijing in 2012 (see page 30-31). As of next year, the course will take place in Beijing in April and in Aarhus during the fall.

We are currently finalizing projects investigating monoaminergic neurotransmission in antidepressant therapies in minipigs using PET imaging. We evaluated the effects of electroconvulsive therapy and vagal nerve stimulation on dopamine, noradrenaline and serotonin neurotransmission. Overall data suggest increases in monoaminergic neurotransmission, which may account in part for the therapeutic effects of brain stimulation therapies. To complement the PET data from these studies, we are now performing dual PET tracer and microdialysis experiments evaluating a noradrenaline receptor tracer, [11C]yohimbine, which holds great promise for neuropsychiatry research.

The OAK 2011 Best Talk Prize - a Nikon digital camera - is presented to Sanne Simone Kaalund from Copenhagen by one of the judges, Jens Randel Nyengaard.
Photo: Jørgen Scheel-Krüger

OAK Meeting 2011.
Participants and sponsors in front of the Palle Juul-Jensen Auditorium at Aarhus University Hospital.
Photo: Jørgen Scheel-Krüger

OAK organizors Arne Møller and Henriette Vuust during the official OAK dinner at Restaurant CANblau in Aarhus.
Photo: Jørgen Scheel-Krüger

We are performing pilot studies investigating a novel model of Parkinson's disease in minipigs induced by direct injections of proteasome inhibitors into the brain. Administration of these drugs can prevent the proper breakdown of proteins and lead to abnormal protein accumulation which is observed in human Parkinson's disease. We are assessing behavioural impairments and disturbances in dopaminergic neurotransmission at different timepoints after disease initiation.

New studies funded by the Aarhus University Ideas competition are underway to establish the minipig as a model of obesity and sugar addiction with a focus on dopaminergic and opioidergic neurotransmission.

In 2011 a major neuroimaging and treatment study of Alzheimer's disease was initiated in a collaboration between the Department of Pharmacology, CFIN / PET and the clinic of Dementia. Forty patients will be scanned (MR and PET) and then randomized (double-blinded) into two treatment groups: Victoza or placebo. After 6 months of treatment, patients will be scanned again, the hypothesis being that there will be a different change in the amyloid load between groups. The study is a part of MD Lærke Egefjord's PhD project.

A new study is in progress by postdoc Michael Winterdahl and teammates to validate a novel tracer of Neuropeptide Y2 (NPY2) for PET neuroimaging studies. NPY2 is a receptor involved in complex behaviours such as anxiety, mood and cognition, and is implicated in diseases such as depression, epilepsy and obesity. At present, there is a lack of a reliable, non-invasive method for determining the role of NPY2 receptors in the living brain. Validation of a novel NPY2 tracer can have a very high impact and advance a number of different studies and fields of research.

An extremely bright and motivated medical research year student Jenny-Ann Phan has begun studies at PET/CFIN to establish a novel model of Parkinson's disease in rat under the supervision of Albert Gjedde. This new model aims to replicate the human pathogenesis according to Braak staging by targeted lesions to locus coeruleus and substantia nigra. The hypothesis is that the early decreased noradrenergic innervation and its anti-inflammatory role can contribute to, and exacerbate, the later disease progression. Jenny is also performing micropet studies at the PET center to study the displacement of yohimbine binding after amphetamine treatment in rats.

SELECTED RESEARCH PROJECTS:

Rikke Fast, Mette Berendt, Anders Rodell, Aage KO Astrup, Arne Møller: Dementia in Geriatric Canines: A Neuroimaging Study.

Jenny-Ann Phan, Adjmal Nahimi, Gregers Wegener, Marina Romero-Ramos, Albert Gjedde. The Neuroprotective Role of Noradrenaline on Dopaminergic Neurotransmission in Parkinson´s Disease.

Michael Winterdahl, Dirk Bender, Aage Olsen Alstrup, Anne M. Landau and Donald F. Smith. PET Neuroimaging of Neuropeptide Y2 Receptors.

Anne M. Landau, Aage K.O. Alstrup, Steen Jakobsen, Dirk Bender, Morten L. Kringelbach, Jørgen Scheel-Krüger & Arne Møller. Imaging the obesity epidemic: Cortical prosessing of wanting, liking and homeostatic regulation in minipigs.

Anne M. Landau, Steen Jakobsen, Aage K.O. Alstrup, Jens Christian Sørensen, Arne Møller, and Doris Doudet. Validation of a novel progressive model of Parkinson's disease in minipig.

Doris Doudet, Anne M. Landau, Steen Jakobsen, Aage K.O. Alstrup, Jan Jacobsen, Arne Mørk, Jens Christian Sørensen, and Gregers Wegener. Evaluating noradrenaline release *in vivo* by PET.

Mette Buhl Callesen, Jakob Linnet, Albert Gjedde, Arne Møller: Pathological gambling in Parkinson's disease.

Arne Møller, Jakob Linnet, Albert Gjedde, and Mette Buhl Callesen. Pathological Gamling and depression.

Rikke Fast, Anders Rodell, Aage KO Alstrup, Albert Gjedde, Mette Berendt, Arne Møller. 11C-PIB PET in dogs with cognitive dysfunction.

Trine Gjerløff, Mahmoud Ashkanian, Poul Videbech, Arne Møller, Donald Smith et al. ADHD in Adults

Yoshitaka Kumakura, Arne Møller, Mette Buhl Callesen, Doris Doudet, Jakob Linnet, Albert Gjedde. Dopamine in Sensation Seeking

Jakob Jakobsen, Lilli Lundbye, Steen Buntzen, Kim Vang, Albert Gjedde, Søren Laurberg, Arne Møller. Sacral Nerve Stimulation

The valproate syndrom: a rodent model of autism

by Freja Bertelsen, Arne Møller, Anne M. Landau & Jørgen Scheel-Krüger

Introduction

Autism is a neural developmental disorder characterized by impaired social interaction and communication, and by restricted and repetitive behavior. The social dysfunction represents a key feature of autism, and this debilitating aspect of this disease is still largely untreated by current medication, depriving the patients of one of the most rewarding aspects of human life, namely social interaction. Today, autism affects 1 in 100 newborns and a high percentage (30-40%) of autistic subjects demonstrates co-morbidity with epilepsy. The aim of our project is to evaluate a new animal model for autism with the goal of improving our knowledge of this heterogeneous disorder. We hope this will ultimately lead to improved treatment of patients.

Our rodent model is developed by early prenatal subchronic administration of the antiepileptic drug valproate (VPA) to pregnant rats. The approach is based on the first VPA study by members of our academic team (Anne Sabers and Arne Møller), who found that the administration of VPA to rats during pregnancy unexpectedly produced a ***enhanced*** number of neocortical cells in the offspring (Sabers et al., 2012 submitted). This neuropathological finding underscores the risk of VPA in epileptic patients. VPA is known to represent a higher risk of teratogenic effects in pregnancy compared to newer available antiepileptic drugs (Spina and Perugi 2004). However, despite clinical guidelines recommending the avoidance of VPA during pregnancy, it is still commonly used in developing countries due to its low cost. The "fetal valproic acid syndrome" in the human clinic is characterized by a constellation of somatic malformations and long-term cognitive dysfunction in the offspring. The developmental and cognitive deficits, which arise from VPA administration during pregnancy, include the autistic spectrum disorders (ASD) and epilepsy.

Our current hypothesis

It is well known from the literature that the major pharmacological and biochemical effects of VPA are related to its enhancement of the GABA system. In addition, VPA may produce an antagonism of the glutamate system and influence the histone system, which in turn may influence the expression of various genes. The most parsimonious explanation of enhanced neocortical cell numbers may be that it reflects the influence of VPA on the endogenous GABA system in the embryonic rat brain.

During the very early embryonic stage, GABA is present and functions as an endogenous paracrine neurotrophic factor. This occurs prior to the development and maturation of the GABA receptors. It has been shown by several groups that the presence of GABA as a paracrine excitatory factor facilitates and mediates the migration of early neuroblast cells, originating from the deep ventricular zones, into an accumulation of cells in the final superficial zones in the brain. Owing to the newly established inhibitory influence of the GABA receptors (type A and C), the migrating cells receive a stop signal which leaves them at their final destinations in the respective layers in neocortex, hippocampus, amygdala and other areas of the central nervous system.

This role of GABA and its transition from inactive to active receptors is illustrated in figures 1-2, taken from the papers by Denter et al., 2010 and Wang and Kriegstein 2009.

In contrast to the proposed developmental disorders, it has been shown that the exposure of high doses of VPA and other GABA-mimetic compounds to rats in the early postnatal period produces apoptosis leading to a major decline in cortical and hippocampal pyramidal cells (Bittigau et al., 2002; Ikonomidou 2009). The early postnatal period in the rat, represented by days 5-16, comprises the "brain growth spurt phase" where the first neuronal networks are pruned and established. This pruning phase is highly dependent on neuronal excitation and activity. The exposure to high doses of inhibitory GABA agonists (or glutamate antagonists) during this phase may inhibit neuronal activity resulting in increased vulnerability of inactive neurons to apoptosis.

Thus, both the timing and the dose of VPA are crucial for the final outcome of teratogenic effects in the offspring. Our initial data (Sabers et al. 2012, submitted) suggests that our low dose regimen of VPA produces a dominant effect in the early migration phase of the prenatal period.

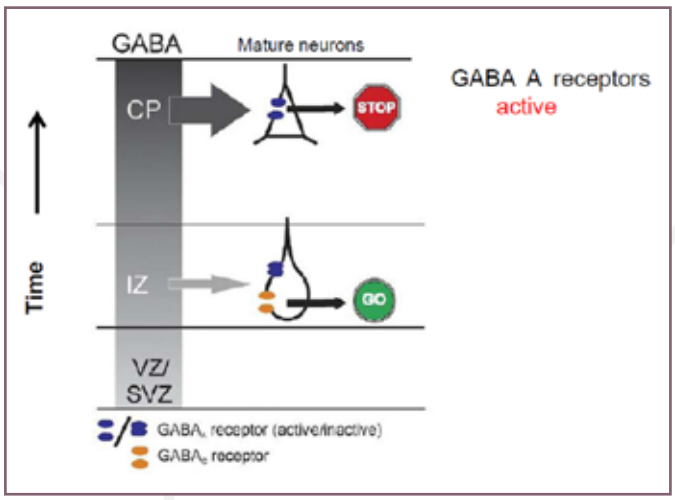

Figure 1
GABA$_C$ receptors are functionally expressed in the intermediate zone and regulate radial migration in the embryonic mouse neocortex. D.G. Denter, N. Heck, T. Riedemann, R. White, W. Kilb, and H.J. Luhmann. Neuroscience 167 (2010): 124-34

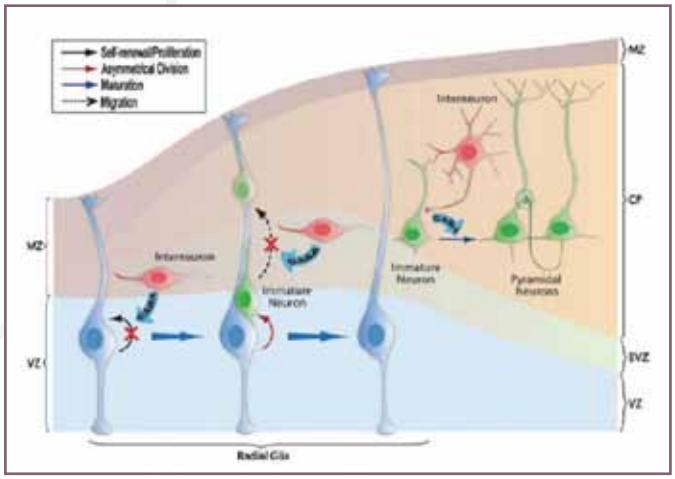

Figure 2
Defining the role of GABA in cortical development. GABA's role in regulating embryonic development, D.D. Wang, and A.R. Kriegstein, J Physiol 587.9 (2009): 1873-79

Figure 3

VPA is teratogenic in most animal species tested so far, and produces various neuropathological changes when administered either pre- or post-natally. In fact, the timing and dose levels of VPA exposure to the rats during various periods of the pregnancy may be used to produce different pathological disturbances in the offspring brain. Indeed, offspring of female rats injected with just one high neurotoxic dose of VPA (300 or 600mg/kg) on the 12.5th day of gestation, which lasts 21 days in the rat exhibit brain abnormalities at autopsy.

The first study (Sabers et al., 2012 submitted) included rats which were exposed to daily injections of VPA during the last

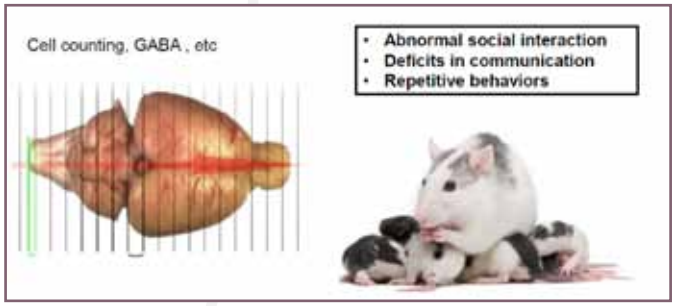

Figure 4
Pathological changes - behavioral changes

9-12 days of pregnancy, and this treatment continued for the following 23 postnatal days. The selected doses of 20 and 100mg/kg VPA were comparable to doses administered in the human condition (Vorhees 1987; Manent, Jorquera et al. 2007). The chosen dose period in rats corresponds to the 2nd and 3rd trimester of human pregnancy and the data in offspring demonstrated a significantly ***increased*** number of neocortical cells in the offspring (Sabers et al., 2012 submitted).

The expected neuropathological changes will be evaluated by stereological cell counting, and presence of biomarkers of degeneration (NAA, GABA and glutamate). Behaviour in offspring will be evaluated by studying social behavior and memory. At various days after birth, eight young rats from various litter groups will be evaluated histologically (slices from prefrontal cortex and hippocampus). The behavioural effects in the offspring of VPA exposed rats will be studied in paradigms for a) juvenile play behaviour in the males at postnatal days 28-32, b) social interactions in the adult female rats (days 50-60) and in c) selected tests for learning and memory abilities such as the object recognition test. The social interaction and

in particular the engagement in juvenile social play with peers is essential for the development of communicative skills, to acquire cognitive skills and for obtaining the rewarding aspects of social competence in adulthood (Vanderschuren et al., 1997; Trezza et al 2011).

The behavioural studies will be performed according to recommendations and publications by our external advisors and collaborators Dr Louk Vanderschuren in Utrecht and Viviana Trezza in Rome (the Juvenile play model) and Jo Neill`s team in Bradford (the social interaction and the object recognition tests). Freja Bertelsen´s PhD project is to further extend these studies and to validate the VPA rodent model and its possible relevance to autism and epilepsy.

The behavioural tests

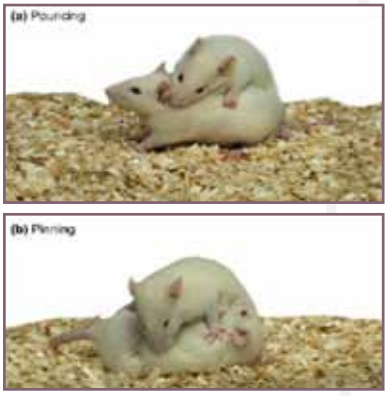

Figure 5
The pleasure of play: Pharmacological insights into social reward mechanisms. Viviana Trezza and Louk Vanderschuren, TIPS 2010 31: 463-9

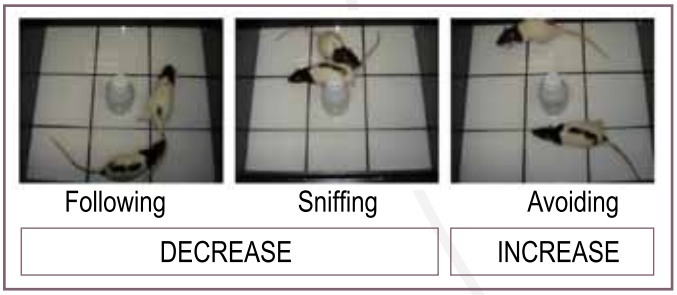

Figure 6
Social interaction - Jo Neill's model

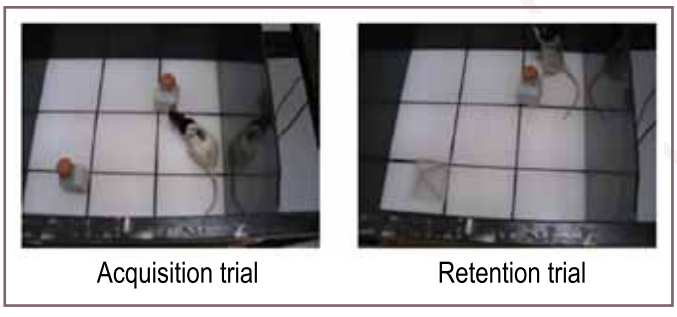

Figure 7
The Novel Object Recognition Task (Jo Neill model)

Results

Sabers et al., 2012 submitted:

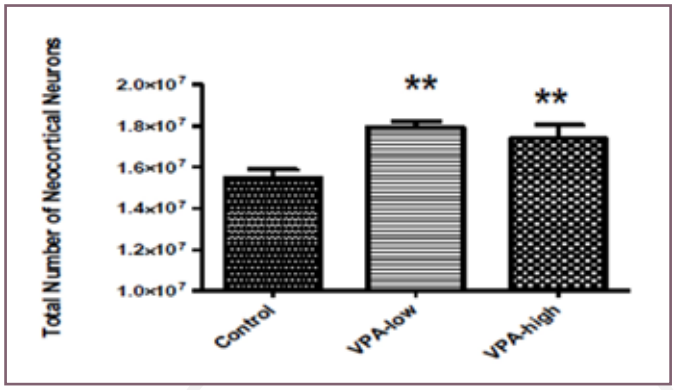

Figure 8
The rat pups exposed to both the low (20mg/kg) and high (100mg/kg) clinically relevant doses of valproate had significantly higher total number of neurons in the neocortex compared to controls (** P< 0.01)

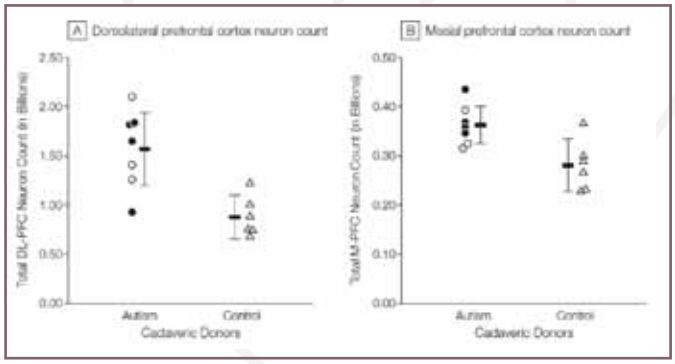

Figure 9
Courchesne et al., 2011. In this small preliminary study, brain overgrowth in males with autism involved an abnormal excess number of neurons in the PFC. (2-8 years, 1m 16 Y). JAMA, 2011; 306(18): 2001-10

Our first results in the rat VPA model have shown a neuropathological enhancement in cortical cell number induced by the prenatal chronic administration of VPA, and this finding is consistent with the clinical results published by Courchesne et al., 2011.

We are currently investigating the effects of daily exposure of pregnant rats to VPA (20 and 100mg/kg ip) on their offspring during the critical brain development periods. The first behavioural result showed that the offspring of the female adult rats exposed to VPA during pregnancy showed superior memory at both doses in the novel object recognition test. These results are consistent with the fact that some patients with autism have an incredible memory.

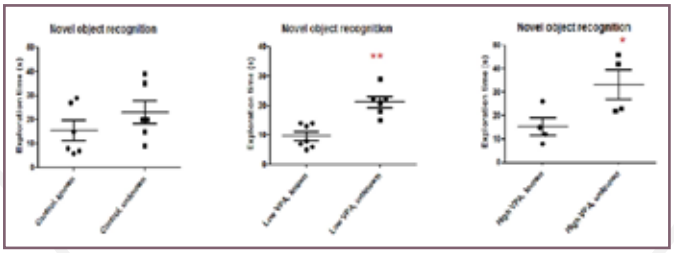

Figure 10
The Novel Object Recognition Task. VPA rats show superior performance for novel, unknown target.

Concluding comments

Clearly, in order to develop new therapies, we need to have an improved understanding of the neurobiology of social behaviour across species. Many species used in research, including rats and humans, have a highly organized social structure and complex social interactions are an essential part of survival of the species. When this social interaction is disturbed, as in many disorders as in autism and schizophrenia, successful treatment becomes more difficult. Restoration of normal social function must therefore be a key feature of successful therapy. Evaluation of new treatments in valid animal models is a critical stage in the development of improved therapies.

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NEW FACE AT CFIN

Freja Bertelsen, PhD student has a bachelor degree in biology and a master degree in biomedical engineering. Her main interest for neurotoxins started in 2009 where she was involved in a research project examining the potential risk when nanoparticles enter the environment, including a project evaluating the accumulation of silver nanoparticles in brain tissue of trouts.

Her interest for psychiatric disorders and in particular autism grew when she started as a research assistant at CFIN in the beginning of 2011. Autism is a neurodevelopment disorder, which may also be induced in the fetus by drugs affecting the GABA system (alcohol, antiepileptic drugs) by their neurotoxicant exposure during pregnancy. The major focus of Freja´s work at CFIN is thus how the prenatal exposure of the antiepileptic drug valproate can change the development of the rat brain.

In August 2011 Freja started her PhD at CFIN. The purpose of the PhD project is to establish and optimize a new rodent animal model which may be relevant for autism and epilepsy. She studies the neuropathological, behavioural and biochemical changes induced during various development phases in the valproate rat model testing whether it is relevant and related to the neuropathology of the human autistic brain.
Hopefully this new animal model may help us increase our knowledge of autism and improve prevention and lead to novel treatments of this disease in the future.

The PhD project is financed by Aarhus University.

Volume transmission

by Albert Gjedde

Monoaminergic neurotransmission gave rise to a concept called “volume” transmission to distinguish the transmission from “wired” transmission, where neurotransmitters interact directly with receptors infacing a synaptic cleft, and the action is terminated rapidly by uptake into cells adjacent to the synapse. In contrast, volume transmission is served by molecules that diffuse considerable distances before they reach specific receptors and eventually undergo uptake into cells where the transmitters interact with enzymes. This mechanism applies to a considerable fraction of monoamines in cerebral cortex, where the monamines exert af modulatory effect on excitability of cortical neurons. It is of considerable interest that a number of brain stimulation methods, including deep-brain stimulation, electro-convulsive therapy, vagus nerve stimulation, trans-cranial magnetic stimulation, and sacral nerve stimulation (Lundby et al. 2011) all lead to increases of noradrenaline, which is a product of the metabolite dihydroxyphenylalanine (DOPA) and the monoamine dopamine.

The concept is not limited to classical transmitters but may apply to metabolites as long as they fulfill certain criteria, which need to be fully established. One such example is the glycolytic endproduct lactate which serves several forms of transfer of information about metabolic states of brain tissue. In 2011, we extended the novel perspective of brain metabolites as volume transmitters to the amino acid DOPA. Previously, we presented the perspective of lactate as a volume transmitter of metabolic states in brain (Bergersen & Gjedde 2012), and we now make the same case for DOPA as a modulator of monoaminergic brain activity. Metabolites can be said to serve as volume transmitters of regulatory information only when specific criteria are fulfilled. The necessary and sufficient criteria all relate to the stereoselective interactions with dedicated proteins, including transporters that mediate the unlimited passage across cell membranes by means of facilitated diffusion, and enzymes and receptors that mediate the mediate the effects of DOPA on or in cells that are far removed from the cells of synthesis. Whether competitors or inhibitors are also required is not certain at this time. DOPA fulfills the criteria that qualify the molecule for the role of volume transmitter of information necessary to adjust and redistribute monoaminergic activity in brain tissue. As such the concept is not new, as Goshima et al. (1986) promoted this role of DOPA repeatedly, and claims of actions of DOPA in cells other than dopaminergic neurons were reported as early as in 1970 (Ng et al. 1970). However, the concept remains poorly understood, and we now reintroduce the arguments in favor of this role in the light of new evidence. The concept is of considerable additional interest to specific disease states such as dyskinesia in Parkionson’s disease and toxoplasmosis gondii.

DOPAergic Volume Transmission

Synthesis. DOPA is the precursor of dopamine in numerous cells in brain, some of which are not neurons, and some of which do not make DOPA from tyrosine because they lack tyrosine hydroxylase (TH). DOPA is synthesized in catecholaminergic neurons as well as in cells that do not convert DOPA to dopamine because they lack DOPA decarboxylase (DDC) (Ershov et al. 2002).

Transmission. DOPA is present in all regions of the brain, with concentrations that vary from 2.5 to 7.5 pmol/g (Thiede & Kehr 1981), with the highest levels in regions of the highest TH activity. The question is how DOPA gets into serotonergic neurons and other cells that do not contain TH. We claim that DOPA enters all cells from the extracellular space by means of the transporter that transports neutral and aromatic amino acids by means of facilitated diffusion as affected by the concentrations and occupancies of competitors on both sides of the membranes. The large neutral amino acid transporters LAT2 and b0 are responsible for the permeation of native aromatic and branched-chain amino acids such as L-DOPA and are both Na-independent with a broad specificity for small and large neutral amino acids, but they also function as tightly coupled exchangers. By the presence of the transporters in the blood-brain barrier, the circulation is an effective sink for DOPA, depending on the sign and magnitude of the gradient.

Remote action. In monoaminergic cells, as well as in cells reached by diffusion, DOPA interacts with at least two different proteins, including DDC that catalyzes the conversion to dopamine and 3-O-methyltransferase (COMT) that catalyzes the conversion to 3-O-methyl-DOPA. In contradiction of the conventional view, these enzymes actually regulate the DOPA gradient and hence control the supply of DOPA to cells that do not possess TH, as well as the supply of DOPA from cells that that possess TH but neither DDC nor COMT. The ubiquitous presence of DOPA and the generally unsaturated state of DDC means that dopamine is synthesized wherever DDC is present, in more or less direct proportion to its concentration. This means that all the noradrenergic and serotonergic

neurons of the cortex, and the serotonergic and dopaminergic neurons of the striatum produce dopamine in proportion to the local DOPA concentration, as shown in the figure.

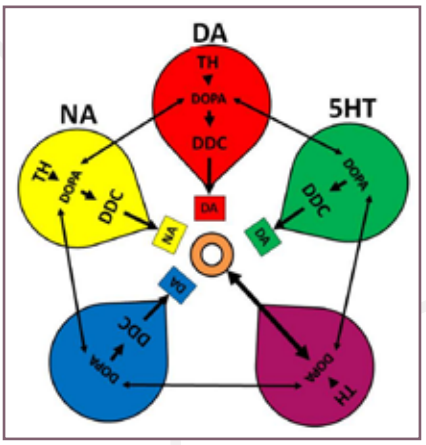

Figure 1
DOPA diffuses among at least 5 different cell types with TH or DDC activity, or both, in all of which it is now clear that DOPA is synthesized, metabolized or both. By this action, DOPA distributes and adjusts the generation of DA, NA, and 5HT across large volumes of brain tissue.

Pathological Modulation

Parkinson's disease. Treatment of Parkinson's disease with DOPA's provides the most emphatic evidence of volume transmission with additional effects that are independent of DOPA's conventional function as a precursor of dopamine and noradrenaline in the respective neurons. Cells that contain only TH appear in the striatum and elsewhere in parkinsonism where they provide additional DOPA (Darmopil et al. 2008). Endo-and exogenous DOPA supports the synthesis in, and release from, serotonergic and noradrenergic neurons of dopamine, in relation to the appearance of dyskinesia in an animal model of parkinsonism (Nahimi et al. 2012).

Toxoplasmosis. Mice and other rodents infected with the protozoan Toxoplasma gondii show indifference to more exposed or novel areas than uninfected mice, suggesting that T. gondii changes the behavior of rodents so as to make them more likely to be predated on by cats, the parasite's definitive host (Webster 2007). T. gondii may also change behavior in humans. Novotna et al (2005) demonstrated that subjects infected with T. gondii, compared to uninfected subjects, were less prone to engage in novelty seeking. A mouse with acute T. gondii infection shows a 40% rise in homovanillic acid as an indicator of increased level of dopamine (DA) in the brain, only in chronically infected mice is it possible to measure a direct increase in DA of 14% compared to healthy controls (Stibbs 1985). T. gondii-induced behavioral changes in rodents are normalized by the dopamine D2 antagonist: haloperidol (Webster et al 2006), therefore it is most likely that these are caused by a raise of extracellular DA. Recent evidence suggests that the mechanism of this increase is the presence in the lesions of a combined phenylalanine and tyrosine hydroxylase, which converts these amino acids to the fellow amino acid DOPA.

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NEUROCONNECTIVITY

by Peter Vestergaard-Poulsen & Brian Hansen

The neuroconnectivity research group develop and use MRI methodologies to study how the brains structural plasticity and function is regulated by changes in neurotransmission. Diffusion weighted magnetic resonance imaging (DWI) is the primary modality used in our research, owing to its unique sensitivity to structural changes at the cellular level.

MRI is a dominating tool in human neuroimaging. However, the limited spatial resolution often prevents the understanding of how image contrast is linked to the certain cellular mechanisms in the imaging voxel and thereby limit the ability to test methods, hypotheses or therapies. In order to investigate these mechanisms at the cellular level, we use a combination of biophysical modelling, ultra high-field magnets (14-17 T) and radiofrequency micro coils due to the much higher sensitivity and image resolution compared to current clinical MR-systems.

Specifically, we attempt to develop MR-based methods to study the microstructural effects of neuroplastic changes in Alzheimers disease, depression and mental stress.

Mental stress

Chronic stress has detrimental effects on physiology, learning and memory and is involved in the development of anxiety and depressive disorders. Investigations of dendritic remodeling during development and treatment of stress are currently limited by the invasive nature of histological and stereological methods. In a recent paper (Vestergaard-Poulsen et al. PLoS One 2011) we have shown that 17.4 T diffusion weighted MRI quantifies regional dendritic loss in the hippocampus of 21 day restraint stressed rats that highly correlates with former histological findings. The study strongly indicates that diffusion weighted MRI is sensitive to regional dendritic loss and thus is a promising candidate for non-invasive studies of dendritic plasticity in chronic stress and stress related disorders.

Development of MR microscopy

The development of MR microscopy techniques has been a focus point for the neuroconnectivity group for some time. The Danish National Research Foundation's International Recruitment Programme funded Dr. Jeremy Flint , University of Florida (employed at CFIN in 2008 through 2011) with his main task to develop MR microscopy methods and bridge the neuroscientific research over the Atlantic Ocean. We are very grateful for his contributions to the research at CFIN.

The collaboration will continue under a common grant shared between CFIN and UFL researchers at the University of Florida's McKnight Brain Institute obtained in 2010 funding from the US National Institutes of Health: *Development of MR Microscopy at the Cellular Level* - 3.2 million USD (RO1 project). Louise M. Rydtoft has been assigned as a PhD student to the Danish subcontract of this grant with focus on the visualization of regional hippocampal neurogenesis caused by electroconvulsive therapy. This study uses diffusion weighted MRI along with histological techniques.

Part of the The Danish National Research Foundations International Recruitment Programme grant was earmarked for two summer schools/workshops on MR microscopy and related techniques. The first of these workshops was held in Florida in 2009 and in 2011 CFIN hosted the second workshop with attendees from many countries including USA, Canada, France, Germany, Norway and Great Britain.

With so many prominent researchers from the diffusion MR and MR microscopy field gathered in Aarhus to present and discuss their work, it was made clear that these techniques continue to hold a lot of potential. One promising aspect of the ability to image tissues at microscopic resolutions with MR is the validation and improvement of MR data analysis techniques currently employed in the clinic.

One such validation study was completed by the collaboration in 2011, with the first example of MR diffusion tensor microscopy with direct and quantitative comparison to tissue structure obtained from histology of human spinal cord. These results were presented to the community at the ISMRM meeting in Montreal in May 2011 and published in NeuroImage in August where illustrations from the article were featured on the journal cover (see figure 1).

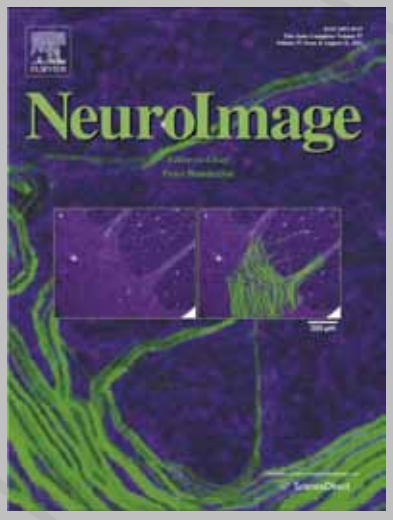

Figure 1
The cover of NeuroImage from August 2011 showing figures from Hansen et al.: *Diffusion tensor microscopy in human nervous tissue with quantitative correlation based on direct histological comparison*.

The study shows that fiber structure as predicted by MR diffusion tensor microscopy techniques overlap with actual tissue fiber structure in 89% of the cases on average. This confirms the assumptions behind diffusion tensor MRI and shows how high-field MR microscopy techniques can be used to quantify the precision of MRI techniques employed in the clinic.

Research stays

The collaboration with the Florida group is still very much alive. As part of the collaboration CFIN physicist Brian Hansen visited the Blackband lab to participate in experimental work in April 2011 and again in January 2012. The work currently focuses on refinement of the data analysis and further development of the experimental techniques to enable us to perform MR microscopy in the acute brain slice model (i.e. live tissue samples) commonly employed in e.g. electrophysiological studies of neuronal networks in hippocampus. Another aim of our current efforts is MR microscopy of intracellular detail in sections of brain tissue in an attempt to further our understanding of the basic contrast mechanisms built into the diffusion weighted imaging techniques employed in clinical diagnosis of e.g. stroke. To this end a thorough understanding of the diffusion and relaxation properties of individual tissue compartments is needed. Here, the MR microscopy techniques established during the collaboration between the Blackband lab and the neuroconnectivity group at CFIN are ideal because they allow direct comparison to tissue microstructure thereby enabling MR derived parameters to be precisely mapped to individual tissue compartments and structures. A future goal is to bring these techniques together so that the diffusion properties of live tissue samples may be explored in both tissues in steady state and in perturbed states (ischemia or neural activation). Such studies would enable us to investigate MR signal contrasts in live tissues with cellular resolution. With modeling such studies are expected to improve our ability to interpret clinical MRI as well as inspire new techniques for diagnostic scanning.

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Vestergaard-Poulsen P, Wegener G, Hansen B, Bjarkam CR, Blackband SJ, Nielsen N, Jespersen SN. 2011 Diffusion-Weighted MRI and Quantitative Biophysical Modeling of Hippocampal Neurite Loss in Chronic Stress. PLoS ONE 6(7): e20653. doi:10.1371/journal.pone.0020653

SELECTED RESEARCH PROJECTS:

Louise M. Rydtoft, Peter Vestergaard-Poulsen, Gregers Wegener, Brian Hansen, Doris Doudet, Sune Jespersen et al. Electroconvulsive therapy: regional visualization of hippocampal neurogenesis by diffusion weighted MRI?

Micah Allen, Peter Vestergaard-Poulsen Andreas Roepstorff, Chris Frith, Martijn van Beek, Michael Stubberup, Jes Bertelsen, Paul Grossman. Longitudinal effects of meditation.

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.

Mads Sloth Vinding, Thomas Vosegaard, Niels Chr. Nielsen, Sune N. Jespersen, Ryan Sangill and Peter Vestergaard-Poulsen. Optimal Control for reduced field-of-view MRI.

Brian Hansen, Jeremy J. Flint, Choong Heon-Lee, Michael Fey, Daniel Schmidig, Michael A. King, Peter Vestergaard-Poulsen and Stephen J. Blackband. Diffusion tensor microscopy in human nervous tissue with quantitative correlation based on direct histological comparison.

NEUROPHYSICS

2011

by Sune Nørhøj Jespersen

Introduction

A main topic for neurophysics at CFIN, involves the modeling of how brain micro-structure and function may reveal itself through the application of magnetic resonance imaging (MRI), especially diffusion weighted magnetic resonance imaging (DW MRI). In this context, the overarching goal of diffusion weighted MRI is to increase the amount and the specificity of the biological information which may be attained from MRI.

Progress

In 2011 a long-lasting collaboration with Christopher D. Kroenke's lab at Oregon Health and Science University culminated with a publication in IEEE TMI[1]. In it, we addressed the microstructural underpinnings of so-called fractional anisotropy in brain tissue, using modeling, DW MRI, and validation by fluorescent microscopy based histology. Fractional anisotropy (FA) refers to the observation that the rate of water diffusion in the brain depends on the direction of observation. This property is widely used as the basis of fiber tracking, i.e. the mapping of fiber connections in the brain, but also as a sensitive marker of various pathologies affecting white matter. However, fractional anisotropy is known to be affected by several fiber properties, including axonal radius, myelination, fiber density, and fiber coherence. Using a previously developed model for water diffusion in the brain[2, 3], we forwarded a theory predicting quantitatively how fractional anisotropy depends on underlying tissue characteristics such as those listed above. To evaluate the model, we compared predictions from the theory based on DW MRI, to quantitative histological measurements from 3-D reconstructions of neurons. The data showed excellent agreement with theory (see Figure 1), providing a first step towards more complete interpretation of fractional anisotropy in terms of underlying biological characteristics. Subsequently, the Lundbeck Foundation awarded 2 million DKK to continue this study, e.g. applying the methodology to various animal disease models such as stress and depression. The main idea is to use modeling to increase the sensitivity and specificity of diffusion imaging to microstructural tissue properties that are known to change in disease - for example dendrite branching lengths in depression - and assess the validity on the basis of immunohistochemistry combined with quantitative histology. A complementary approach to disentangle the biological underpinnings of FA, rests on the development of new MRI

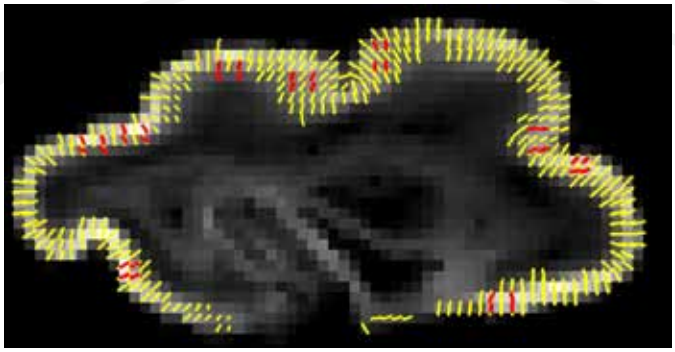

Figure 1
The yellow line show the main diffusion direction in the cortex in an immature ferret. The red lines show the main diffusion direction as predicted from the model and based on fluorescent microscopy.[1]

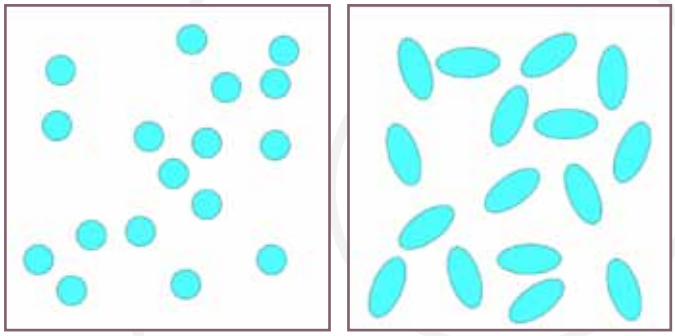

Figure 2
Two examples of microstructure which are difficult to distinguish on the basis of the directional dependence of the diffusion signal. In contrast, these two cases are readily distinguished using double wave vector diffusion imaging.

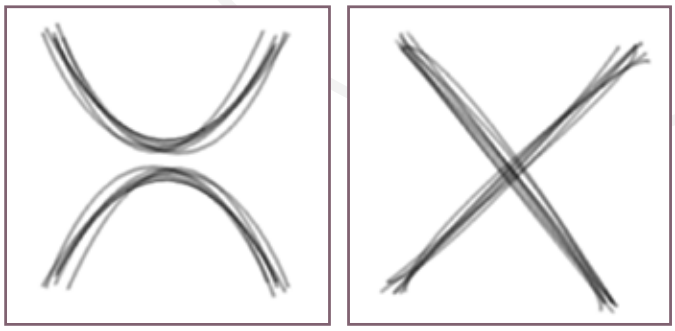

Figure 3
Voxels containing "kissing" or crossing of fibers look very similar in terms of the standard diffusion signal. In reference 11, we show that they each affect the double wave vector diffusion signal in a unique way.

pulse sequences, such as the so-called double wave vector diffusion sequence[4]. Early on, it was discovered that this technique is sensitive to the shape of the compartments in which water diffuses, for example neurons. It has been speculated that this technique could be used to distinguish regions with comparable fractional anisotropy, but different

microstructure. For example, a low fractional anisotropy may be due to the absence of anisotropic cells, or it may be due to an isotropic arrangement of anisotropic cells (see Figure 2 and references 5-9). In reference 10, we demonstrated that double wave vector diffusion sequences may potentially be used to address yet another long-standing problem in DW MRI, namely distinguishing crossing from kissing fiber bundles. This is a problem, for example in fiber tracking: when two fiber bundles converge in a voxel, the subsequent resolution of their paths becomes ambiguous (see Figure 3). Double wave vector diffusion techniques may hold the key to resolve this paradox, because, in contrast to standard DW MRI, they encode correlations in the spin displacements, which are present in curving fibers, but absent in crossing fibers[11].

Diffusion models developed at CFIN, are currently being applied to explore changes in microstructure in a number of animal disease models. For example, a study led by Peter Vestegaard-Poulsen (see page 16), which came out in 2011[12], demonstrated the ability of the model parameters to reflect microstructural changes occuring as a consequence of mental stress, in contrast to standard diffusion measures. This study is presently being extended to animals receiving electroshock therapy as a treatment (see page 16), and to mouse models of Alzheimer's disease in studies by Louise Rydtoft.

New projects

Physics master student, Jakob Hedager Kristensen, has initiated a large-scale Bayesian data analysis of DW MRI obtained from fixed rat brain. His goal is to compare a subset of the various diffusion models developed at CFIN and elsewhere, in order to find out which models best reflect actual tissue characteristics. His results will guide future experiments as well as the continued development of theoretical models.

CFIN researcher Birgitte Fuglsang Kjølby and Tue Skallgard, master student from biomedical engineering, are developing realistic simulations of blood flow in capillaries. The aim is to characterize the extent to which it would be possible to measure capillary blood flow distributions using diffusion like sequences (so-called into voxel incoherent motion, IVIM). According to a recently published work from CFIN[13], not only net blood flow, but also flow distribution at the capillary level substantially affects the delivery of oxygen to neurons. As such, noninvasive methods to measure capillary blood flow distributions will be key in further research in brain metabolism.

On a somewhat different topic, Andre Ødgårdstuen (physics), has initiated a Masters project on computational models of orientation selection in visual cortex, intending to explore their consequences and predictions for e.g. the wagon wheel illusion.

PhD degrees

Niels Buhl obtained his PhD degree in physics in 2011, based mainly on work involving theoretical models of diffusion on various networks. His results could potentially be used for analyzing the influence of branching lengths and dendrites from diffusion measurements, something that is known to change in various conditions, including learning and mental stress. In addition, he applied his models extensively to describe diffusion of helium in the human lung, which, when used in conjunction with helium MRI, can be used to interrogate lung microstructure in much the same way as water diffusion is used to interrogate brain microstructure. On the occasion of Niels Buhls PhD defense, a mini symposium on diffusion in heterogeneous media was held at the Department of Physics.

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FUNCTIONAL HEMODYNAMICS

by Leif Østergaard

Ten Years of Research - and the Road Ahead

When the Functional Hemodynamics project group set out to understand the implications of capillary flow heterogeneity over a decade ago, our work involved some hope, but perhaps more skepticism and precautions.

Working with David A. Chesler and other colleagues at the Athinouala A. Martinos Center of Biomedical Imaging at Massachusetts General Hospital and Harvard Medical School, we had realized that erythrocyte velocity differences among the capillaries paths in tissue introduced reductions in the net extraction of oxygen, relative to a condition of homogenous flow (see Figure 1). Using perfusion weighted imaging data from acute stroke patients, we had obtained pixel-by-pixel vascular flow distributions, and compared the capillary flow heterogeneity in hypoperfused tissue with that of brain tissue that was unaffected by the stroke. Unexpectedly, abnormal flow heterogeneity predicted tissue infarction, judged from the patient's subsequent follow-up scan (Østergaard et al., 2000), much more closely than the maps of blood mean transit time (MTT), developed a few years earlier and by then the gold-standard of perfusion MRI in stroke (Østergaard et al., 1996). The finding that flow heterogeneity affected tissue vulnerability confirmed the hopes that we could be measuring a phenomenon of metabolic significance by this novel MRI technique. Indeed, as part of our initial CFIN research plan, we repeated - and confirmed - the finding in two independent stroke patient cohorts (Perkio et al., 2005, Simonsen et al., 2002).

The complexity of the susceptibility physics involved in perfusion MRI, and the inherent instability of deconvolution approaches used in determining flow heterogeneity from noisy tissue and arterial raw data, was overwhelming. The past decade has therefore been dedicated to the cumbersome task of understanding the physics of susceptibility contrast formation in a collaboration with Valerij Kiselev at Freiburg University (Kjølby et al., 2006, Kjølby et al., 2009), of reducing operator bias in selecting arterial input functions used in data analysis (Mouridsen et al., 2006a), and finally of estimating the transit time distribution of single voxels based on perfusion MRI (Mouridsen et al., 2006b, Mouridsen et al., 2011). Meanwhile, the mathematical difficulty of formulating an analytical expression which describes the extraction of solutes such as oxygen for a given MTT, capillary transit time heterogeneity (CTTH) and tissue oxygen tension had haunted our efforts until 2008-2010, when Sune N. Jespersen

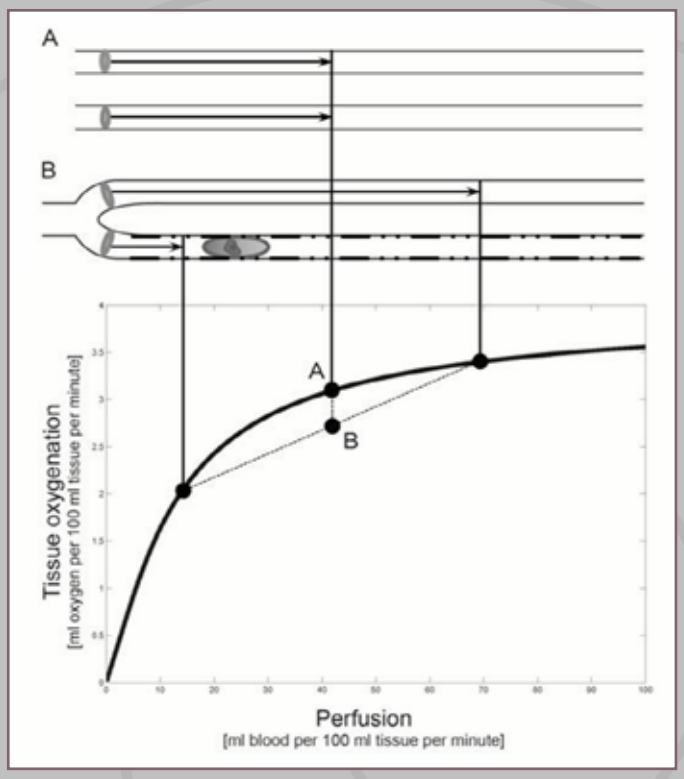


Figure 1
Classical Bohr-Kety-Crone-Renkin flow-diffusion equation for oxygen
The classical BKCR curve shows the maximum amount of oxygen which can diffuse from a single capillary into tissue, for a given perfusion rate. The curve shape predicts three important metabolic properties of parallel-coupled capillaries: (1) the curve slope decreases towards high perfusion values, making vasodilation increasingly inefficient as a means of improving tissue oxygenation, towards high perfusion rates. (2) If erythrocyte flows are inhomogeneous (case B) instead of having equal flows (example A), net tissue oxygenation declines (the point labeled B is always below the point labeled A, which corresponds to homogenous flows). Conversely, homogenization of capillary flows during hyperemia has the opposite effect, and serve to compensate for property (1). (3) If erythrocyte flows are hindered (rather than continuously redistributed) along single capillary paths (as indicated by slow-passing immune cells and/or rugged capillary walls) upstream vasodilation amplifies redistribution losses, as erythrocytes are forced through other branches at very high speeds, with negligible net oxygenation gains.

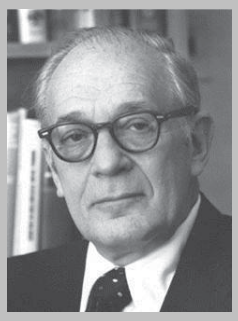
formulated expressions that allowed us to address the hemodynamic limitations to oxygen extraction in more detail. This model was accepted for publication in 2011 in *Journal of Cerebral Blood Flow and Metabolism*, and from the time it became available online on 2 November 2011, and for 4 consecutive months, it was among the ten most downloaded papers from the Journal's website.

The progress of our work over the past decade is noteworthy in two respects. Partly because dedicated CFIN researcher

has overcome a number of challenges and defined the state-of-the-art within our field in an exemplary, interdisciplinary collaboration among physicists, mathematicians, statisticians, engineers and medical doctors. But mainly because our results could herald major, conceptual breakthroughs in relation to century-old paradigms regarding the physiological significance of capillary function, and the balance between tissue perfusion and tissue metabolism.

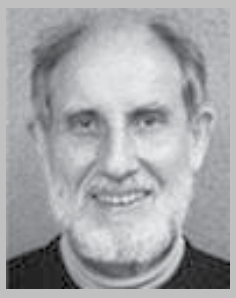
For example, the analysis of oxygen extraction from heterogeneously perfusion capillaries published in 2010 extends our understanding of capillary solute extraction, which is traditionally modeled by the Bohr-Kety-Crone-Renkin (BKCR) equation (Renkin, 1985), named after four founders of modern physiology, two of whom were Danes (see Figure 2). This equation, also named the *flow-diffusion* equation, relates the extraction of diffusible substances from a single capillary

Christian Bohr
1855-1911



Seymour S. Kety
1915-2000

Christian Crone
1926-1990



Eugene M. Renkin
1926-

to CBF, capillary surface area and the capillary permeability to the substance. The equation (and its extensions to specific tissue compartments) is readily applicable to tracer uptake recordings by autoradiography, *in vivo* neuroimaging methods and so forth, and has therefore formed the basis of extensive studies of blood-brain-barrier permeability to various substances, as well as non-invasive quantification of CBF, and

SELECTED RESEARCH PROJECTS:

The role of Capillary Dysfunction in Alzheimer's Disease Pathogenesis: Rasmus Aamand, Eugenio Gutiérrez Jiménez, Kartheeban Nagentiraja, Kim Ryun Drasbek, Hans Brændgaard, Sune Nørhøj Jespersen, Morten Skovgaard, Mark J West.

The role of Capillary Dysfunction in Acute Stroke and Carotid Stenosis: Nina Kerting Iversen, Kristina Dupont, Grethe Andersen, Boris Modrau, Paul von Weitzel-Mudersbach, Kristjana Jonsdottir, Kim Mouridsen, Irene K. Mikkelsen, Kartheeban Nagenthiraja.

Capillary Dysfunction in Cardiovascular Disease: Hans-Erik Bøtker, Steen Buus Kristensen, Michael Hasenkam, Jens Christian Djurhuus, Søren Møller Madsen, Christian Aalkjær, Martin Snejbjerg

The Role of Capillary Dysfunction in Diabetes: Johannes Jakobsen, Toke Bek, Jens Sandahl Christiansen, Jørgen Rungby, Thomas Ledet, Søren Møller Madsen.

Neurocapillary Coupling: Yi Ching Lynn Ho, Jakob Blicher, Changsi Cai, Torben E. Lund, Rasmus Aamand.

Capillary Dysfunction in Brain Edema and Critical Illness: Mads Rasmussen, Else Kirstine Tønnesen, Anna Tietze, Leif Østergaard

The metabolic correlates of angiogenesis: Anna Tietze, Kim Mouridsen, Thomas Nielsen, Mike Horsman, Martin Snejbjerg.

Imaging capillary hemodynamics by confocal microscopy: Sebastian Frische, Eugenio Gutiérrez Jiménez, Morten Skovgaard, Nina Kerting Iversen, Changsi Cai.

Pericyte Biology: Kim Ryun Drasbek, Jesper Just, Therese Ovesen, Eugenio Gutiérrez Jiménez, Morten Skovgaard, Sebastian Frische, Toke Bek, Arne Møller, Thomas Ledet, Mark J West, Jens Randel Nyengaard, Peter Kristensen.

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of metabolite and receptor ligand uptake for decades. Figure 1 demonstrates a fundamental limitation of the BKCR equation, when used to model the extraction of solutes based on an idealized, single capillary with a unique flow rate: In tissue, the flow of erythrocytes through each of the individual capillaries depends on perfusion patterns through multiple, parallel capillary paths. These patterns, in turn, are complex functions of blood viscosity, the adhesion of blood cells to capillary walls, factors which reduce local capillary diameter, and the relative number, deformability and size of the blood cells. This property is not predicted by the BKCR equation, and while attempts to model capillary flow heterogeneity (King et al., 1996, Knudsen et al., 1990, Rose and Goresky, 1976) have confirmed its significance, model complexity has limited our understanding of this phenomenon until now. Instead, single-capillary models have implicitly been adapted into our thinking, for example when we assume that at tissue perfusion is normal, so is tissue oxygenation. In fact the most commonly accepted prediction of the BKCR model, namely that oxygenation is always improved as perfusion increases, may not hold true in biological systems, as shown by Figure 3 and discussed more in (Jespersen and Østergaard, 2012).

In *Neurovascular Coupling II*, a sequel to our initial findings regarding this model in last year's Annual Report, we explain how the extended BKCR model may prompt us to revise even the most fundamental aspects of the coupling of cerebral blood flow and tissue oxygen consumption.

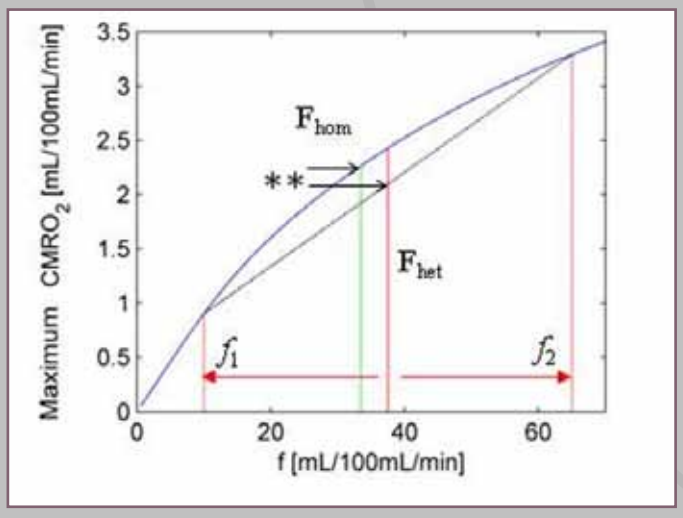

Figure 3
As an extension of the example displayed in Figure 1, imagine that a net, homogenous tissue flow F_{hom}, is increased to F_{het} and subdivided into two capillary populations with flows f_1 and f_2. Then, oxygen availability has decreased (marked by **), albeit net perfusion has increased.

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In the footsteps of great explorers

In the early 1900's Danish scientist from across disciplines gathered to convince the Danish government that a research station should be built in Greenland. This would give unparalleled opportunities for Danish researchers to study the unique Arctic marine life, geology, glaciology, botany, zoology and the history of its Inuit population. This effort was lead by the great Danish arctic explorer, Knud Rasmussen, and leading scientists such as the Nobel Prize winner August Krogh (see 2010 Annual Report) and wife Marie, who visited Greenland to study the physiology of the Inuits and the ways in which ocean water can accumulate man-made carbondioxide.

Over a century later the Arctic Station stands a unique example of how researchers, universities and private benefactors can create unique opportunities for generations of scientists, who now lead aspects of both Arctic and Climate research. The library of the Arctic Station is a unique source of information about these early explorers, and their work. In the summer of 2011, Leif Østergaard had the opportunity to visit Northwestern Greenland and the Arctic Station with a group of research leaders; here in the library of the Arctic Station with Nils O. Andersen, Dean of the Faculty of Sciences at Copenhagen University and leader of the 'expedition'. Together, the participants form a group of research leaders (FL-1) who meets for discussions on research leadership, research policy and so forth. The awareness of how to lead research groups is becoming increasingly important, as research take place increasingly complex networks, which again are embedded in complex organizational structures and changing research policies. The visit to Greenland provided opportunity for intense discussions and exchange of ideas on these and other issues in the ever-present Arctic light.

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Measurement of capillary transit time heterogeneity by DSC imaging: Methods and Validation: Kim Mouridsen, Sune Nørhøj Jespersen, Mahmoud Ashkanian.

Measurement of capillary transit time heterogeneity by spin labeling and velocity encoding: Sune Nørhøj Jespersen, Birgitte F. Kjølby, Brian Hansen, Thomas Nielsen, Niels Christian Nielsen (InSpin), Peter Jezzard (Oxford University).

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): Niels Hjort, Kristjana Ýr Jonsdottir, Kim Mouridsen, Lars Ribe, Leif Østergaard.

FUNCTIONAL HEMODYNAMICS

Beyond Neurovascular Coupling II

by Leif Østergaard & Sune Nørhøj Jespersen

Neurocapillary coupling. And what may happen when capillary flows become disturbed.

As we described in the 2010 CFIN Annual Report, the current dogma for understanding the brain's supply of oxygen - *Neurovascular Coupling* - evolves from the assumption that a close coupling exists between local metabolic needs and vessel (arteriolar) tone - as measured by changes in cerebral blood flow (CBF) and blood volume (CBV) in response to changes in local neuronal activity.

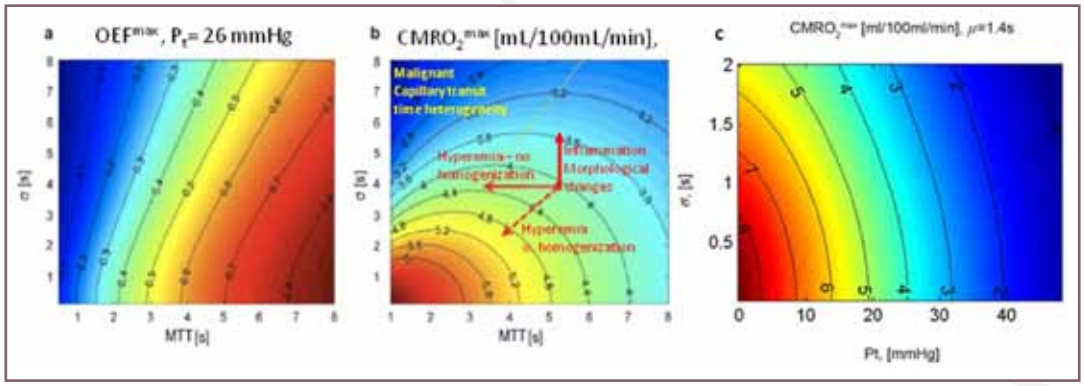
During 2011, a biophysical model which describes tissue oxygen availability as a function of not only CBF and CBV (vasodilation), but also capillary transit time heterogeneity (CTTH - redistribution of capillary flows) and tissue oxygen tension (P_t) was finalized (Jespersen and Østergaard, 2012). As we had anticipated, CTTH, measured by the standard deviation σ of RBC transit times across the capillary bed, greatly influences the maximum achievable oxygen extraction fraction (OEF^{max}) that can be extracted from arterial blood for a given CBV/CBF ratio - commonly known as the mean transit time (MTT). See Figure 1.a.

The model was then applied to erythrocyte velocity data recorded during a range of physiological stimuli in rats, assuming commonly accepted changes in tissue oxygen tension - See (Jespersen and Østergaard, 2012). Much to our surprise, the changes CBF, capillary transit time heterogeneity and tissue oxygen tension seem to act in concert to closely match metabolic needs. Table 1 shows excerpts of the results. The first column show changes in CBF: Note that the large increases in CBF elicited by hypercapnia lead to a parallel decrease in oxygen extraction efficacy (OEF^{max}) which - if CTTH remained constant at its high, resting values (rightmost column) - would actually *reduce* oxygen availability in tissue. However, parallel homogenization of transit times observed in rats seemingly improve oxygen extraction to provide close coupling of hemodynamics to metabolic needs. This finding suggests that hypercapnia-induced CBF increase does not represent a state of profound flow-metabolism un-coupling as hitherto believed: Rather, parallel changes in CTTH and tissue oxygen tension secures close coupling of hemodynamics and metabolism. A similar pattern is observed in cortical activation: Without parallel homogenization of capillary flows, the increase in CBF would not have increased local oxygen availability, and hence meet the increased metabolic needs of neuronal firing. We dubbed the regulation of CTTH *neurocapillary coupling*, noting that it could well be a passive response to increased CBF. It is interesting to note, however, that a specific cell type, the *capillary pericyte*, situated on the abluminal side of endothelial cells, react to a number of neurotransmitters, and to metabolic signals such as oxygen and lactate, in much the same way as upstream arterioles (Attwell et al., 2010, Peppiatt et al., 2006). In a recent paper, it was shown that pericytes indeed control capillary diameter in vivo, while hyperemia is seemingly controlled independently (Fernandez-Klett et al., 2010). While this contradicted the notion that pericytes elicit upstream vasodilation (Attwell et al.,

Figure 1

Effects of vasodilation, capillary transit time heterogeneity and oxygen tension on oxygen extraction.

Contour plot of OEC (1.a.) for a given mean transit time and capillary flow heterogeneity (σ). The corresponding maximum oxygen delivery is shown in (1.b.) assuming fixed capillary blood volume, CBV = 3 %. Resting state values assumed are CBF=60mL/100mL/min; CaO2=19mL/100mL and PtO2 = 26 mmHg. Note that maximum oxygen delivery increases with decreasing flow heterogeneity. The yellow line in 1.b. separates states in which increasing transit times lead to increasing oxygen extraction from states where increasing transit times lead to *decreasing* oxygen extraction: We dubbed this state *malignant capillary transit time* heterogeneity (CTTH). Figure 1.c. shows net oxygenation as a function of tissue oxygen tension and CTTH for fixed CBF. In this figure, CBF and CBV were kept constant (CBF=60mL/100mL/min; CBV 1.6%; mean transit time 1.4 s) to illustrate how tissue oxygen tension and CTTH contribute to the metabolic needs of tissue during rest and as metabolic needs are increased with blocked CBF *and* CTTH (owing to capillary dysfunction). Note that an oxygen tension decrease of 5 mmHg supports a CMRO2 increase of roughly 20%, which correspond to the energy requirements of neuronal firing.



		Relative $CMRO_2^{max}$	
Cortical stimulation	CBF	CTTH change	CTTH fixed
Control	1.00	1.00	1.00
2.0 mA	1.50	1.08	1.03
3.0 mA	2.20	1.17	1.04
4.0 mA	3.00	1.43	1.04
Hypotension			
115 mmHg (Control)	1.00	1.00	1.00
90 mmHg	0.90	1.02	1.02
75 mmHg	0.80	1.02	1.04
50 mmHg	0.60	1.02	1.04
Hypercapnia			
35 mmHg (Control)	1.00	1.00	1.00
67 mmHg	1.69	1.04	0.91
97 mmHg	2.28	0.99	0.84

Table 1

2010, Peppiatt et al., 2006), our findings suggest generalized pericyte dilation could in fact serve to modulate OEF, rather than CBF, during hyperemia.

With the generous support of the Institute of Clinical Medicine (Professor Jens Christian Djurhuus) and the Faculty of Health (Professor Allan Flyvbjerg), Aarhus University is now in the process of establishing a two-photon imaging laboratory at CFIN for the purpose of studying capillary hemodynamics and pericyte properties *in vivo*. With colleagues from a range of departments at the Faculty of Health and the Faculty of Science and Technology, we aim to study the role of the microcirculation, and of the capillary pericyte, in health and in a range of diseases in the years to come.

An intriguing property of the model of oxygen extraction is that if capillary flows become increasingly disturbed (i.e. CTTH increases irreversibly), then CBF increases which usually occur during physiological stimuli, no longer improves tissue oxygenation. This was illustrated by the table above (fixed CTTH) and can be observed in Figure 1.b. which displays the maximum metabolic rate of oxygen ($CMRO_2^{max}$) which can be supported by a given combination of CBF and CTTH at fixed P_t. Note that if capillary flows are disturbed (i.e. σ is irreversibly elevated - vertical arrow) - and CBF subsequently increase (shortening of MTT - horizontal red arrow), then tissue may enter into a condition where oxygenation is reduced in response to vasodilation - dubbed malignant capillary transit time heterogeneity. In tissue, such devastating conditions are likely to be prevented from occurring by intrinsic blockage of normal vasodilation - by powerful oxidants. Figure 1.c. shows that if CBF is kept at resting levels, then the lower tissue oxygen tension, which results from neuronal activation, in fact improves net oxygen extraction to support normal brain function. Interestingly, blocked vasodilator responses, known as *endothelial dysfunction*, is a common finding in most chronic diseases (neurodegenerative disorders, hypertension, diabetes, psychiatric disorder, etc). We speculate that this phenomenon may in fact represent an adaptation to the disturbances in capillary morphology - and thus CTTH - which is also found in these diseases. This would profoundly alter the understanding of the pathogenesis and treatment of these diseases, and is therefore an important future research area within CFIN.

Learn more in the CFIN Annual Report in the coming years, as we explore these phenomena with our collaborators.

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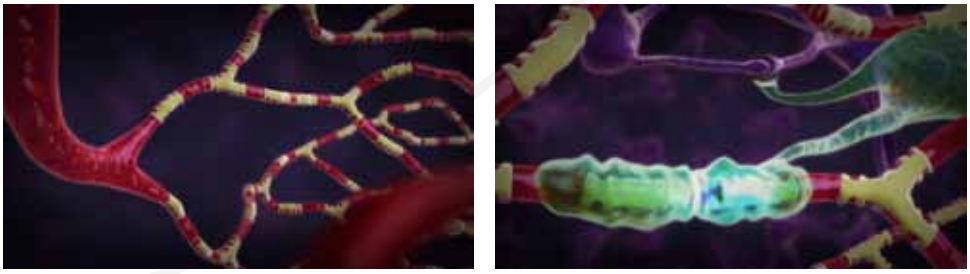

Figure 2
3D illustrations of the mechanisms that ensure oxygen for brain cell activity. The signal substances of brain cells are transported to the smallest blood vessels of the brain (the capillaries) via “supporting cells” (astrocytes).

FUNCTIONAL HEMODYNAMICS

Post stroke neuronal plasticity

by Jakob Blicher

Stroke is a major contributor to death, disability and disease-related expenses in developed countries. Every year, some 12,000 people in Denmark suffer a stroke. Improved acute management has decreased mortality and morbidity; however, roughly half of stroke survivors suffer disability and require post-stroke rehabilitation. It is estimated that 30,000-40,000 Danes suffer some degree of physical and/or cognitive deficits caused by strokes. Our understanding of brain plasticity and, hence, the potential of post-stroke rehabilitation is very limited. So far, recruitment of uninjured cortical areas to attain lost function and modulation of neurotransmitter activity represent the main plastic changes observed post-stroke[1;2]. Despite major improvements in our understanding of cerebral plasticity and learning in the normal brain, little neuroscientific knowledge has been translated into new treatment options for the injured brain, due in part to limited knowledge-sharing between basic scientists and clinicians[3]. Since 2004 CFIN has been collaborating with Hammel Neurorehabilitation and Research Centre, Vanderbilt University Institute of Imaging Sciences (VUIIS), and the Oxford Centre for Functional MRI of the Brain (FMRIB) to test new imaging techniques in stroke patients. Functional MRI (fMRI) is an attractive method for investigating post-stroke neuronal plasticity as it is non-invasive and performed without the use of ionizing radiation[4]. Thus, multiple scans can be performed during rehabilitation without increasing the risk of cancer associated with positron emission tomography (PET). Prior fMRI studies in stroke have used the blood oxygen level dependent (BOLD) technique. The BOLD technique is sensitive to changes in capillary and venous blood oxygenation that is caused by underlying changes in both cerebral blood flow (CBF), cerebral blood volume (CBV) and cerebral metabolic rate of oxygen consumption ($CMRO_2$). However, a recent review failed to find clear associations between functional imaging and recovery, possibly due to a shift in CBF caused by atherosclerosis and/or arteriolosclerosis[5] in stroke patients. Moreover, stroke leads to a disturbance in the balance between excitatory and inhibitory interneuronal activity in cortex[1;2]. This further complicates the interpretation of post-stroke BOLD fMRI results since the size of the BOLD signal depends on the cortical inhibitory activity[6;7]. New fMRI methods, such as vascular-space-occupancy (VASO) and Arterial spin labeling (ASL), are sensitive to changes in CBF and CBV. In combination with BOLD data these techniques provide information on underlying $CMRO_2$ changes during functional activity[8]. To explore the added value of VASO and ASL fMRI in stroke, we scanned 11 patients 9 - 64 months post stroke as well as a group of healthy subjects. The study was performed at FMRIB in Oxford. Participants performed alternating periods of rest and 1 Hz wrist-extension/flexion in the scanner. All three fMRI modalities showed clear activation during wrist movement in the group of healthy subjects (see Figure 1a), however, in stroke patients BOLD fMRI showed no significant difference between periods of rest and movement. In contrast, ASL and VASO showed significant increases in CBF and CBV in primary motor cortex in the patient group (see Figure 1b)[9].

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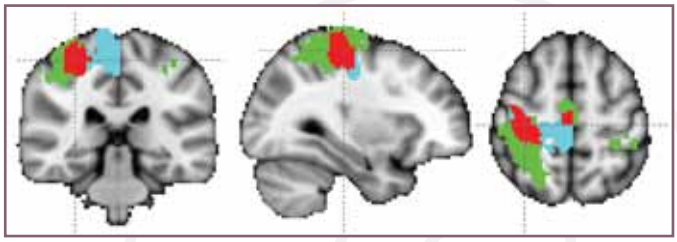

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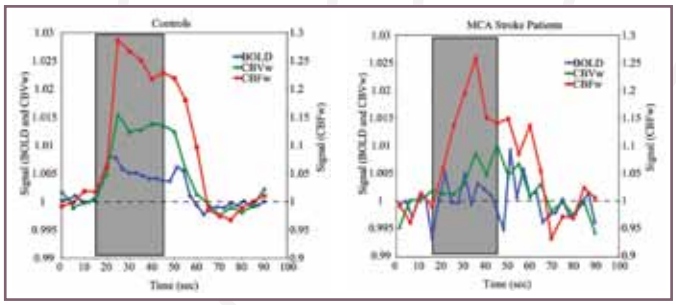

Figure 1
Hemodynamic time courses from chronic middle cerebral artery (MCA) stroke patients and controls acquired using BOLD, ASL, and VASO fMRI in sequence.
A. Activation maps (green), anatomic M1(blue), and common regions (red) for all subjects, normalized to standard space.
B. Time courses in common regions (**A**, red) show robust hemodynamic responses (gray box denotes stimulus period) in control subjects, but discord in CBF and CBV coupling in patients, eliciting absent ensemble patient BOLD reactivity[4].

To investigate the relationship between fMRI techniques and recovery from stroke, CFIN and Hammel Neurorehabilitation and Research Centre are now conducting a follow-up study of stroke patients during rehabilitation. Patients are scanned at CFIN before and after a training stay at Hammel Neurorehabilitation Centre. In addition to the above-mentioned fMRI techniques, changes in cortical excitability are investigated using GABA-edited Magnetic Resonance Spectroscopy (MRS) and Transcranial Magnetic Stimulation (TMS). Stimulating the brain using TMS can elicit movement

and a motor evoked potential (MEP). Thus, the technique can be used to map the motor cortex and measures neuronal plasticity from a different perspective than fMRI. Figure 2 shows an example of TMS that elicited hand movement in a stroke patient despite the remnants of a small infarct in the hand area of the motor strip. By combining these techniques we hope to increase our understanding of post-stroke recovery and to develop methods that can be used to guide decisions on training methods used during post-stroke recovery in individual patients.

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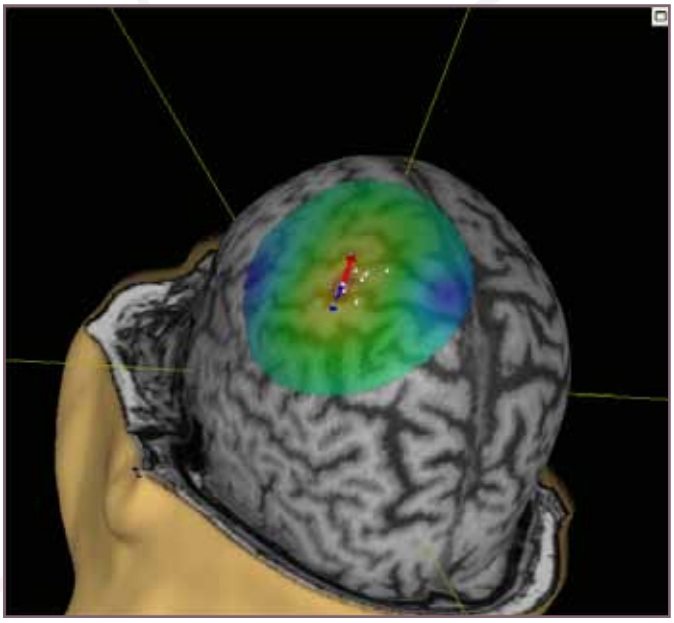

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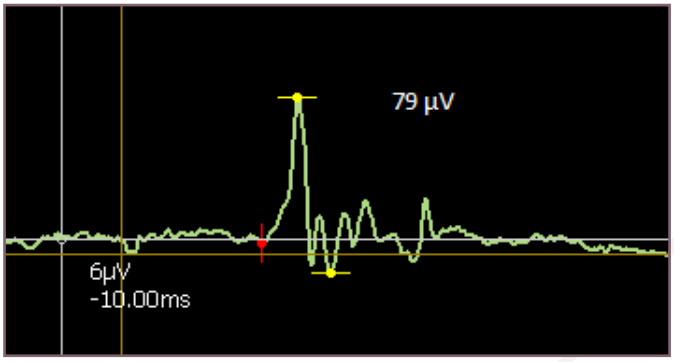

Figure 2
Example of transcranial magnetic stimulation (TMS) of primary motor cortex in a stroke patient.
A. The white markers show where a motor evoked potential (MEP) could be elicited in the paretic abductor pollicis brevis muscle.
B. An example of a MEP recorded during stimulation as shown in **A**.

We expect that our ongoing collaboration with imaging centers like VUIIS and FMRIB and clinicians at Hammel Neurorehabilitation and Research Centre and Department of Neurology at Aarhus University Hospital will lead to new and improved MRI technique that can be of benefit in guiding clinicians in stroke treatment and rehabilitation.

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Jakob Blicher and Andreas Højlund Nielsen during a coffee break at the CFIN & MIND*Lab* Retreat, August 2011. Photo: Alejandra Zaragoza Scherman

CFIN

Ten years as Danish National Research Foundation Center

By Ida Tolbod for the Danish National Research Foundation
on the occasion of their 20th Anniversary

Given the growing specialization and fragmentation in modern research and education, we face an increasing threat: Unless we keep ourselves and each other updated on conceptual and methodological advances in other fields, we may overlook emerging solutions to our time's grand challenges. Research groups and Universities have to organize themselves to meet this challenge - and harvest the fruits of centuries of disciplinary research.

Leif Østergaard

Respect and Humility

Pick the best scientists. Take into consideration that innovative ideas may come from unexpected quarters. Then add a mixture of respect, humility, curiosity and patience. The Center of Functionally Integrative Neuroscience has used this recipe since 2001. And the recipe has proved more than successful.

In a time when academic fields are increasingly divided into sub-disciplines and where new disciplines emerge in between the more classic ones, the Center of Functionally Integrative Neuroscience (CFIN) has lifted its eyes and chosen a markedly interdisciplinary or integrative approach. The center consolidates disciplines such as medicine, physics, music, anthropology, psychology, linguistics, theology, philosophy, statistics and computer science into a collective ambition to learn more about how the brain works – the grey organ which can form Nobel-Prize-winning ideas but still has great difficulty understanding itself.

By embracing competences and insight from various disciplines, the center has, for instance, contributed new knowledge about which signaling molecules are active when certain moods govern our interior world and how music can be used to alleviate pain.

Interdisciplinary science calls for a high level of expertise

To Leif Østergaard, successful interdisciplinary science depends on the will and ability of individual researchers to meet each other with an open mind and mutual respect. It takes equality among researchers to create a community where 1+1 equals 5 says Leif Østergaard, highlighting the necessity of having the best researchers from various disciplines meet. Because, in scientific circles, only one thing creates respect and results – and that is competence.

Gate-keepers with dual expertise

The success of CFIN has also depended on the fact that several of the center's key researchers have mastered more than one discipline and thus managed to bridge the gap and "translate" concepts and ideas between the disciplines. Leif Østergaard himself has degrees in mathematics, physics and medicine, but other center members have degrees combining mathematics and music, biology and anthropology, and so on. These people have been paramount in establishing a coherent and diverse environment at CFIN; an environment in which a new generation of brain researchers has been raised on vision and insight across disciplines and tradition.

Time and patience

Interdisciplinary research at CFIN has called for more than good scientists and gate-keepers. Time and patience have been equally important conditions for success.
This is because it takes time to gain sufficient understanding and establish a common language when interdisciplinary research based on true cooperation is the actual goal and not just for show. In return, results can be far-reaching and surprising.

En route to groundbreaking results

As a consequence of CFIN's interdisciplinary angle, Leif Østergaard and colleagues are tracking a phenomenon in the smallest blood vessels of the body – the capillaries, a phenomenon that can revolutionize our understanding of how diseases such as diabetes, Alzheimer's Disease, cancer and stroke arise and develop. Leif Østergaard calls the discovery "a conceptual bomb" if the theory can be proved. And the center can continue its work because its period as a basic research center has ensured adequate critical mass of researchers and equipment to pursue problems of this complexity.

High Field Neuroimaging Workshop & Summer School 22-23 June 2011

The workshop was organized by: Peter Vestergaard-Poulsen (CFIN), Brian Hansen (CFIN), Sune N. Jespersen (CFIN), Steve Blackband (University of Florida), and held at Danish NeuroscienceCenter, Aarhus University Hospital, Aarhus Sygehus, Denmark.

CFIN is grateful for the support of The Danish National Research Foundation, Mind*Lab* Aarhus University, and the McKnight Brain Institute, University of Florida, Gainesville, Florida which made the summer school possible.

The diffusion and highfield imaging workshop held in the early summer of 2011 provided researchers and students in this specialized field of neuroscience with an opportunity to get together, to discuss recent results and share ideas. The workshop was attended by leaders in the field and the organizers were proud to have pioneers within diffusion MRI and MR microscopy among the speakers. Approximately 60 attendants from USA, Canada, France, Germany, Norway, Sweden, Great Britain and Denmark came to Denmark for this event.

One of the social high points of the 2011 Highfield Workshop was the conference dinner held at Thor's Mølle in Marselisborg forest. During the summer 2011 Aarhus was host to the exhibit "Sculpture by the Sea" located along the coast line between Aarhus city and Marselisborg forest. The walk through this open air exhibit to Thors Mølle provided a refreshing break from the lectures and ample opportunity for informal networking.

Based on our own experience and the feedback we have received from the participants, the workshop was a great success. The talks and discussions were inspiring to students and senior scientists alike, and many new fruitful contacts were established. We are grateful to the Danish National Research Foundation for supporting this scientific and educational meeting.

Participants (and organizors) of the High Field Neuroimaging Workshop & Summerschool 2011 during the conference dinner at Thors Mølle.
Top row from left: Chris Kroenke, Gracielle Kroenke, Mads Sloth Vinding, Min Sig Hwang, Choong-Heon Lee, Steve Blackband, Niels Buhl, Brian Hansen
Bottom row from left: Tim Dyrby, Daniel Alexander, Sara Flint, Jeremy Flint, Sune Nørhøj Jespersen, Lise Vejby
Photo: Leif Østergaard

Dr. Denis le Bihan, the founding father of diffusion weighted MRI, is presented with a *I LOVE DIFFUSION* T-shirt by organizor Peter Vestergaard-Poulsen
Photo: Leif Østergaard

Denmark - China

SDC and new Master programme in Neuroscience and Neuroimaging

by Kim Ryun Drasbek

Sino-Danish Center for Education and Research (SDC)

The Sino-Danish Center for Education and Research (SDC) is a joint project collaboration concerning education and research between the eight Danish universities, the Danish Ministry of Science, Technology and Innovation, the Graduate University of the Chinese Academy of Sciences (GUCAS) and the Chinese Academy of Sciences (CAS). The overall aim of SDC is to promote and strengthen collaboration between Danish and Chinese research and learning environments for the benefit of both countries.

The Sino-Danish Center will be located at GUCAS' future Yanqihu Campus northeast of Beijing and will be fully operational in March 2013 providing an efficient organizational structure and a modern physical environment. SDC will offer high quality master programmes to 300 master students as well as PhD training programmes to 75 PhD students. In addition to supporting the educational environments, SDC aims to enhance scientific and technological collaboration based on the best competencies and research environments in the two countries in part by supporting the mobility of researchers and scientific personnel between Denmark and China and by facilitating mutually beneficial interaction between universities and the industry.

Master programme in Neuroscience and Neuroimaging specialize in solving the mysteries of the human brain

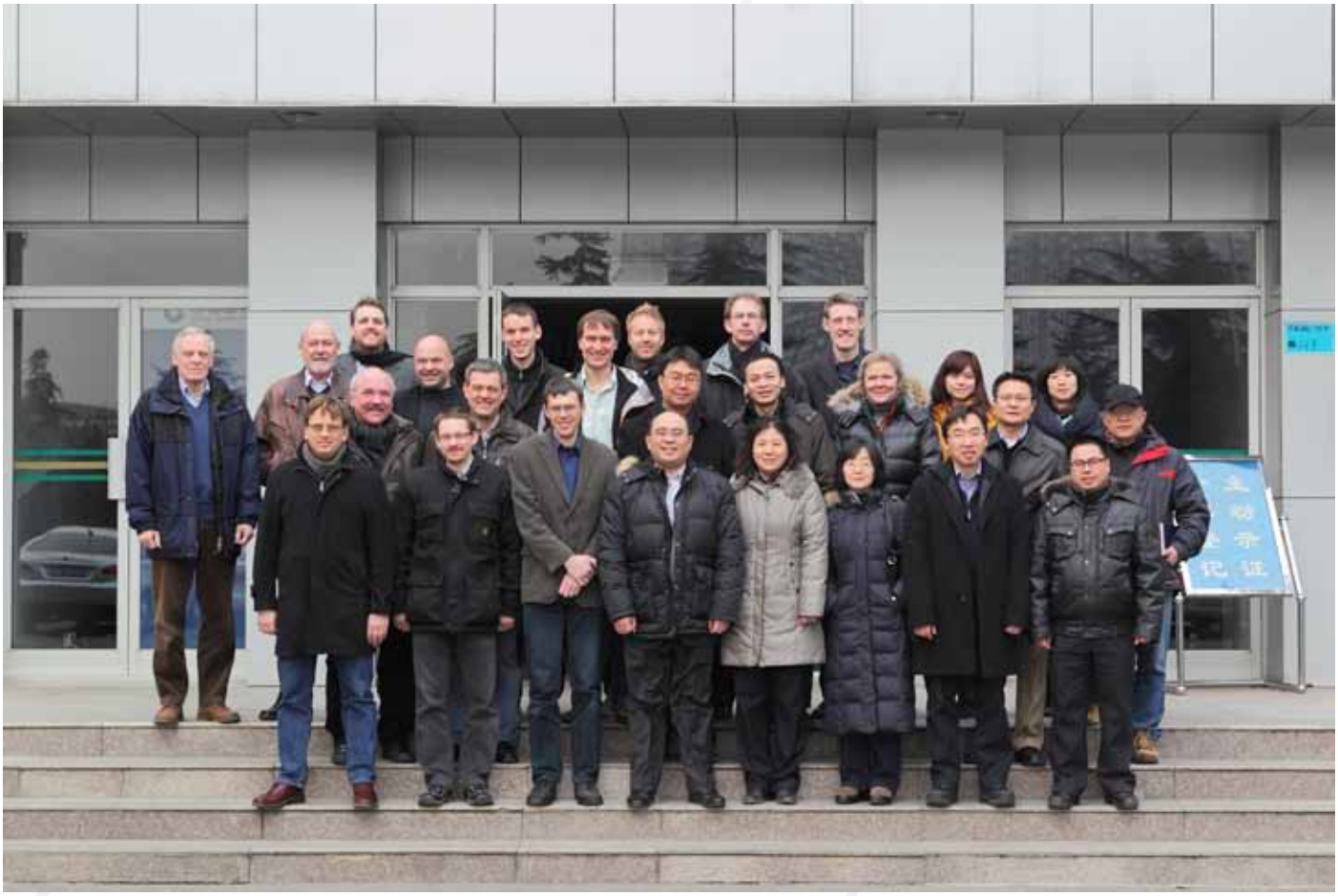
In recent decades, neuroscience has emerged as a fast evolving field that encompass and combine scientific fields from molecule to man, and from genomic profiling to imaging. Neuroimaging is currently becoming relevant to a number of health science disciplines. Importantly this initiative may have a great impact on the future understanding, diagnosis and possible treatment of devastating neurological diseases.

The SDC Master's programme in Neuroscience and Neuroimaging is developed by active researchers from both Denmark and China – uniting the most recent research, modern technology, and problem-oriented learning methods. The unique combination of advanced imaging techniques and a broad knowledge in basic and clinical neuroscience topics enables the students to join the growing field of neuroscience and neuroimaging as well as fill the rising demand for graduates specialized in neuroimaging due to the increasing worldwide availability of advanced imaging methods. As for all SDC master programmes, it is the intention to share the teaching responsibilities equally between China and Denmark, facilitating scientific collaborations as an extra bonus. This Master programme is rooted at Aarhus University but includes course-organizers and lecturers from the other Danish universities as well as several CAS institutes. The programme is scheduled to start in September 2012 enrolling 15 Danish and 15 Chinese BSc graduates.

The 1st Research and Education Workshop for SDC Life Science: Neuroscience and Cognition

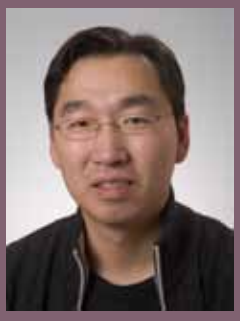
Researchers from GUCAS College of Life Science and the CAS institutes: Institute of Biophysics, Institute of Automation, and Institute of Neuroscience met with scientists from Aarhus University, University of Copenhagen, University of Southern Denmark, and Technical University of Denmark for the first Research and Education Workshop in the Neuroscience and Cognition sub-theme of SDC. The workshop took place in Beijing in January 2012 and focused on discussing and planning the newly accredited Master programme in Neuroscience and Neuroimaging and to strengthen research collaborations within the fields of neuroscience and neuroimaging. To emphasize the collaborative nature of this new education, each course has a Chinese and a Danish co-organizer, who discussed the detailed planning and organization during the workshop. Teachers from all courses were represented at the workshop, providing opportunities to discuss the progression and coherence of the Master program.

The initiation of fruitful Chinese-Danish research collaborations was facilitated by visits to several laboratories at CAS institutes, with Professor Yong Fan, Institute of Automation, Professor Yan Zhuo, Institute of Biophysics, and Professor Zengqiang Yuan, Institute of Biophysics as hosts. These visits were very enlightening for the Danish scientists and promoted interesting discussions, and revealed several avenues of collaborative research projects. To implement these collaborations, research stays in China and Denmark are essential and several exchanges of students and post docs were therefore discussed. Furthermore, two Danish SDC funded PhD students participated in the workshop, which gave them the opportunity to discuss their projects with their future Chinese co-supervisors and plan their stays at the Chinese labs.



Danish and Chinese participants in the 1st Research and Education Workshop for SDC Life Sciences: Neuroscience and Cognition in front of the administrative office building at the GUCAS Yuquanlu Campus in Beijing, China. January 2011.

NEW FACE AT CFIN/MIND*Lab*



Kim Ryun Drasbek, MSc, PhD is employed as an Associate Professor since September 2011. He holds a Master in Molecular Biology and a PhD from Health Sciences, Aarhus University. The PhD project combined molecular biological techniques with electrophysiological measurements in neurons. He extended his electrohysiological research during the following post.doc to neuronal recordings in slices from different animal disease models. During the last 5 years he has worked with antibodies and protein science at the Department of Molecular Biology and Genetics, AU, while also functioning as the scientific administrator of the large integrated EU project, PROTEOMAGE.

Kim was initially employed to plan and formally get a new Master programme for Neuroscience and Neuroimaging accredited. He is now the head of this new education, which will start in September 2012 in Beijing, China as part of the SDC initiative. In addition, Kim is part of the administrative team of CFIN/MIND*Lab* as scientific coordinator but is still involved in research mainly as the coordinator/supervisor of *in vitro*/*in vivo* studies of pericyte function and their impact on capillary blood flow.

Hedonia: TrygFonden Research Group

The development of hedonia

by Morten L. Kringelbach

Aristotle and later psychologists proposed that happiness or well-being is composed of at least two components: hedonia and eudaimonia. Definitions by philosophers and psychologists have varied, but most generally agree that hedonia corresponds psychologically to pleasure (Kringelbach and Berridge, 2010). One important challenge for hedonic psychology and affective neuroscience is to understand how pleasure is generated by brain mechanisms so as to contribute to well-being.

All animals including humans have to survive and procreate, and reward can be thought of as the common currency that makes this happen. Pleasure is probably evolution's boldest trick for sustaining and nourishing our interest in the things most important to us.

Hedonia: TrygFonden Research Group is a transnational research group based both at CFIN/Mind*Lab* and University of Oxford, UK which is dedicated to the investigation of hedonia. Since the inception in 2007, the research group has grown to 16 members who are dividing their time between the two sites. We have many international collaborators, yet one of our foremost aims is to act as a bridge between Aarhus and Oxford to help foster collaborations between researchers.

"Morten's Angels" - Morten Kringelbach and students from the Hedonia: TrygFonden Research Group at the CFIN & MIND*Lab* Retreat at Sandbjerg Manor, August 2011.
From left: Tim van Hartevelt, Maria Witek, Morten Kringelbach, Katie Young, and Christine Parsons.

We are researching many of the aspects of human pleasure but one of our main interests is to understand the development of hedonia over a lifetime. The early relationships between infants and parents are of fundamental importance for the survival and development of one's own infant, and ultimately ensure the survival of the species. Humanity is a very social species that invests heavily in nurturing and protecting the young. Accumulating evidence indicates that early life experiences have a major impact upon adult mental and physical health (Shonkoff et al., 2009).

In this year's Annual Report we report on some novel findings that we have recently published with regards to the impact of infant cries (Parsons et al., 2012). This research is part of a larger research programme to understand the functional neuroanatomy of the parent-infant relationship and its impact on later well-being (Parsons et al., 2010).

Infant crying as a research tool

There are few sounds that carry as much biological clout as the cries of a distressed infant. Consider a crying infant on a plane: the sound is as unpleasant as it is difficult to ignore, even amongst a host of other environmental noises. A distressed infant's cry, characterised by high and variable pitch, elicits autonomic arousal in the listener as measured by heart rate, blood pressure, skin conductance (for review, see Boukydis and Burgess, 1982; Zeskind and Collins, 1987) or hand grip force (Bakermans-Kranenburg et al., 2011). The physiological arousal seen in response to infant cries may reflect a 'high-alert' state that prepares an adult to react rapidly to the infant's distress (Giardino et al., 2008).

We examined whether the reported physiological change in response to infant cries translates into measurable differences in adults' ability to move in a concerted and accurate manner. To this end, we played a series of infant cries and other sounds to a group of adults and measured subsequent performance on an effortful motor speed and dexterity task, in the form of a miniature version of the classic arcade game, 'Whack-a-mole'. This game is brief but engaging and requires participants to press down on a target button (indicated by a light), with a predetermined amount of force, in order to score points. Within the same individuals, we compared performance on this task after listening to infant distress vocalisations, adult distress vocalisations and non-distressed, but high-pitched bird vocalisations. An individual's overall score on the task reflected their success in pressing target buttons quickly

enough and with sufficient force. An additional, subtle measure of change in performance was obtained in the form of effort exerted by participants, by measuring the pressure applied to target buttons during the game.

Similar measures such as hand-grip force in humans (Pessiglione et al., 2007) or lever pressing in animal models have been taken as an index of behavioural activation or motivation to act (Berridge et al., 2009).

Forty adults (twenty males), ranging in age from 19 to 59 years took part (*M* = 26.5, *SD* = 8.2). Three participants were parents, but none had young children. All participants had normal hearing and normal vision or vision corrected to normal.

The task, a small-scale version of 'Whack-a-mole' (Figure 1A, 'Whack it', USB version), requires participants to press one of nine buttons, whose location varies randomly across the game. As the game progresses, the speed of change in location of the target button increases. The game was mounted on top of electronic scales, which were used to gauge the amount of effort participants exerted to push the buttons by measuring peak weight (in grams; minimum, maximum and average weights were recorded by videotaping the scales for the duration of the experiment). The amount of effort participants needed to apply to a target button in order to score was measured on the scales as approximately 350g.

After playing three 30 second practice rounds, each participant listened to 4.5 minutes of one of the sound categories and then immediately replayed the game for 60 seconds. This was repeated for each of the sound categories, with the order that participants heard each sound category in counterbalanced across participants. Each sound category consisted of 15 sounds, clipped to 1500ms, free from background noise and matched to have linear rise and fall times of 150msec and comparable average root mean square intensity. The sounds were presented at 70 dBFS above each participant's absolute hearing threshold using Sony In-Ear earphones. The three sound categories were obtained from video recordings, and the human sounds were independently rated as unambiguously communicating distress.

Scores on the game were significantly higher after listening to the infant cries compared with the other sounds (Figure

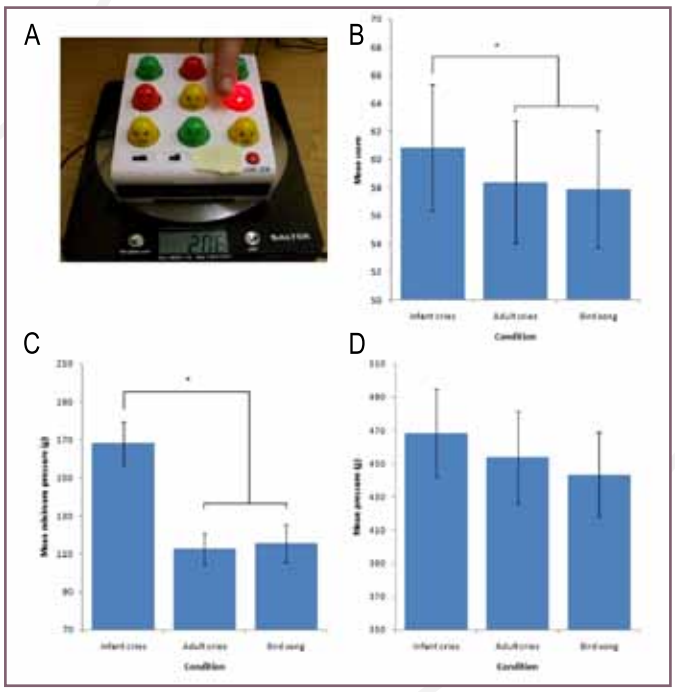


Figure 1
The 'Whack-a-mole' game and participant performance after listening to the different sound categories: A) task and scales B) mean scores across categories, C) mean minimum pressure scores, D) mean pressure scores. Error bars represent the mean +/- standard error, * indicates significance.

NEW FACE AT CFIN

Christine Parsons, PhD, is a post doctoral researcher at the University Department of Psychiatry, Oxford. Her current research focuses on two major themes: 1) The neural correlates of combat-related post-traumatic stress disorders and 2) how we respond to arguably the most biologically salient information in the environment, the sounds and faces of infants. As well as understanding normal brain function, a major aim is to understand what happens in affective disorders such as depression and anxiety. This is accomplished through the study of clinical, nonclinical and neuropsychiatric populations using complementary methods including magnetoencephalography (MEG), deep brain stimulation (DBS), functional MRI, diffusion tensor imaging and behavioural tasks.

1B; $F(1, 38) = 5.47$, $p = .02$, $r = .35$). Men and women had similar scores overall ($F(1, 38) = .13$, $p = .72$, $r = .05$) and the interaction between gender and sound category was not significant ($F(1, 38) = 2.87$, $p = .09$, $r = .26$). The minimum pressure participants applied to the buttons was significantly greater after listening to the infant cries compared with the other sounds ($F(1, 38) = 32.44$, $p < .001$, $r = .68$, Figure 1C). No significant effects of gender or sound category x gender interaction emerged for any of the pressure score data. Participants applied similar average pressure ($F(1, 38) = 3.18$, $p = .08$, $r = .28$, Figure 1D) and similar maximum pressure ($F(1, 38) = 1.27$, $p = .27$, $r = .18$) to the target buttons after listening to each sound category.

Infant cries enhances effortful motor performance

The higher minimum pressure scores after listening to infant cries suggest that participants were consistently attempting to hit the target buttons with close to the amount of force necessary to score a point. This finding, consistent with studies of the 'wanting' component of reward processing which take analogous pressure measures in animals (Berridge et al., 2009), suggests that infant cries can motivate people to act. Average and maximum pressure scores after all three sound categories were substantially higher than the amount of force required and therefore did not reflect relative success on the task.

Here, we report novel evidence to show that infant distress cries can elicit immediate improvements in adults' motor performance, as indexed by rapid, co-ordinated effortful movements. These improvements were not simply a consequence of listening to a high-pitched sound, or a distressed human vocalisation. The specificity of this effect suggests that infant crying is a privileged category of human emotional vocalisation that can have a unique impact upon adults' behaviour. Crying is metabolically costly for the infant, but when it occurs as a result of transient distress, it is highly likely to elicit parental care (Soltis, 2004). It is not hard to imagine how faster, more accurate intentional movements could facilitate such caregiving.

Listening to infant cries has been shown to adversely affect performance on simple cognitive tasks when compared to other noisy environmental sounds (Morsbach et al., 1986). In this study, we demonstrate a positive consequence of hearing distressed infants: improvements in speed and accuracy in intentional movements. Such improvements in accurate effortful movements may reflect an adaptive physiological response that takes effect where an immediate reaction to a distressed infant is required.

NEW FACE AT CFIN

Katie Young is a graduate scholar at Jesus College who is currently reading for a D.Phil. in Psychiatry on an MRC funded studentship. Her research focuses on the neural basis of adult responsiviness to infant vocalisations, particularly in the context of affective disorders. Her research combines behavioural, neuroimaging and observational techniques to investigate how healthy individuals and individuals with affective disorders interpret and respond to different features of infant vocalisations. The aim is to better understand the origins of disrupted responses to infant cues in the context of psychopathology through characterising behaviour and investigating the underlying spatio-temporal neural processing using magnetoencephalography (MEG).

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TrygFonden

NEW FACE AT CFIN

Tim van Hartevelt is a PhD student in the TrygFonden Research Group, a transnational research group based both at CFIN, Aarhus University and in the Department of Psychiatry, Oxford. Before starting his PhD he obtained a BSc in psychology and an MSc in Cognitive Neuroscience from Utrecht University in the Netherlands.

His research focus is on olfactory (dys)functioning in Parkinson's disease using techniques such as Magnetoencephalography and Deep Brain Stimulation. Additionally he is interested in the further understanding of DBS on the human brain including longer term effects.

The Henry Prize

The communication of knowledge and ideas is key to CFIN/MIND*Lab*: Not only to give back to Society, to private and public grant sources, and to the average citizen, who generously support our work - but also in the process of sharing knowledge and ideas across disciplines within CFIN/MIND*Lab*: Only by communicating our thoughts and ideas in a way that engages others, can we gain the synergy that comes from working across disciplines, and the help and support of our colleagues. To reward and acknowledge CFIN employees who make extraordinary efforts in these respects, everyone can nominate colleagues worthy of The Henry Prize.

A Humanitarian Henry Prize has also been instituted, to recognize colleagues who become innocent victims of breaches in scientific communication in the widest sense.

The Henry Prize will be awarded every year, during a ceremony taking place at the annual CFIN Christimas Dinner. It constitutes 5000 DKK, to be used for work-related travel or equipment in the widest sense at the recipients discretion, provided that this activity/need is not currently funded from other sources.

In 2011 The Outreach Henry Prize was awarded to Karen Johanne Pallesen, The Humanitarian Henry Prize was awarded to Kristian Tylén and a Lifetime Achievement Henry Prize was awarded to Henriette Blæsild Vuust.

COGNITION RESEARCH

by Andreas Roepstorff

Synchronized arousal at a firewalking ritual

Every year at summer solstice, the inhabitants in the small Spanish village San Pedro Manrique gather for a festival. This culminates in a evening firewalking ritual. Accompanied by roaring crowds, participants walk on burning coal, often carrying a friend or a relative on their shoulders. Ivana Konvalinka, Dimitris Xygalatas and colleges studied whether experiencing the ritual would lead to synchronized bodily states in participants and observers. With small monitors they studied the heart rhythms of 40 people in parallel during the ritual. Some of these were firewalkers, others were related to the firewalkers while the remaining were unrelated spectators. By employing complex time series analysis, we found that the main difference in the patterns of heart rhythm was between those that were affiliated with the ritual, be that as firewalkers or as relatives, and those that were merely observers of the event. This indicated that the ritual enabled participants to experience synchronized arousal, and that participation was delineated by affiliation to the group, rather than by whether one did the firewalk or not. This lends experimental and physiological support to the classic claims that rituals may support group cohesion and enable collective effervescence (Emile Durkheim). The study, published in PNAS[1], attracted worldwide media attention, including the front page of the New York Times.

New directions: modeling and complex systems approaches to interaction

The Firewalking study is one instance of the development of new methods, derived from modeling and complex systems approaches, to study interaction. A similar strategy has been employed in further developments of the optimally interacting minds paradigm, which have allowed us to quantify linguistic coordination[2] and to study the role of feed-back in collective decision making[3].

Fear circuits involved in story processing

Controlled experiments are necessary to ensure that scientific results can be interpreted. However, by imposing very strict control you run the risk of eliminating the object of interest in the process. Most human activities do not play out in strongly controlled laboratory environments. It is therefore very important to combine controlled experiments with experiments that may have less rigid control over all variables but come across to participants as more ecologically valid.

In the case of language processing, a lot of experiments have been conducted at the single word and at the sentence level. But how do these results relate to the experience of meaning processed during longer stretches of speech, such as when listening to a story?

We conducted an fMRI experiment (Wallentin, et al. 2011) to investigate if emotions evoked by stories are processed by the same brain regions that process more “simple” emotions, such as conditioned fear responses. Learned couplings between sounds and unpleasant experiences, such as electric chocks are known to be processed through a network of brain regions, centered around the amygdala. In our experiment we had a group of raters listen to The Ugly Duckling, the famous story by Hans Christian Andersen, and continuously rated their emotional arousal. In a subsequent fMRI experiment other participants listened to the same story, and the rating pattern of intense and boring parts of the text was used as input in the analysis of the brain imaging data. We found a significant correlation between the rating pattern and activation in the fear network. We also found a correlation between story intensity and heart rate variability, thought to reflect sympathetic fight/flight response. This suggests that more complex emotional responses evoked by stories do indeed hinge on the same processes as simple fear responses.

Major review article

Chris and Uta Frith have published an extended review article Mechanisms of Social Cognition in Annual Review of Psychology[4], arguably the most important review journal in the field.

Interacting Minds project 2011

2011 has been a highly productive year in the Interacting Minds research group in terms of publications, research grants, collaborations, teaching and new appointments.

The Interacting Minds research group had more than 40 publications accepted for publication, several in top-ranking journals. We are benefitting from the groundbreaking design of interactive experiments, pursued in the first phase of the Niels Bohr professorship to Chris Frith, and we are increasingly extending into clinical research. This research has attracted considerable media attention.

We have strengthened our links to clinical departments, e.g. with studies on on pain, autism, schizophrenia, depression,

brain lesions etc. We have intensified collaborations with groups, which develops novel methods, through extended research stays by Ivana Konvalinka (DTU) and Daniel Campbell-Meiklejohn (NYU). We have also recruited Sebastian Wallot from the Center for Action and Perception, University of Cincinnati, to strengthen our time-series analysis strategies. We have joined two new European research networks, the Marie Curie Initial Training Network TESIS and the EUROUNDERSTANDING/EUROCORES project DRUST. As part of TESIS, we have also begun a collaboration with Lego Learning Institute, Billund to study the interface between objects, cognition, and action.

The neuroimaging infrastructure at MIND*Lab* is now well in place in terms of EEG, fMRI, MEG and TMS. There is a rapidly growing need for behavioral experimental facilities. We are currently negotiating with the faculties of Arts and Business and Social Science at Aarhus University to have such facilities established with access to researchers from Interacting Minds, MIND*Lab* and other related groups.

Chris and Uta Frith were in Aarhus at an unpaid visit through July and August 2011. They mentored research students, took part in design, analysis and write-up of experiments, and were involved in the Aarhus University Summer School. Whenever possible, Chris Frith took part in the weekly Interacting Minds seminar via video link.

The weekly Interacting Minds seminar forms the core research training activity. We have also contributed to two Aarhus University Summer Schools (Experimental Studies of Cognition and Culture and LEADER), and we have been involved in research training abroad (e.g. Ann Arbor and Bergen).

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SELECTED RESEARCH PROJECTS:

Andreas Roepstorff, Kristian Tylen, Karsten Olsen, Riccardo Fussaroli: Digging for the Roots of Understanding (DRUST, Eurocores project)

Andreas Roepstorff, Tylen, John McGraw, Sebastian Wallot: Towards an Embodied Science of Instersubjectivity (TESIS, Marie Curie project)

Francesca Farda, Else Marie JEgindø, Andreas Roepstorff: Neural mechanisms underlying cognitive top-down modulation of pain: insights from electrophysiology:

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.

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

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

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

Joshua Skewes, Bryan Patton and Jakob Hohwy : Predictive coding binocular rivalry and brain function.

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

Joshua Skewes: Bioagency and behavioural science.

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.

COGNITION RESEARCH

A Paradigm Shift in Consciousness research: Re-introducing causality

by Hans C. Lou

The neural basis for conscious experience continues to be a challenge to modern neuroscience and is a key to our understanding of major neurological and psychiatric disorders. In spite of early, seminal demonstrations of causal effects of stimulus length and duration for conscious experience by Libet and coworkers, research in consciousness has long been limited to establish correlations between neural activity and conscious experience. This attitude has been eloquently formulated about 15 years ago by the philosopher David Chalmers. According to David Chalmers, the "hard problem" of consciousness is why and how subjective experience arises from a physical basis. He considered the hard problem to be un-accessible with current technology at the time. With few exceptions, the position has been so influential that contemporary research has been stymied by focusing on what David Chalmers considered to be the "easy" problem of consciousness, i.e. its neural correlates. This limitation has the inherited risk of leading to a dualistic concept of human nature with two different worlds, the physical and the mental, without understanding their relationship. It also impedes our understanding of the biological function of self-awareness and conscious experience, and how its disturbance in pathology may account for major symptoms in self-regulatory disorders like addiction, autism, ADHD, and schizophrenia. However, recent methodological advances justify a paradigm shift to focus on causality in consciousness research. Research at CFIN and collaborating centers have profited by these new possibilities, using both new brain stimulation techniques and pharmacological intervention to manipulate neural activity and examine the behavioral consequences.

Access to conscious experience from sensory stimuli or memory retrieval requires cortical or thalamic signal strength and duration to transgress a certain threshold, which is typically a few hundred ms, dependent on signal strength. New data suggest that access to consciousness is regulated in part by dopamine, which is released in paralimbic regions with a latency of only 100ms by salient stimuli. Dopamine is known to enhance the stimulus to noise ratio in the brain. Its effect may occur (partially) via interneuron activation and GABA release which is known to control pyramidal cell synchrony, fingerprint of cognition, including self-awareness. To further enhance meaningful stimulation to access consciousness via a paralimbic network of self-awareness, it has been proposed that bi-directional, or re-entrant, re-activation of regions in cortico-thalamic networks may lead to sufficient strength and

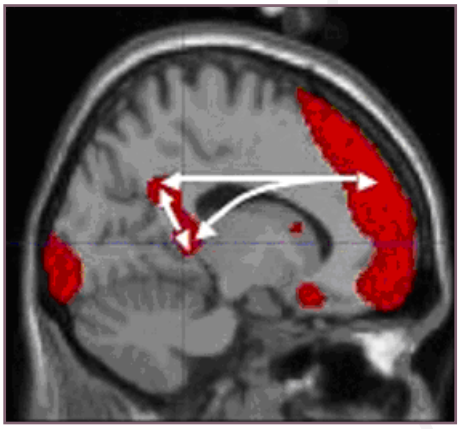

Figure 1
A paralimbic network of self-reference. Network was identified in a previous PET study of hemodynamic paralimbic interactions elicited by extended self-reference (*X*=+0, Talairach coordinate; ref. 1). Arrows indicate interactions between medial prefrontal/anterior cingulate and medial parietal (precuneus)/posterior cingulate cortical regions and pulvinar thalami (Lou et al., PNAS 2004, with permission).

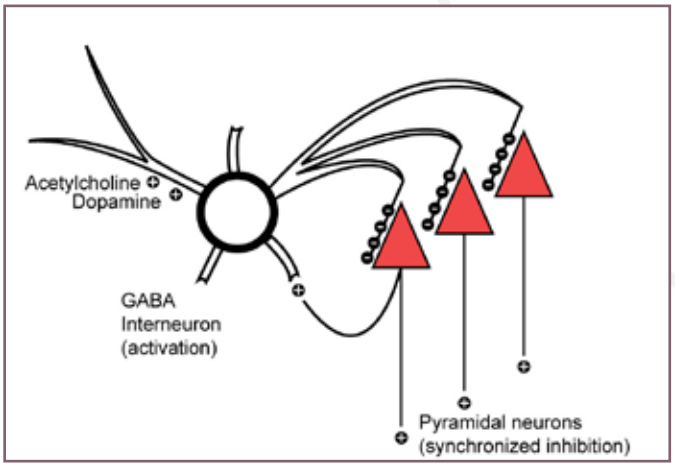

Figure 2
Acetylcholine and dopamine regulating γ synchrony via GABA interneurons. Pyramidal cells, constituting ~75% of cortical neurons, are exhibiting γ synchrony for interaction between cortical regions, i.e., in the paralimbic circuitry of self-reference. Fast-spiking GABAergic neurons are responsible for this synchrony by inhibitory influence on pyramidal cell excitation. In turn, interneuron activity is enhanced by acetylcholine (muscarinic) receptors and dopamine D1 and D2 receptors located at or near the soma. By this common path, acetylcholine and dopamine both enhance paralimbic synchrony for self-reference, a crucial constituent of any conscious experience. Modified from Gonzalez-Burgos and Lewis, with permission.

duration of their activity to induce conscious perception. Re-entrant re-activation means that one neural assembly (A) in a given network activates another (B), which again re-activates A, etc. In this way a "bootstrapping effect" is obtained with increasing signal duration and intensity in the network. It has recently been shown that this mechanism in fact does constitute the backbone of cortico-thalamic integration in a paralimbic system of self-awareness.

Self-awareness is a pivotal component of any conscious experience. This is evident already from the fact that any experience requires someone to have that experience. Conscious experience has been likened with a coin, with one face illustrating comparatively stable self-awareness and paralimbic activation, inseparable from the other face, consisting of shifting contents supplied from the outside world through sensory and semantic or procedural sources. During the past decade, the paralimbic neural network of self-awareness has been described in detail. It includes anterior cingulate/medial prefrontal, and posterior cingulate/medial parietal cortices interacting with bilateral angular gyri at the temporo-parietal junctions and with subcortical structures. The network is located medially in the two hemispheres at the interface between information from emotions, memory, and body via the limbic system, and from the environment via neocortical and trans-modal association regions. The network interacts by gamma synchrony which increases with the degree of self-awareness in conscious experience. Our recent data link gamma synchrony to self-awareness and conscious experience, their development in early life, and, in default, to developmental neuropsychiatric disorders involving deficient self-awareness and self- control.

Importantly, we have now established causality of the paralimbic network in self-awareness in collaboration with the brain stimulation departments at Columbia University and Duke University (Bruce Luber, Holly Lisanby, and Julian Keenan). This was done by using single pulse transcranial magnetic stimulation (TMS) to examine the behavioral consequences of disturbing normal function of a given neural assembly by means of magnetic induction of non-physiologic neural activity (12-14). These findings were corroborated by granger causality analysis, a mathematical tool to ascertain causal influence of one neural assembly on another, and by pharmacological manipulation, for instance dopaminergic activation. Neural organization of self-awareness has been further explored by establishing its link to gamma synchrony in the paralimbic network. However, at the present time this link is purely correlative with no evidence for causality. In the near future we plan to test the hypothesis of a causal effect by manipulating gamma synchrony, using transcranial alternating current stimulation, in collaboration with the Brain Stimulation Unit at the Department of Psychology, University of Glasgow (Professors Gregor Thut and Joachim Gross).

Professor Hans C. Lou at the CFIN & MIND*Lab* Retreat at Sandbjerg Manor, August 2011
Photo: Leif Østergaard

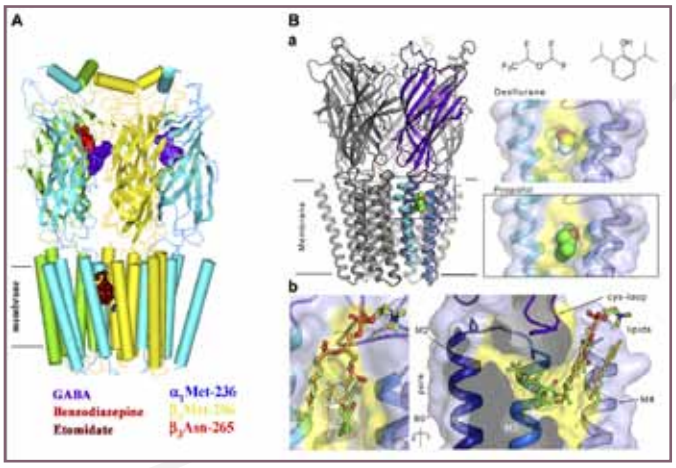

Figure 3
Molecular model of the GABA-A receptor and of the main categories of binding sites for pharmacological agents (A) and X-ray structure of the allosteric site for general anesthetics on a pentameric ligand-gated ion channel (B). A) The neurotransmitter GABA (violet) and its homologue orthosteric ligands bind to defined subunit interfaces in the extracellular (synaptic) domain; the benzodiazepine (red) site is located at nonconventional subunit interfaces of the extracellular domain; the allosteric site for general anesthetics, here etomidate (brown), is present within the transmembrane domain. B) a) The pentameric receptor channel from the bacteria Gloeobacter violaceus is a close structural homologue of brain neurotransmitter-gated ion channels like the nicotinic acetylcholine or GABA receptors. b) The general anesthetic (propofol, desflurane) binding site is located within the transmembrane domain near the interface with the extracellular domain and in close relationships with membrane lipids, which may behave as endogenous ligands. Reproduced from Li et al. and Nury et al., with permission.

CNRU

Cognitive Neuroscience Research Unit

by Morten Overgaard

The Cognitive Neuroscience Research Unit, CNRU, is an interdisciplinary research group, performing experimental and theoretical research within cognitive neuroscience, neurorehabilitation, and philosophy of mind and science. For CNRU it is a fundamental ideology that the interdisciplinary cooperation between basic science, clinical research and philosophy is reflected in all research projects.

Morten Overgaard, head of CNRU

Consciousness research

CNRU researchers have devoted much effort into the ambition of unravelling the relation between mental and neural states. This work entails the invention of experimental paradigms that reliably study the contents of subjective consciousness and that are able to relate such findings to objective measures of brain activity or behaviour.

In 2011, we published ten publications directly relevant to this question. From a theoretical perspective, we have devoted particular focus to definitional and methodological challenges regarding subjective experience. Intuitively, it seems difficult if not impossible to study phenomena that are inherently subjective and only accessible from a "first person perspective" in objective experiments. However, several aspects of our work have been devoted to the development of methods to address this issue.

A number of collaborations with national and international partners have contributed with important expertise. Kristian Sandberg, who was employed as a post doc from the ERC Starting Grant funding after his PhD defence in February 2011, received a part-time fellowship from University College London to strengthen our collaborations. Thus, we are working on different methods to "decode" mental states from neural activity measured by MEG. Future experiments will use this method to test predictions of mind-brain relations, and to give indications about subjective experiences in non-communicating patients.

Lau Møller Andersen joined CNRU after his MSc from Amsterdam University and internship at Emory University. While preparing his PhD he will conduct experiments on spatial cognition in neglect patients and a TMS experiment, tracking neural signals related to conscious visual perception. This latter experiment will hopefully be able to test current hypotheses that conscious perception is mediated by reentrant activation of primary visual cortex.

Motor control and action

Based on a grant from The Danish Council for Independent Research, we investigate another difficult aspect of mind-brain interactions in collaborations with Søren Kyllingsbæk and Thor Grünbaum, University of Copenhagen. As mentioned above, consciousness is typically defined as subjective experience: A basically non-functional definition that in itself does not entail that we have to be conscious in order to perform any cognitive or motor function. In fact, cognitive psychology has found dissociations between conscious experience and almost every possible cognitive function.

Nevertheless, most people entertain the idea that consciousness is somehow related to action, e.g. as "free will", or that we at least by way of being conscious cause certain actions, if nothing else then verbal reports such as "I am conscious". However, if there is any truth behind such ideas, states of subjective consciousness must be in some or other causal relationship to functional and physical states.

Mads Jensen is currently running experiments and theoretical analyses of neuropsychological syndromes, e.g. "anarchic hand syndrome", in order to study interrelations between awareness and ownership of action. Mikkel Vinding joined CNRU in 2011 and, while preparing for a PhD, is running a variety of continuations of the classical Libet-experiment, arguably showing a "delayed" experience of wanting to move in relation to the readiness potential preceding physical movement.

Cognitive neurorehabilitation

One basic ambition of CNRU is the integration of basic and clinical research. Different ongoing experiments are currently investigating disorders of working memory following brain injury. One longitudinal, conducted by PhD student Jonas Lindeløv, investigates effects of computerized cognitive training programs. In another, larger, study, Jonas Lindeløv and Rikke Overgaard investigate the effect of hypnotic inductions on brain injury. A pilot study indicated that certain inductions have a strong and seemingly lasting improving

effect on working memory. PhD student Lars Evald, using a different approach, investigates whether the use of electronic devices (Smartphones) may assist or even rehabilitate working memory functions.

Coma and vegetative state research

Most consciousness research focuses on the contents of consciousness as e.g. the difference between a cognitive process with and without accompanying conscious experience. A different area of study with great ethical implications, however, is the study of levels of consciousness, as in the difference between being comatose and being awake and alert. Here, also, we have performed theoretical investigations of how to study subjective states in non-communicating patients, resulting in different publications, e.g. one in the prestigious medical journal The Lancet. Based on these considerations, experiments to study mental states in patients with so-called disorders of consciousness will be initiated early 2012.

Theoretical modelling

The entire field of cognitive neuroscience, from basic to clinical research, is producing an increasing amount of experimental investigations each year. However, overarching theoretical models to explain mind-brain relations are developing at a much slower pace. One reasonable explanation of this could be that most experiments can be theoretically explained from several different perspectives. Stated as a critique, many experiments in cognitive neuroscience may say nothing or very little about how we might conceive of mind-brain relations. From 2011, Morten Overgaard started a theoretical attempt to construct overarching models, showing how theories of mind-brain relations can be put to a direct empirical testing.

Masters program in Cognitive Neuroscience

In 2011, Morten Overgaard accepted a part-time professorship at Dept. of Communication and Psychology, Aalborg University, while keeping his current position as associate professor in Aarhus. The main purpose of the professorship is the development of a Masters programme in neuropsychology and cognitive neuroscience, which has launched summer 2011. In an intensive and international environment, students are introduced to experimental, clinical and theoretical work in this branch of science with the ambition of strengthening the neuropsychological arena in Denmark. Students will not simply be introduced to science, but will perform 1-3 empirical investigations themselves during the 2-year Masters programme.

Funding

Until Morten's professorship in 2011, CNRU has supported itself entirely by research grants. Currently, CNRU is funded by a Starting grant from European Research Council, The Danish Council for Independent Research: Communication and Culture, Karen Elise Jensen's Foundation, and several smaller grants.

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CNRU

Knowing and feeling that you did it

by Mads Jensen

We all know a situation when a person asks if you have pen. Not having one at hand, we look around to locate a pen, pick it up and hand it over. We do not have difficulties performing the task, and importantly, we know we did it. Our research is concerned with the question of how we get this unique feeling and knowledge of having performed an action. This feeling of doing is called *sense of agency*. It is an important part of performing actions, but it is poorly understood.

Interestingly, the sense of agency can break down. There are a group of pathologies in which patients claim the action does not belong to them. In Anarchic hand syndrome patients perform what seem like deliberate actions, e.g. picking up a pen from a table, but they say *they* did not do it. They know their own hand moved, but they say it was not their action (see e.g. Della-Sala & Marchetti, 2005).

This paradoxical behaviour implies there is a difference between the knowledge and feeling that your hand moved and the knowledge and feeling that it was you who did it. We have, however, all experienced dissociations between feelings of movement and agency. If someone grasps your hand and move it around, you are fully aware that your hand moved and that you did not do it. Although feelings of moving and that you caused the movement are both very familiar, they are very different.

We try to investigate this dissociation between the knowledge and feeling that your hand has moved and the knowledge and feeling that you have moved it: the difference between awareness of action, ownership of action, how they are related, and how they might influence each other. One important question is whether the sense of ownership is different in planned and spontaneous actions. In other words, does free will change sense of agency?

There are several ways in which these questions can be approached and different perspectives are needed to understand the sense of agency. Magnetoencephalography (MEG) is a brain-imaging technique that records tiny magnetic changes that occurs when neurons in the brain are activated. These changes can be compared to a structural scanning of a person (a structural scan can be thought of as a 3 dimensional image of the brain), and the change in the magnetic fields can tell us something about the brain activity at a region in space. While the spatial resolution of MEG is not as good as with Functional MRI, it does however have a better temporal resolution. That is, with MEG we can track brain activity at the scale of milliseconds. This gives us an opportunity to measure the temporal exchange of information in the brain.

MEG scanner at CFIN

In one experiment, following the ideas of Blakemore, Oakley, and Frith (2003), we use hypnosis to investigate how the belief that you moved your hand or that your hand is moved by someone else affects your feeling of ownership of the actions. Differences in neural activity between those conditions are investigated using MEG. In one condition, we hypnotise participants to move their own hands while believing it was actually not her who moved the hand. In another condition participants will move their hands normally. We can compare the two conditions and in that way compare brain activity when participants believed it was them who moved their hand and when they believed it was someone else. As the participants actually perform the same physical action, the only difference between the two conditions is the belief of the causal origin of the movement.

Another method that we use to investigate this difference is transcranial magnetic stimulation (TMS). TMS produces a magnetic field causing neurons under the coil to fire. When this is done over the hand's area in mortor cortex, the hand moves involuntarily. This can be used in different ways to compare voluntary and involuntary actions. We are currently investigating whether we are better at remembering what we did (i.e. voluntary movements) or what happen to us (i.e. involuntary movements).

We hope our research will contribute to a better understanding of the sense of agency but also how so-called voluntary actions might create the sense of agency, and in particular, how we end up with this unique knowledge and feeling that we performed an action.

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New Neuropsychology Master Program at Aalborg University

Jesper Mogensen (University of Copenhagen) and Morten Overgaard at the Professor Inaugural Lecture at Aalborg University, February 2011

In February 2011, Morten Overgaard accepted a Professorship at Department of Communication and Psychology, Aalborg University. As Morten decided to stay with a 50% employment in Aarhus, the position is split between the two universities.

One of Morten's main tasks as Professor in Aalborg is to develop a Masters Program in Neuropsychology and Cognitive Neuroscience, and in the Fall 2011, the Masters Program was launched.

The Neuropsychology Master Program is internationally oriented, offering all courses in English, and preparing students for research and clinical practice in the field of neuropsychology. As a somewhat unusual aspect of the program, students will be involved in the planning and conducting of 2-3 experiments during the study, preparing them optimally to pursue a PhD.

The program is based on collaborations between Department of Psychology in Aalborg, Danish Neuroscience Center (DNC) in Aarhus, Hammel Neurorehabilitation and Research Center, Unit for Cognitive Neuroscience, Copenhagen, and Center for Sensor-Motor Integration, Aalborg. Students will benefit from the scientific expertise in this network, as well as in the network of international collaborators. Together with Morten, the main teaching staff counts Jesper Mogensen (University of Copenhagen), Laura Petrini and Thomas Alrik Sørensen (Aalborg University). With the study program, two laboratories are constructed in Aalborg to support the increased need for experimental facilities.

Morten Overgaard at his Professor Inaugural Lecture at Aalborg University, February 2011

Currently, the program is open to psychology students only. It is currently debated whether the program could be opened for students of other disciplines interested in cognitive neuroscience as well.

CNRU
Cognitive Neuroscience Research Unit

MUSIC IN THE BRAIN

by Peter Vuust

The Music In the Brain group (MIB) is an interdisciplinary research group benefiting from environments of musical excellence at Royal Academy of Music, Aahus/Aalborg and of outstanding neuroscientific facilities at CFIN. MIB aims to create breakthroughs in our understanding of brain function and plasticity in relation to music, and to influence future music education and clinical use of music. MIB searches to answer central questions:
1) How is music perception and experience guided by underlying predictive brain mechanisms and networks and how are these shaped by long-term music training and expertise? and 2) How can music inform our understanding of prediction as a fundamental brain principle? This research promises to uncover mechanisms fundamental to music perception, brain plasticity, learning, and neurorehabilitation.

It remains a mystery why humans get so much fun and enjoyment out of music. One specific aspect of music that seems to cause enjoyment and pleasure by people in all cultures is rhythm. For a number of years, a special focus of the MIB group has been to understand the neural mechanisms behind rhythm perception and production. Earlier results from the MIB group have indicated that Brodmann area 47 (BA47), a brain area associated with processing of language, is activated bilaterally when musicians tap the main meter in a polymetric context emphasizing a counter meter. This suggests that the processing of metric elements in music relies on brain areas that are also involved in language processing[1]. In that study, the tension was created entirely by changes in the stimulus while participants were tapping the main meter. In 2011, Vuust et al.[2] found left-hemispheric BA47 activation in response to a self-produced counter meter on top of a main meter provided by an ecological music excerpt. This data indicates that the activation is linked to polyrhythmic tension, regardless of whether it arises from the stimulus or the task. This finding gives us important information on the cognitive processing of polyrhythms. Now, PhD student Maria Witek, in a collaboration between Oxford University and the MIB group, is trying to uncover the brain mechanisms which underlies the pleasure and the desire to move when we “feel the beat”. The behavioral data clearly shows that an optimal amount of syncopation is linked to our experience of pleasure and “musical swing”. Putative links to the reward system in the brain are now investigated using fMRI.

One of the main aims of the MIB group is to use advances in our understanding of the fundamental principles of brain processing of music to improve music education and the clinical use of music. A promising lines of research within the MIB group research is the recent development of the musical multi-feature paradigm (see the following pages), which studies sound deviations in melodic patterns[3-5]. This EEG/MEG paradigm tests pre-attentive processing of 6 different types of deviants embedded in a melodic context and is able to distinguish jazz musicians from other types of musicians and non-musicians. Even though the EEG technology is not as of yet developed to a point where the signal-to-noise ratio allows for single subject analyses, the musical multi-feature paradigm has obvious potentials for testing musicians’ auditory capabilities, and may in the future provide a neuro-cognitive tool that could be interesting for music schools and academies of music, as a supplement to the behavioral testing such as implemented for scientific purposes in the so-called “Musical Ear Test” (the MET) described later in this report[6] (see page 50-51). Patients in Aarhus, Helsinki, and Hannover are now being exposed to variations of the muMUFE paradigm. Incidentally, so is a monkey in Minnesota!

Clinical applications of music are being studied intensively in the MIB group. Music has great potential in rehabilitation after stroke and for treatment of other cognitive, sensory, and motor dysfunctions resulting from disease of the human nervous system. Currently MIB is investigating the effect of musical training on linguistic skills in cochlear implantees[7], and the influence of music on pain perception[8], on sleep quality in traumatized refugees[9], and on patients suffering from autism spectrum disorder in close collaboration with clinicians at AUH. In future studies, this research may be extended to assess the benefits of music in patients suffering from a multitude of disorders such as stroke, anxiety, stress, depression and schizophrenia.

In march, two PhD students from the MIB group successfully defended their theses: Eduardo Adrian Garza Villarreal on the cognitive[10] and analgesic[8] effect of music, and Bjørn Petersen on the influence of musical training on auditory abilities in cochlear implantees (CI). Eduardo Garza showed in one of his experiments that listening to the music of Mozart reduces the experience of acute pain more than listening to noise but less than performing mental arithmetic. This is a quite provocative result, especially since the unfamiliar Mozart music used in this experiment did not reduce pain more than listening to environmental sounds. Nevertheless, considering its significant analgesic effect compared to noise in the clinical context, music used as an analgesic adjuvant, would be preferable to mental arithmetic as the mental calculations

could be highly stressful for the patient. In contrast to this study of passive music listening, Bjørn Petersen trained his participants with a specific music program specifically adapted for CI-users. The promising results of his research indicates a beneficial effect of music training especially on skills related to perception of melody. This study is of great importance since the number of CI-users is growing fast world-wide and rehabilitation strategies are still sparse.

As a culmination of 2011 the whole MIB group attended the most important conference within the field of neuroscience and music: The Neuroscience of Music IV, in Edinburgh, where they presented more than 10 posters and one oral presentation.

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MIB researchers Eduardo Garza and Anders Dohn at The Neuroscience of Music IV, in Edinburgh, June 2011

SELECTED RESEARCH PROJECTS:

Dohn A, Wallentin M, Tommerup N, Roepstorff A, Østergaard L, Vuust P. The neural foundation of absolute pitch ability.

Garza-Villarreal E, Brattico E, Vase L, Østergaard L, Vuust P. The placebo effect of music: A behavioral and physiological pain study.

Gebauer L, Heaton P, Skewes JC, Møller A, Vuust P. Music in Autism.

Gebauer L, Overgaard M, Vuust P. Transcranial Direct Current Stimulation and Music learning.

Konvalinka I, Vuust P, Roepstorff A, Frith C. Joint tapping as a model of minimal social interaction.

Jespersen, K, Vuust P. The effect of music on sleep-quality in traumatised refugees.

Petersen B, Hansen M, Therese Ovesen, Vuust P. Reestablishing speech understanding through musical training after cochlear implantation

Rahman S, Vuust P, Christensen K, Bhattacharia J, Dickens R, Psillas A, Jensen H. Musical creativity.

Vuust P, Brattico E, Seppänen M, Näätänen R, Glerean E, Tervaniemi M. Differentiating Musicians Using a Fast, Musical Multi-feature Paradigm.

Vuust P, Josefsen LG, Hansen NC, Ramsgaard Jørgensen S, Møller A, Linnet J. Sensation seeking in professional musicians.

Vuust P, Kringelbach M. The pleasure of music

Wallentin M, Nielsen AH, Friis-Olivarius M, Vuust C, Vuust P. The Musical Ear Test, a new reliable test for measuring musical competence.

Witek M, Clarke E, Hansen M, Wallentin M, Kringelbach ML, Vuust P. Groovin' to the Music: The relationship between body movement, pleasure and groove-based music.

Trusbak-Haumann N,Wallentin M, Rørdam M, Vuust P. Neural Bindings for social bonding

Trusbak-Haumann N, Vuust P. Interactions between Rhythm, Tonality and Emotion: A Psychological Experiment and Connectionist Model of Temporal-Tonal Cognitive Processes in Emotional Evaluation of Music

MUSIC IN THE BRAIN

The musical multi-feature studies

by Peter Vuust

Learning to play music at a professional level requires years of targeted training and dedication to music. The study of how musicians' brains evolve through daily training has recently emerged as an effective way of gaining insight into changes of the human brain during development and training[1-4]. The mismatch negativity (MMN), as measured with electroencephalography (EEG) or magnetoencephalography (MEG) with subjects' attention diverted from the stimuli, is a pre-attentive brain response originating mainly from the auditory cortices at around 100-200 ms after a change in sound features such as pitch, timbre, intensity[5-7]. The MMN (its amplitude and latency) is considered a candidate index of auditory capabilities. Mismatch negativity (MMN) studies have consistently revealed neural differences in early sound processing between people with different musical backgrounds. The stimuli used in these studies, however, have often been far from musical sounding, hours long, and very repetitive making the experiments less ecologically valid. In order to disclose fine-grained processing differences between musicians' and non-musicians' MMN responses, the musical context in which the feature change is placed is crucial. Therefore we needed to investigate stimuli consisting of realistic, complex musical material.

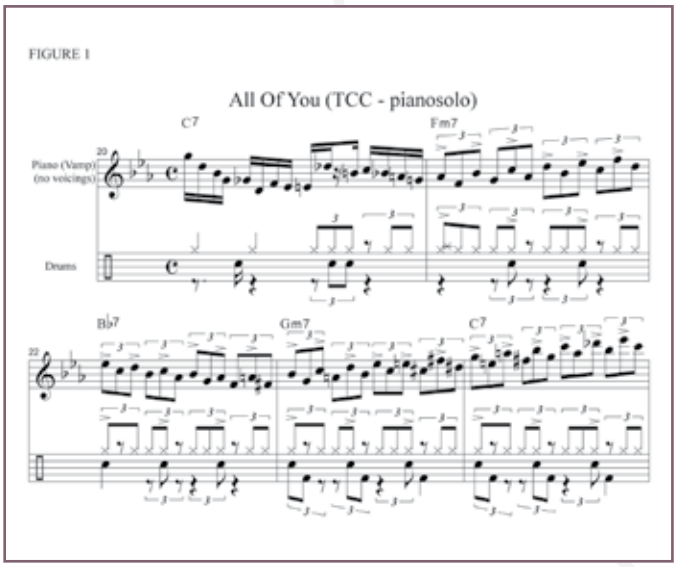

Figure 1
Example of patterns in "real" music. Transcription of measure 20-24 in Herbie Hancock's piano solo (upper system) and drum accompaniment (bottom system) on "All of You", from the record Four and More (1964)[28]. The example shows how patterns are woven into each other in real music. The patterns include simple patterns in rhythm, intensity, pitch height and more abstract musical patterns such as rising and falling sequences of thirds.

In a series of studies we have tried to answer the questions: Can the MMN paradigms be adapted to resemble a musical context while keeping the experimental duration contained, and will they reveal differences in sound-related brain activity among different types of musicians?

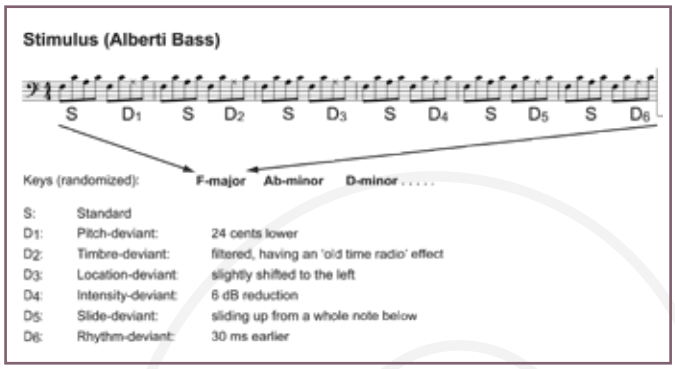

Figure 2
Stimulus. "Alberti bass" played with piano sounds.

In order to simulate the patterns of real music, we made two changes to the classical MMN-paradigm. First, we emulated harmonic progressions found in real music by using the socalled Alberti bass which is a musical accompaniment encountered in Mozart's sonatas or Beethoven's rondos and later adopted with variations in other contemporary musical genres[8]. This reflected an arpeggio-like texture underlying a harmonic scheme of major and minor chords. Second, we need the stimulus to embed more than one type of sound deviant into music with alternating pitches. This feature is common to patterns in more complex music where different musical and auditory features, such as pitch, rhythm, and intensity create intertwining patterns embedded within the musical phrases[9]. For this purpose we used the idea from the "Optimal MMN-paradigm" developed by Risto Näätänen and collegues. In this paradigm several types of acoustic changes are presented in the same repetitive sound sequence. This technique allows for several MMNs to be independently elicited according to features of auditory attributes within the same music sequence in a very short time. Importantly, no difference was observed between the MMNs recorded using the new paradigm and the ones obtained in the traditional longer oddball-paradigm in which only one feature is repeated and changes are randomly interspersed. In the present study we could therefore accommodate the two characteristics of musical patterning by combining the fast multi-feature MMN-paradigm with an Alberti bass sequence which simultaneously shifted among different major and minor chords. Using this

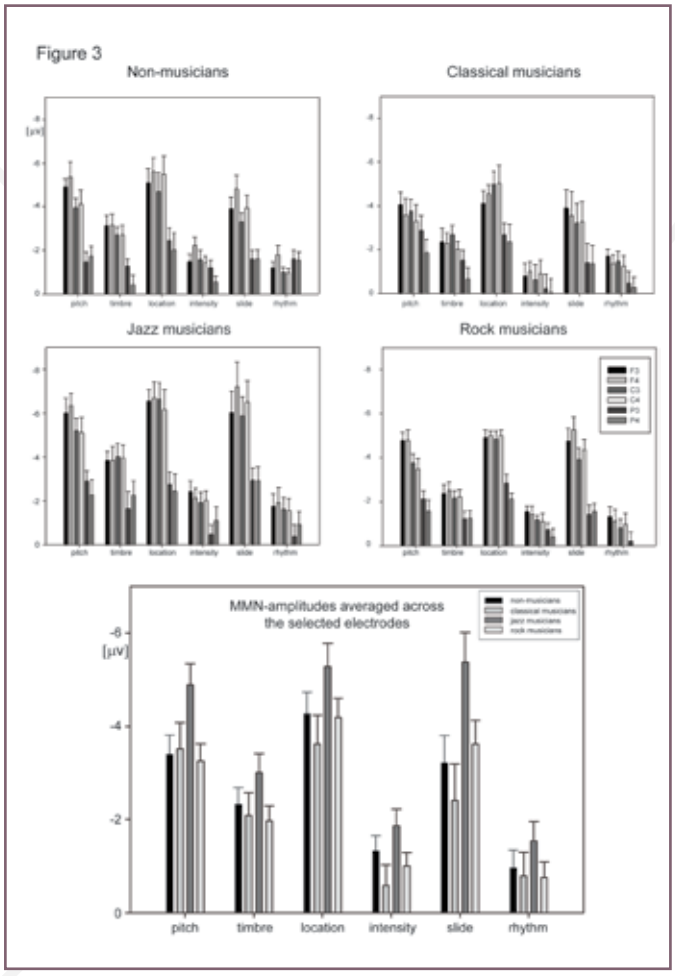

Figure 3
MMN amplitudes for each deviation, group and electrode.

musical multi-feature paradigm we tested for differences between musicians playing different styles of Western music, specifically between classical, jazz and pop/rock musicians.

There are several differences between these musical genres both regarding the listening experience, but also in relation to how they are taught and learned. Jazz musicians typically learn and perform music by using the ear[10,11] and separate ear training classes are taught at all the primary jazz schools around the world. Furthermore, jazz music in its modern form is characterized by complex chord changes, rich harmonies and challenging rhythmic structures such as polyrhythms[9,12,13] that place great demands on listeners' and performers' theoretical and ear training skills. In contrast, the teaching tradition within classical music focuses less on learning by ear. Instead, training is founded in notated music, even though some schools such as those teaching according to the Suzuki method[14] teach music by ear in the early years of childhood.

In the present study, we applied the new fast musical multi-feature MMN paradigm with classical musicians, jazz musicians, band musicians and non-musicians. In this paradigm, 6 types of acoustic changes (pitch, mistuning, intensity, timbre, sound-source location, and rhythm) that are relevant for musical processing[15-18] in different musical genres were presented in the same sound sequence, lasting in total about 15 minutes.

We found reliable MMNs even in non-musicians to 6 different sound deviants embedded in a musical sounding structure, showing that the MMN paradigm can be adapted to reflect processing of real music. Furthermore, we found differences in MMN to these deviants between musicians playing different

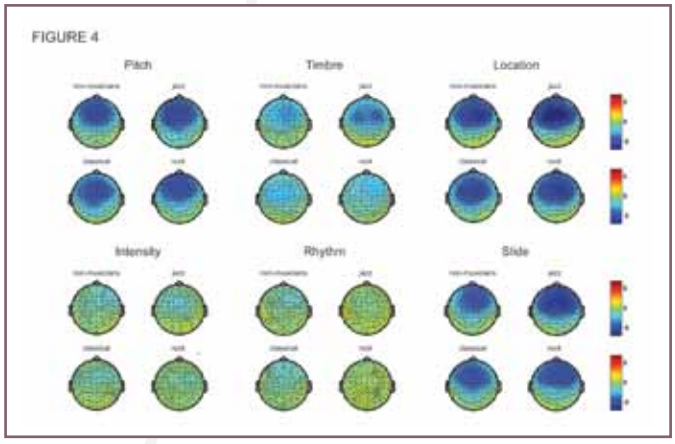

Figure 4
EEG voltage isopotential maps of the difference between the responses to deviants and standards averaged in an interval of +-20 ms around maximal peak amplitudes.

types of music. In particular, we obtained larger overall MMN amplitude in jazz musicians as compared with classical musicians, rock musicians and non-musicians across six different sound features. This indicates a greater overall sensitivity to sound changes in jazz musicians as compared to other types of musicians. Notably, in jazz musicians we found evidence of enhanced processing particularly of the pitch deviant and pitch slide deviant. The present paradigm is the first MMN-paradigm to include the pitch slide deviant. Sliding to tones is a typical feature in improvisational music such as jazz music as opposed to classical music, where it is mostly considered to be inappropriate. We also observed a tendency for a shorter MMN latency in jazz musicians compared to rock musicians and a significant modulation of the scalp topography for pitch and location features in jazz musicians.

When interpreting these results, it should be kept in mind that jazz musicians score higher in musical aptitude tests than rock musicians and non-musicians, especially with regards to tonal abilities.

There are interesting implications and applications of this study. First, the MMNs obtained in relation to the auditory deviants in our musical multi-feature paradigm shows that it is possible to develop highly controlled brain measuring paradigms which still resembles "real" music. Our paradigm resembles chord progressions that could have been found in e.g. jazz from the modal period, such as e.g. "Sketches of Spain" from Miles Davis' Kind of Blue[19], where of random chord plateaus were frequent[20]. Therefore we may be able to track brain measures (MMN) involved in survival-related attentional processing during 'real' music listening, and thereby study other important aspects of music. Second, this paradigm provides a novel ecological method of comparing MMNs in musicians from different musical genres. This is important because musical complexity, in many instances, is crucial in order to detect fine-grained auditory processing differences between participants from various musical backgrounds[21-24]. This study is first to show differences in pre-attentive brain responses between classical musicians, jazz musicians, and band musicians to a range of deviants embedded in continuous streams of music-like material. If we can refine the ERP method to reach sufficient sensitivity and reliability at the individual level, it may be possible to draw multi-attribute 'profiles' of sound-discrimination abilities in single individuals. The musical multi-feature paradigm present itself as a possible objective measure of auditory skills relevant to music perception, because MMNs are pre-attentively elicited without the need for behavioral task, while correlating with individual behavioral measures and musical expertise[16,25-27]. Third, the musical multi-feature paradigm increases the melodic complexity of the multi-feature paradigm, requiring more cognitive processing than former MMN-studies. Therefore it may find usage in clinical studies, where it may be used to identify the cognitive limitations related to musical processing.

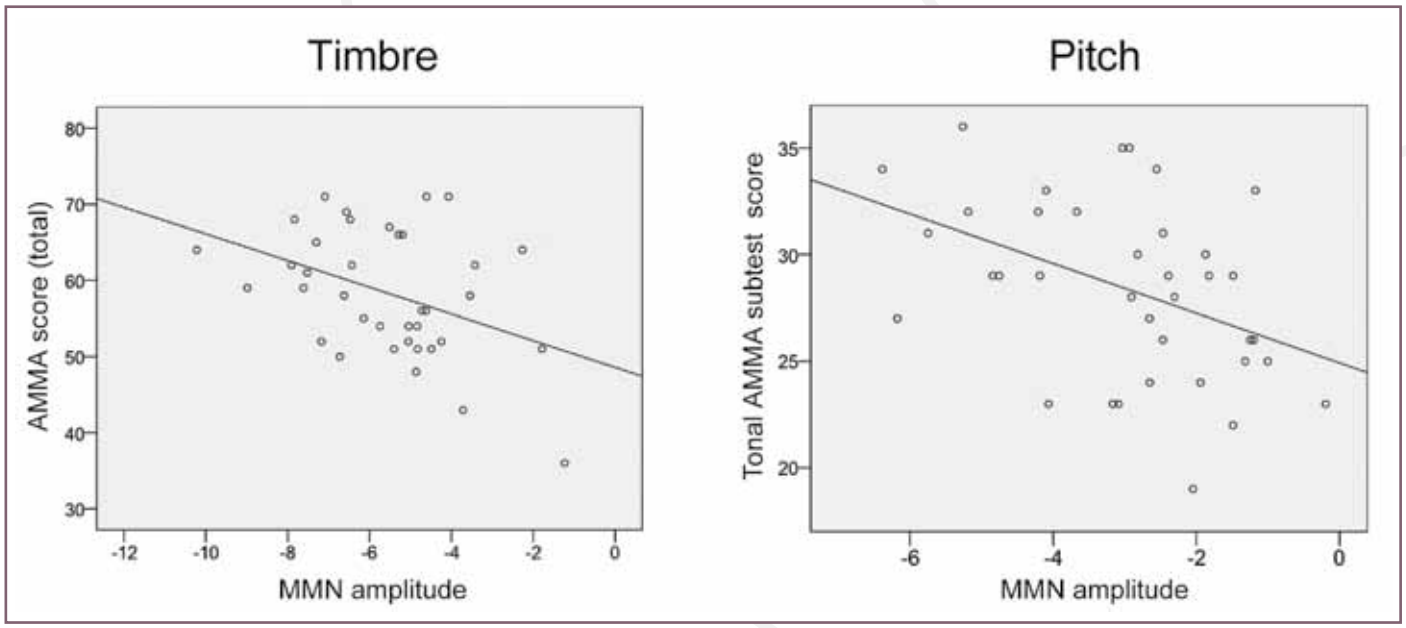

Figure 5
Significant correlations between the Advanced Measures of Music Audiation (AMMA) test and MMN-amplitudes recorded at the Fz electrode in all subjects (musicians and non-musicians). The left panel shows the correlation between the total AMMA test scores and the amplitude of the timbre deviant (r = -0.4, p = .008), the right panel the correlation between the tonal AMMA subtest and amplitude of the pitch deviant (r = -0.4, p = .01).

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NEW FACE AT CFIN

Cecilie Møller, BSc in Psychology, Music Teacher.
If her face looks strangely familiar to you it may be because Cecilie Møller has been at CFIN since early 2008 when she joined the Music In the Brain group and shortly there after started working as an assistant to Peter Vuust. Before this, she spent four years taking a degree in music teaching at the Royal Danish Academy of Music in Copenhagen and is currently finishing her masters studies at the Department of Psychology, Aarhus University, whilst working on her 4+4 PhD project on multimodal perception and cross-modal correspondences.

Cross-modal correspondences between visual and auditory dimensions have been used for centuries by music teachers, conductors etc. Cecilie's project investigates the extent to which visual features that correspond to auditory features (for example the correspondance of visually perceived vertical position to auditory pitch) can modulate participants' auditory capabilities (specifically pitch change detection), as measured behaviourally and by MEG.

Professional musicians are known to have lower pitch detection thresholds than non-musicians. By including two such groups of participants in the project, it is possible to study the interaction effect of musical expertise. It is hypothesized that when performing a pitch change detection task, non-musicians will benefit more from simultaneuous presentation of congruent visual stimuli than musicians, thus diminishing the difference in pitch detection threshold between the two groups.

The mechanisms that are suggested to underlie the effects of cross-modal correspondences differ depending on the theoretic approaches of the researchers who study them. In this project, which emphazises the primacy of multimodal perception, it is hypothesized that congruent visual stimuli will enhance even very early auditory brain responses to pitch changes whereas incongruent visual stimuli will suppress such responses.

MUSIC IN THE BRAIN

The Musical Ear Test – a short and reliable test of musical ability

by Mads Hansen
CFIN / Department of Otorhinolaryngology, Aarhus University Hospital

The Musical Ear Test (MET) is a measure of musical ability developed by CFIN researchers Mikkel Wallentin, Andreas Højlund Nielsen, and Peter Vuust in collaboration with Morten Friis-Olivarius, Copenhagen Business School, and Christian Vuust of the Royal Academy of Music, Aarhus.

Participants take the test by listening to a recording of musical phrases and then indicating on a response sheet whether the phrases are identical or different. A range of simple and complex musical phrases are used, allowing the test to be used with non-musicians and musicians alike. The MET has not been found to show any ceiling or floor effects.

One of the main goals when developing the MET was to provide separate tests for melodic and rhythmic listening skills. As a consequence, the MET is divided into two subtests: a melodic subtest consisting of 52 pairs of short melodic phrases played on a piano, and a rhythmic subtest consisting of 52 pairs of short rhythmic phrases played on a woodblock (see sample phrases, Figure 1).

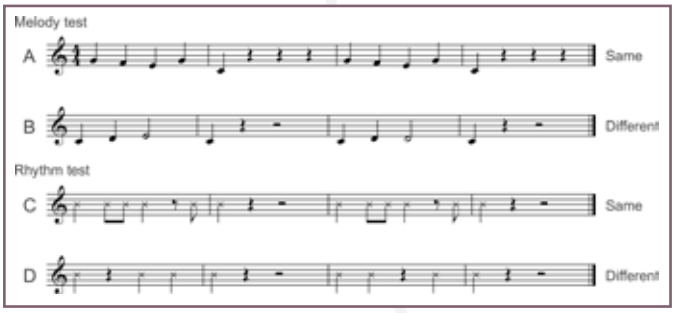


Figure 1
Sample melodic and rhythmic phrases

The MET differs from other measures of musical ability in that it has a relatively short duration (18 minutes), it is easy to administrate, and it does not require participants to be able to sing or play an instrument.

A number of experiments have established that the MET is able to discriminate between levels of musical ability. Two studies (Hansen, Wallentin, Vuust, 2012; Wallentin et al., 2010) found that groups of non-musicians scored significantly lower on the MET than did groups of professional musicians. Additionally, when using well-defined inclusion criteria for musicians, the MET is able to distinguish between groups of musicians of different ability levels. As an example, Wallentin and colleagues (2010) found that a group of 21 non-musicians obtained significantly lower MET scores than did a group of 21 amateurs who in turn obtained significantly lower MET scores than did a group of 18 professionals (see Figure 2). Lastly, Wallentin and colleagues found that the MET scores of amateurs and professionals were strongly correlated with measures of weekly practice: those who practiced the most had the highest MET scores, and vice versa. Taken together, these results show that the MET provides an objective, accurate and sensitive measure of musical ability.

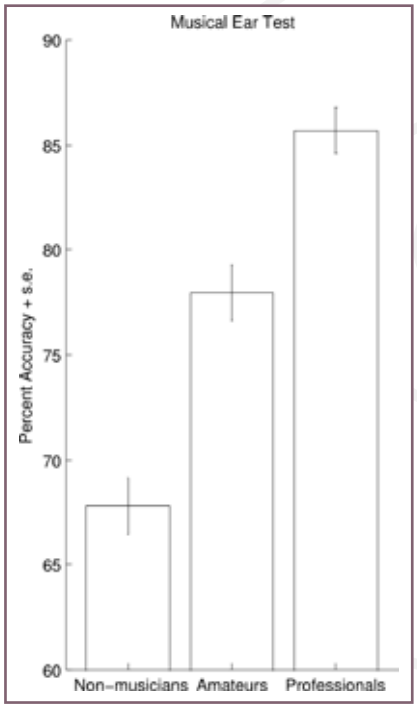


Figure 2
The MET discriminates between levels of musical ability (from the study by Wallentin et al., 2010)

In another experiment by Wallentin and colleagues (2010), the authors found strong correlations between MET scores and scores on the musical imitation test used by the Danish musical academies when auditioning prospective students. This suggests that the MET provides a valid replacement for tests of musical ability that require participants to sing or play an instrument.

Another interesting finding is that musical ability appears to be associated with a slight enhancement of auditory working memory. We (Hansen et al., 2012) and Wallentin and colleagues (2010) found participants' scores on the MET to be correlated with their raw scores on the so-called digit span tests, which measure auditory working memory (see Figure 3).

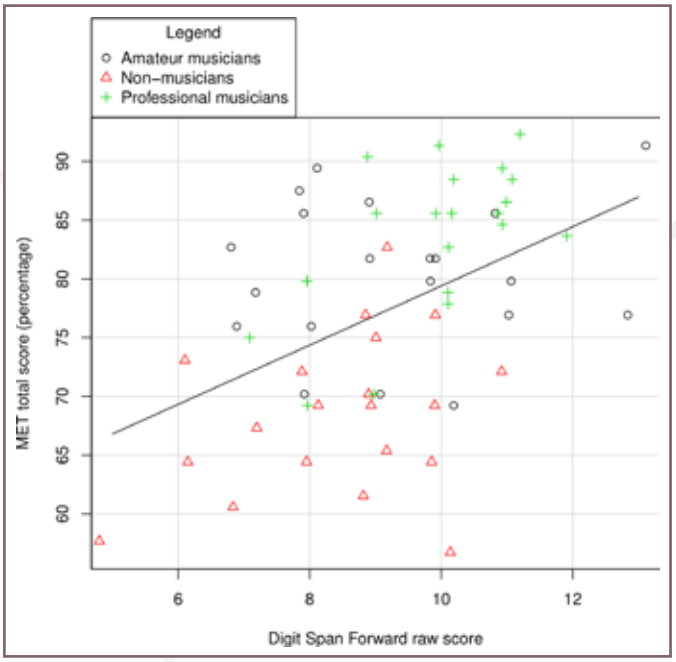


Figure 3
Correlation between MET scores and digit span scores (raw scores; r=.45, p<0.01; from the study by Hansen et al., 2012)

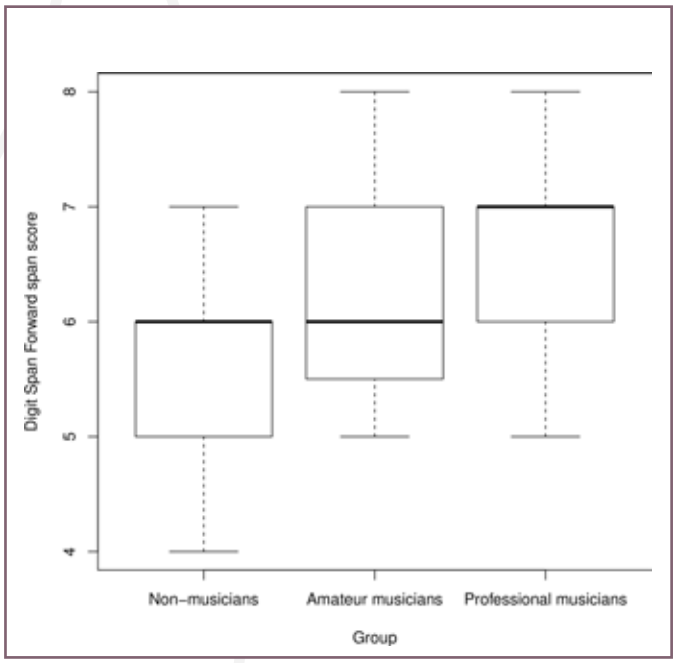


Figure 4
Digit Span scores (longest span; from the study by Hansen et al., 2012)

Put another way, those who do well on the MET tend to do well on the auditory working memory test, and vice versa. We also found that a group of professional musicians significantly outperformed a group of non-musicians on the digit span test (span scores; see Figure 4) (Hansen et al., 2012). One might wonder, then, if this working memory enhancement generalizes to other modalities. This appears not to be the case, however, at least regarding visual working memory: we found that – while professional musicians significantly outperformed non-musicians on the digit span test – all groups, including a group of amateur musicians, performed similarly on a test of visual working memory (Hansen et al., 2012).

In future studies, the Music in the Brain group will further investigate the association between musical ability and auditory working memory. Also, we intend to develop a web-based version of the MET which will allow us to use the test as a part of online surveys. PhD student Niels Trusbak Haumann is currently making great progress in this regard, so we expect to see an online version of the MET in the near future.

Aside from Niels' project, the MET is currently being used in ongoing projects by CFIN researchers Anders Dohn, Line Gebauer, Andreas Højlund Nielsen, and Cecilie Møller; as well as by Maria Witek at Oxford University. Danish and English versions of the test are available.

References

Hansen, M., Wallentin, M. & Vuust, P. (2012). Working Memory and Musical Competence in Musicians and Non-Musicians. Article submitted for publication.

Wallentin, M., Nielsen, A. H., Friis-Olivarius, M., Vuust, C. & Vuust, P. (2010). The Musical Ear Test, a new reliable test for measuring musical competence. Learning and Individual Differences, 20(3), pp. 188–96. doi:10.1016/j.lindif.2010.02.004

NEW FACE AT CFIN

Mads Hansen, (MSc Psych) is a clinical and research psychologist at the Department of Otorhinolaryngology at Aarhus University Hospital. He has been affiliated with CFIN's Music In the Brain research group since 2009.

Highlights in 2011

VILLUM FONDEN ✕ VELUX FONDEN

Oficial opening of the MEG scanner

Monday 29 August 2011 the official opening of the new MEG scanner facility took place during an event in the Palle Juul-Jensen Auditorium, Aarhus University Hospital.

Head of the Central Denmark Region, Bent Hansen cut the red ribbon to mark the opening, and Professor Leif Østergaard (CFIN), Professor Anders Fuglsang-Frederiksen (Department of Neurophysiology), Professor Jens Christian Sørensen (Department of Neurosurgery), and Professor Karen Østergaard (Department of Neurology) gave short talks to describe the future use of MEG in research and in patient management.

Head of Central Region Denmark, Bent Hansen, cutting the red ribbon to mark the official opening of the MEG scanner.
Photo: Michael Harder, AUH

The VELUX FOUNDATION has donated 16 million DKK for buying the new MEG scanner. The scanner will be used for research within ultrafast brain processing, and for research based patient examinations prior to treatment of severe epilepsy.

The MEG scanner is placed below ground level between building 9 and 10 at Aarhus University Hospital, Nørrebrogade, close to the other research scanners, the researchers in Danish Neuroscience Center, and the clinical researchers at the hospital. Funding for the building which now houses the MEG scanner was secured by the Institute of Clinical Medicine, Aarhus University. The MEG scanner detects magnetic field changes in the femto-Tesla range, and therefore has to be isolated from outside sources such as moving vehicles and electrical fields.

After the official program in the auditorium, the new MEG scanning facilities in the basement was demonstrated by MEG physicist at CFIN, Christopher Bailey.

CFIN and the departments at the Aarhus University Hospital NeuroCenter has benefited from the generous support of the VELUX FOUNDATION over the years.

The VELUX FOUNDATION is a non-profit foundation established in 1981 by Villum Kann Rasmussen, the founder of the VELUX Group and other business enterprises in the VKR Group. The VELUX FOUNDATION supports a range of areas, including initiatives to ensure healthy ageing and research projects within gerontology, ophthalmology and the humanities. The foundation has funded the advanced high-resolution, head-dedicated PET camera at the PET Center, Department of Nuclear Medicine.

From chaos to state-of-the-art MEG scanning facility. The building of the new home to the Neuromag TRIUX design from Elekta started at Aarhus University Hospital, Nørrebrogade during 2010. At the official MEG Opening in August 2011, MEG physicist Christopher Bailey was showing the MEG facilities to the invited guests.
Photos: Christopher Bailey and Michael Harder/AUH

The Brain Prize winner, Tamás Freund's visit in Aarhus

5 October 2011 one of the three 2011 winners of The Brain Prize, Tamás Freund, visited Aarhus University and Aarhus University Hospital.

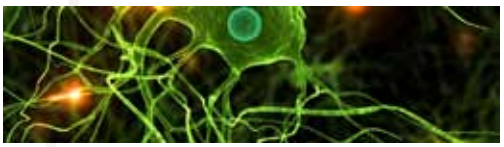
Grete Lundbeck European Brain Research Prize – 'The Brain Prize'- is awarded to one or more scientists who have distinguished themselves by an outstanding contribution to European neuroscience. The Prize recognizes a highly original and influential advance in brain research.

In 2011 The Brain Prize was won by three Hungarian scientists, Péter Somogyi, Tamás Freund and György Buzsáki, *for their wide-ranging, technically and conceptually brilliant research on the functional organization of neuronal circuits in the cerebral cortex, especially in the hippocampus, a region that is crucial for certain forms of memory*.
Read more at: http://www.thebrainprize.org/

During the visit in Aarhus, NeuroCampus Aarhus hosted a Master Class and an afternoon mini symposium with a guest talk by Professor Freund in the Palle Juul-Jensen Auditorium at Aarhus University Hospital.

At the Master Class selected PhD students within neuroscience participated and presented their research ideas - among these were Freja Bertelsen from CFIN, who talked about her project on the valproate model of autism (see page 10-13).

At the afternoon mini symposium Tamás Freund gave a guest talk entitled *Hippocampal interneuron types specifically related to complex behaviours* and also met with several brain researchers from Aarhus University and Aarhus University Hospital - among these several CFIN researchers.



MIND*Lab* Opening Symposium

19 January 2011 the official MIND*Lab* Opening Symposium was held in the Lake Auditoriums at Aarhus University. MIND*Lab* is the name of the cross-cutting university investment capital (UNIK) research initiative within neuroscience and cognition at Aarhus University. The accompanying 120 million DKK grant from The Danish Agency for Science Technology and Innovation now funds a large portion of CFIN researchers and our infrastructure.

Programme:
- Welcome by Rector Lauritz Holm-Nielsen
- *The UNIK initiative*, Director Inge Mærkedahl, The Danish Agency for Science Technology and Innovation
- *What is MINDLab?* Leif Østergaard, CFIN
- Coffee break and poster session
- Key note speaker, Patrik Brundin, Neuroscience Group, Lund University, Sweden
- Reception and Poster presentation by MIND*Lab* Researchers
- End of Symposium

The MIND*Lab* opening Symposium, 19 January 2011. From left: CFIN/MIND*Lab* Director Leif Østergaard, CFIN researchers Kristina Dupont Hougaard and Kristjana Yr Jonsdottir at the poster session, keynote speaker Patrik Brundin, Head of AU/AUH Research Support Unit John Westensee in conversation with Dean of Health at Aarhus University Allan Flyvbjerg, Director Inge Mærkedahl, The Danish Agency for Science Technology and Innovation.
Photos: Lars Kruse/AU

CFIN staff

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Doris Doudet
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Uta Frith
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Irene Klærke Mikkelsen
Paul von Weitzel-Mudersbach

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Joel Fredrik Astrup Aanerud (PhD degree 16 February 2011)
Micah Allen
Freja Bertelsen
Vibeke Bliksted Fuglsang
Niels Buhl (PhD degree 15 August 2011)
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Martin Dietz
Anders Dohn
Rikke Fast (Copenhagen University, LIFE)
Jesper Frandsen
Line Gebauer
Trine Gjerløff
Niels Trusbak Haumann
Tim van Hartevelt (University of Oxford)
Kristina Dupont Hougaard
Else Marie Jegindø

CFIN & MIND*Lab* Retreat at Sandbjerg Manor, 22-24 August 2011
Photo: Leif Østergaard

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Jesper Just
Morten Jønsson (University of Oxford)
Ivana Konvalinka (PhD degree 20 June 2011)
Sita Ramchandra Kotnis
Line Burholt Kristensen
Jonas Lindeløv
Sanne Lodahl
Simon Lykkemark
Kaare Mikkelsen
Christa Løth Myhre (University of Southern Denmark)
Cecilie Møller
Kartheeban Nagenthiraja
Adjhmal Nahimi
Andreas Højlund Nielsen
Karsten Olsen
Rasmus Aamand Olesen
Bjørn Petersen (PhD degree 14 March 2011)
Peter Mondrup Rasmussen
Louise Munk Rydtoft
Kristian Sandberg (PhD degree 17 Januar 2011)
Joshua Charles Skewes (PhD degree 31 Januar 2011)
Kristine Rømer Thomsen
Anna Tietze
Eduardo Adrián Garza Villarreal (PhD degree 15 March 2011)
Mads Sloth Vinding
Ethan Weed (PhD degree 3 May 2011)
Maria Witek (University of Oxford)

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Riccardo Fusaroli
Anders Christian Green
Søren Haack
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Rikke Overgaard
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Mikkel Vinding

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Mads Bjørn Christiansen, Secretary
Mai Drustrup, Secretary
Anne-Mette Pedersen, MIND*Lab* Administrative Leader
Arndis Simonsen, Secretary
Henriette Blæsild Vuust, Communications Coordinator

Coffee break during the CFIN & MIND*Lab* Retreat at Sandbjerg Manor, August 2011. Photo: Alejandra Zaragoza Scherman

Facts about CFIN

Invited lectures

Chris Frith:

- *Introspection enables us to optimise group decision making.* St. Catherine's College Oxford, UK. 11 February 2011
- *What is special about human social cognition?* Opportunities and Challenges in Social Neuroscience, Utrecht, Holland. 21-23 March 2011
- Colloquium: *Captivated by Social Cognitive Neuroscience* (with Uta Frith). Ecole Nationale Superieure Rue d'Ulm, Paris, France. 10 May 2011
- *New Developments in theories of 'Theory of Mind.* Collége de France, Paris, France. 25 May 2011
- *The Cognitive Basis of Hallucinations and Delusions.* Collége de France, Paris, France. 1 June 2011
- *The role of meta-cognition in social interaction.* Perception in Social Interaction Workshop, Institute of Philosophy, London, UK. 9 June 2011
- *Meta-cognition and the social mind.* New Thinking: Advances in the Study of Human Cognitive Evolution, Oxford, UK. 24 June 2011
- *Using Brain Imaging to study Cognition and Culture.* Summer School: Experimental Methods in the Study of Cognition and Culture, Aarhus University, Denmark. 18 August 2011
- *Mechanisms of Social Cognition and Interacting Minds.* Riken Brain Sciences Institute, Wako-Shi, Japan. 9 September 2011
- *What is consciousness for?* Royal Philosophical Society of Glasgow, Glasgow, UK. 30 November 2011

Uta Frith:

- *Neuroscience and Education. Between Euphoria and Rejection.* COEDUCA Workshop on Neuroscience and Education, Seville University, Italy. 14 January 2011
- Introductory Keynote Lecture: *Forschung: Aus der grauen Theorie ins bunte Leben.* Dyslexia Congress Erfurt, Erfurt, Germany. 18 March 2011
- *The social and the cognitive in Social Cognitive Neuroscience.* BPS Annual Conference, Glasgow, UK. 5 May 2011
- Colloquium: *Captivated by Social Cognitive Neuroscience* (with Chris Frith). Ecole Nationale Superieure Rue d'Ulm, Paris, France. 10 May 2011
- *New developments in Theory of Mind.* Collége de France, Paris, France. 18 May 2011
- *What is the link between talent and autism?* Collége de France, Paris, France. 25 May 2011
- *The Learning Brain – insights from neuroscience.* ISBC Conference (International Boys School Coalition), City of London School, London, UK. 10 July 2011
- Leopoldina Symposium: *Theory of Mind and Psychopathology.* Theory of Mind in Context: History, Evolution, and Development. Organiser. Leipzig, Germany. 10 July 2011
- *Social Cognition*, Aarhus MIND*Lab* Summer School, Experimental Methods in the Study of Cognition and Culture, Aarhus University, Denmark. 11 August 2011
- *What is Social in Social Cognition.* MIND*Lab* Retreat Sandbjerg, Sønderborg, Denmark. 23 August 2011
- *Introduction to Autism.* Folkeuniversitet, Aarhus, Denmark. 29 August 2011
- *Developmental Disorders - a window on the mind.* 34th Annual Meeting of the Japan Neuroscience Society, Yokohama, Japan. 17 September 2011
- Response: *The power of belief and the power of authority. Tanner Lectures by Ernst Fehr.* Clare Hall, Cambridge, UK. 8 November 2011
- *Neuroscience Implications for education.* Wellcome Trust Event: Understanding Learning, London, UK. 30 November 2011

Riccardo Fusaroli:

- *The Dialogically Extended Mind: Bridging dynamic and symbolic coordination.* Methods workshop on measuring and testing the temporal unfolding of cognitive processes, Aarhus, Denmark. 11 May 2011
- *Building common ground.* EuroUnderstanding Launch Conference, Malmö, Sweden. 15 October 2011
- *Investigating Linguistic Coordination in Dialogical Problem Solving.* Workshop on Synchronization, Aarhus, Denmark. 17 November 2011
- *Qualities of coupling in semiotic interactions.* Sequence Alignment Methods Inspired by Dynamical Systems: Symbols in Time, Aarhus, Denmark. 8 December 2011

Else-Marie Elmholdt Jegindø:

- *Når hjernen tror - religion og hjerneforskning.* Senioruniversitetet, Silkeborg, Denmark. 24 February 2011
- *Smerte og kultur.* Dansk Smerteforums forårsmøde, Denmark. 19 March 2011
- *Do you see my pain? Pain expression and empathy for others' pain in people with Asperger syndrome.* NeuroCampus & DNC Seminar: Autism@Aarhus – Ongoing projects. 25 August 2011
- *Kan tro lindre smerte?* Opening ceremony for Golden Days Festival 2011, Copenhagen, Denmark. 9 September 2011
- *Kan du se min smerte?: Smerteoplevelse, smerteudtryk og sympati for andres smerte hos personer med ASD.* Research conference, Kredsforening Østjylland's 40th anniversary, Denmark. 8 October 2011
- *Videnskaben eller gud: Religion og hjerneforskning.* Folkeuniversitetet, Aarhus, Denmark. 10 October 2011
- *Beliefs in the lab and pain in the wild.* Researching Religion Conference, Aarhus, Denmark. 18 October 2011
- *Smerte og kultur.* Netværksgruppen af Palliations- og hospicesygeplejerskers efterårsmøde, Denmark. 12 November 2011
- *Videnskaben eller gud: Religion og hjerneforskning.* Folkeuniversitetet, Emdrup, Denmark. 22 November 2011
- *Tro og smerte: Psykologiske og neurobiologiske mekanismer.* Temadag om smerter på Tandlægeskolen, Aarhus, Denmark. 9 December 2011

Sune Nørhøj Jespersen:

- *Cellular underpinnings of MRI diffusion contrast in gray matter.* Max Planck Institute of Human Cognitive and Brain Sciences, Leipzig, Germany. 29 March 2011
- *New possibilities with double wave vector diffusion sequences.* Workshop on Highfield Imaging, Aarhus University, Denmark. 23 June 2011
- *Diffusion MRI for studies of brain microstructure.* Medical Physics, Aarhus University Hospital, Denmark. 7 November 2011
- *Cellular underpinnings of MRI diffusion contrast in gray matter.* UK diffusion group, Brighton, UK. 30 November 2011
- *Cellular underpinnings of MRI diffusion contrast in gray matter.* Diffusion Imaging Group, Hvidovre Hospital, Denmark. 13 December 2011

Morten Kringelbach:

- *Hedonia: TrygFonden Research Group.* Psychiatry, Oxford, UK. 12 January 2011
- *Maximizing pleasure and happiness?* Plenary, Bremen, Germany. 13 January 2011
- *Deep brain oscillations.* Department of Pharmacology, Oxford, UK. 17 January 2011
- Keynote: *Den nydelsesfulde hjerne.* Folkeuniversitetet, Aarhus, Denmark, 1 February 2011
- *Sing the mind-body electric.* CenSes Workshop, London, UK. 4 February 2011
- *Finding pleasure.* DanceLab, Axminster, UK. 19 February 2011
- *The Functional Neuroanatomy of Pleasure.* Plenary Lecture, Annual Meeting for American Neuropsychiatric Association (ANPA), Denver, USA. 26 March 2011
- *The functional neuroanatomy of reward and pleasure.* Symposium lecture at CNS conference, San Francisco, USA. 2 April 2011
- *TrygFonden Research Group: progress.* Oxford, UK. 9 April 2011
- *Pleasures of the brain.* Special lecture, Royal Institution, UK. 5 May 2011
- *Deep pleasure oscillations.* Oxford Synoptics FHS lecture, UK. 5 May 2011
- *Pleasure of music.* Music In the Brain Conference, Aarhus, Denmark. 26 May 2011
- *Hedonia in the brain.* Society for Affective Disorders, Denmark. 27 May 2011
- Keynote: *Pleasure networks in the human brain.* 9th ENP Meeting, Holland. 31 May 2011
- Keynote: *Pleasure principles for food intake.* Mars Lecture, Society for the Study of Ingestive Behavior (SSIB) annual meeting, Florida, USA. 15 July 2011
- *Creativity and the brain.* UCLA, USA. 19 August 2011
- *The neurobiology of motivation, pleasure and learning.* Pangborn, Toronto, Canada. 5 September 2011
- *Den nydelsesfulde hjerne.* Helenekilden, Tisvilde, Denmark. 15 September 2011
- *Cognitive studies with DBS.* NDS, Oxford, UK. 16 September 2011
- *Den nydelsesfulde hjerne.* The Queen's College, Oxford, UK. 6 October 2011
- *The neurobiology of pleasure.* Medical students, Psychiatry, Oxford, UK. 7 October 2011
- Keynote: *Finding pleasure.* Sussex University, UK. 12 October 2011
- *Scars of War.* Presentation to CDS, MOD HQ Whitehall, UK. 18 October 2011
- *Imaging the parental brain.* Karolinska, Sweden. 26 October 2011
- *The pleasure of food.* Plenary lecture, Brain & Cognition, Utrecht, Holland. 2 November 2011
- *MEG and DBS.* Düsseldorf, Germany. 3 November 2011
- Keynote: *Neuroimaging pleasure.* Portuguese Brain Network, Portugal. 5 December 2011

Risto Näätänen:

- *Dysfunction of the central auditory system as an index of cognitive decline in different neurological and neuropsychiatric disorders and in aging.* FinBioNet Symposium, Helsinki University, Finland. 22 November 2011.
- *The mismatch negativity: An index of cognitive decline in neuropsychiatric and neurological diseases and in aging.* 14th European Congress on Clinical Neurophysilogy (ECCN 2011), Rome, Italy. 21-25 June 2011

Morten Overgaard:

- *Experimenting with introspection*. Cognitive Science Talk Series, City University of New York, New York, USA. 28 July 2011
- *Experimenting with introspection*. Varieties of Cortical Colour Vision, Vancouver, Canada. 7 August 2011
- *Subjective reports in blindsight*. EU COST Meeting, Brussels, Belgium. 18 October 2011

Andreas Roepstorff:

- *Projektansøgninger og forskningsledelse*. 27 January 2011
- *Ansøgning til Strategiske Vækstteknologier.* Komiteen for Strategiske Vækstteknologier, Aarhus, Denmark. 11 March 2011
- *Functional neuroimaging and cognition III: Social cognition and social relations*. ENSN Neuroschool: Recent advances in functional and structural neuroimaging from area "blobology" to network connectivity, Bergen, Norway. 12 March 2011
- *Spontaneous Coupling and Metamapping of Interactions.* Empathy, Simulation and Narrative, Aarhus, Denmark. 13 March 2011
- *Ethnography of Imaging Studies*. ENSN Neuroschool: Recent advances in functional and structural neuroimaging from area "blobology" to network connectivity, Bergen, Norway. 14 March 2011

- *Experimenting as research method or research aesthetics?* Eksperimentel arkæologis fremtid, Aarhus, Denmark. 24 March 2011
- *Interdisciplinær forskning: Muligheder og udfordringer*. Aarhus, Denmark. 14 April 2011
- Commentator: *Key note speach by Kirsten Hastrup.* Megaseminar 2011: Reconsidering Ethnographic Comparison. Sandbjerg Manor, Sønderborg, Denmark. 30 May 2011
- *Traveling Experiments: Mapping Meta Comparison.* Megaseminar 2011: Reconsidering Ethnographic Comparison. Sandbjerg Manor, Sønderborg, Denmark. 1 June 2011
- *Naturalizing the Mind - Culturalizing the Brain.* 7th NAHM conference: Culture - Nature revisited, Grenå, Denmark. 7 June 2011
- *Mapping the Plastic Brain: Nature, Culture and Agency.* The Plastic Brain, Basel, Switzerland. 10 June 2011
- *Mapping the Plastic Brain.* The brain, the person, and the social. Probing neuroscientific ideas and practices from STS & history of science perspectives, Zürich, Switzerland. 23 June 2011
- *Brain and mind technologies.* 2nd Cultural Neuroscience Summer Institute, Ann Arbor, USA. 26 July 2011
- *Persons, Narratives and Practices: it matters what version of 'bullshit bingo' we play.* Other Minds Embodied Interaction and Higher-Order Reasoning, Bochrum, Germany. 21 September 2011
- *Building Common Ground - Experimental Approaches.* EuroUnderstanding Launch Conference, Malmö, Sweden. 15 October 2011
- Commentary: *What's in the Experimental?* Researching Religion: Methodological Debates in Anthropology and the Study of Religion, Aarhus, Denmark. 18 October 2011

Uffe Schjødt:
- *Hypnose og hjerneforskning*. Ordrup Gymansium, ATU, Denmark. 24 March 2011
- *Reklamepsykologi.* Aarhus Midt Foredrag, Aarhus, Denmark. 10 October 2011
- *Hvordan virker bøn?* Horsens provstikonvent, Horsens, Denmark. 1 November 2011
- *Cognitive resource depletion in religious interactions.* American Academy of Religion, San Francisco, USA. 19-22 November 2011

Kristian Tylén:
- *Coming to Terms: an experimental view on dialogical meaning-making.* Language Use - Language Structure, Winter Symposium, Aarhus, Denmark. 27 January 2011
- *The Semiotically Extended Mind.* Seventh Conference of the Nordic Association for Semiotic Studies, Lund, Sweden. 6 May 2011
- *The Linguistic Shaping of Social Coordination.* SALC III, Copenhagen, Denmark. 14 June 2011
- *Co-constructing Meaning: the socially interactive trajectory of material symbols.* CfS/CCS seminar, DPU Copenhagen, Denmark. 8 September 2011
- *Signs as Trajectories of Social Interaction.* International Conference on Linguistic Cognition, Tambov, Russia. 15 September 2011
- *Investigating Linguistic Synchronization in Dialogical Problem Solving.* MIND*Lab* Workshop on Synchronization, Aarhus, Denmark. 17 November 2011
- *Qualities of Coupling in Semiotic Interactions.* Symbols in Time Workshop, Aarhus, Denmark. 8 December 2011

Peter Vestergaard-Poulsen:
- *Brain tissue microstructure investigated by diffusion MR microscopy.* The Danish Research Centre for Magnetic Resonance (DRCMR), Hvidovre Hospital, Denmark. 2011

Peter Vuust:
- *Musik og hjerne.* Musikudvalget i Høje Tåstrup Kommune, Denmark. 2 February 2011
- *Lyd i hjernen.* Rytmisk musikkonservatoriums Lyddesign/ Designlyd, Copenhagen, Denmark. 22 February 2011
- *Musik og smerte.* Dansk Smerteforums Årsmøde, Denmark. 19 March 2011
- *Hjerne og musik.* Brøruphus Efterskole, Denmark. 25 March 2011
- *Musik og hjerne.* Skt Annæ Gymnasium, Copenhagen, Denmark. 29 March 2011
- *A senior moment:* Foredragskoncert med trio. Aarhus Kommune, Denmark. 3 May 2011
- *Just Do It! Hvordan man øver sig, og hvad det gør ved hjernen.* Ringsted Gymnasium, Denmark. 6 May 2011
- *Korsmusik og hjernen.* Aarhus Vocal Festival 2011, Aarhus, Denmark. 6 May 2011
- *Musik og hjerne: Foredragskoncert med trio.* Summerschool folkesundhedsvidenskab, Korsør, Denmark. 17 May 2011
- *Musik som bevæger : om musiks indflydelse på den menneskelige hjerne.* Dansk Oplysningsforbund (DOF), Gerlev Idrætshøjskole, Denmark. 28 May 2011
- *Musikalsk kommunikation og samarbejde.* Aarhus Kommune, Denmark. 14 June 2011
- *Hvordan musik påvirker hjernen.* Dansk Medicoteknisk selskabs Årsmøde, Aalborg Kongres og Kulturcenter, Denmark. 15 June 2011
- *Musik og hjerne*. Neurologisk Afdeling, Aarhus University Hospital, Denmark. 16 June 2011
- *Just Do It! Hvordan man øver sig, og hvad det gør ved hjernen.* Sønderborg Musikskole, Denmark. 22 June 2011
- *Musik og Ledelse.* Kolding Kunstmuseum, Denmark. 15 September 2011
- *Musik som medicin.* Lægeforeningen. Snekkersten, Denmark. 23 September 2011

- *Musikkens påvirkning af den samarbejdende hjerne.* CETT Vejle, Uddannelse og udvikling, Vejle, Denmark. 30 September 2011
- *Musik och Hjärna:* Foredragskoncert med trio. Tonspråk, Vänersborg, Sweden. 31 October 2011
- *Just Do It! Hvordan man øver sig, og hvad det gør ved hjernen.* Vänersborg Musikskole, Vänersborg, Sweden. 1 November 2011
- *Hvordan virker hjernen?:* Foredragskoncert med trio. Østjysk Kulturforsyning, Skanderborg Kulturhus, Denmark. 9 November 2011
- *Musik som medicin : Kan vi skabe bedre fysiske forbedringer med musik?* Hobro Sygehus Himmerland, Denmark. 16 November 2011
- *Miles Davis.* Hovedbiblioteket i Birkerød, Holte Bibliotek, Denmark. 24 November 2011
- *Lydbranding.* Aalborg Bibliotekerne, Aalborg, Denmark. 29 November 2011

Mikkel Wallentin:
- *Sprog og hjerne.* Fredericia Gymnasium, Fredericia, Denmark. 18 January 2011
- *Sprog og kognition.* Jysk Kunstakademi, Aarhus, Denmark. 21 January 2011
- *Hjernen i sprog og fortællinger.* Danskfagets Dag, Aarhus, Denmark. 4 February 2011
- *Hjernens gåder: Hjernen og sprog.* Folkeuniversitetet, Aarhus, Denmark. 28 February 2011
- Paneldebat*: Post-Das Beckwerk: en nekrolog.* IKK Festival '11, Copenhagen, Denmark. 4 March 2011
- *Hjernens gåder: Hjernen og sprog.* Folkeuniversitetet, Hjernens gåder: Hjernen og Sprog, Aarhus, Denmark. 30 March 2011

Leif Østergaard:
- *What is MINDLab?* MIND*Lab* Opening Symposium, Aarhus University, Denmark. 19 January 2011
- *The Sino-Danish Center for Research and Education: Life Sciences and Biomedicine.* Danish Delegation Visit, Sino-Danish Center for Research and Education, Shanghai, China. 24 January 2011
- *A Reinterpretation of the Blood Oxygen Level Dependent fMRI Signal.* Chinese Academy of Science, Institute of Automatics, Beijing, China. 27 January 2011
- *The Neurocapillary Coupling: Re-interpreting the BOLD signal.* Chinese Academy of Sciences, Institute of Biophysics, Beijing, China. 27 January 2011
- *Interdisciplinary Research at the Center of Functionally Integrative Neuroscience.* Human Health and Disease: A clinical Approach, Aarhus, Denmark. 3-4 February 2011
- *To Assess Cerebral Oxygenation, Knowing Cerebral Blood Flow is Not Enough*. Danish Neuroscience Center Seminar, Aarhus, Denmark. 28 February 2011
- *The Metabolic Role of Capillary Transit Time Heterogeneity (CTTH): To Assess Cerebral Oxygenation, Knowing Cerebral Blood Flow is Not Enough*. Staff Meeting Charité, Berlin, Germany. 1 March 2011
- *CFIN and MINDLab - Interdisciplinary Neuroscience and Cognition Studies at Aarhus University*. EUA Annual Conference 2011: Investing Today in Talent Tomorrow, Aarhus, Denmark. 13 maj 2011
- *Establishing World Class Research in Denmark: Barriers and Opportunities : Comment to Dr. Jamil Salmi: The Challenge of Establishing World Class Universities*. Are We Winning the Race? The Role of Universities in a Global Perspective, Aarhus Denmark. 25 May 2011
- *MR Perfusion Parameters:Testing of Models and Thresholds*. Brain 2011, Barcelona, Spain. 28 May 2011
- *Neurocapillary Coupling: An important Paradigm in Cognitive Research and the Study of Disease?* CFIN/MIND*Lab* Annual Retreat 2011, Sønderborg, Denmark. 22 August 2011
- *Towards Neurocapillary Coupling?* Functional Neurosurgery Seminar, Oxford University, Oxford, UK. 16 September 2011
- *Clinical Utility of Dynamic Susceptibility Contrast (DSC) MRI: Stroke*. Lectures on MRI: Current Concepts in Spin Labelling and Contrast-Enhanced Perfusion MRI, Oxford University, Oxford, UK. 20 September 2011
- *What You Need to Know Before You Measure Cerebral Perfusion*. Lectures on MR: Current Concepts in Spin Labelling and Contrast-Enhanced Perfusion MRI, Oxford University, Oxford, UK. 20 September 2011
- *Hot Topic Debate: Arterial Spin Labeling is not ready to replace contrast agent perfusion MRI (DSC-MRI) in the clinic*. ESMRMB 2011 Congress, Leipzig, Germany. 7 October 2011
- *A new look at Oxygen Extraction in Tissue*. Dept. Biomedical Engineering, Linkjöping, Sweden. 12 December 2011

Other CFIN researchers:
- Donald F. Smith. *Molecular Brain Imaging of Depression - Myths and Music*. Kvartalskursus i Selskabet Danske Neuropsykologer, Risskov, Denmark. 23 May 2011
- Kristine Rømer Thomsen. *Den nydelsesfulde hjerne*. Herning, Denmark. 2 March 2011
- Kristine Rømer Thomsen. *Begær og Behag*. Forskningens Døgn, Aarhus, Denmark. 29 April 2011
- Ethan Weed. *The Sounds of Sadness and the Sounds of Joy: Hemispheric Differences in the Processing of Emotion-bearing Spectral Information.* Music and Language in the Brain, Aarhus, Denmark. 27 May 2011

Conferences

Andreas Roepstorff:
- TESIS: opening workshop, Heidelberg, Germany. 14-15 March 2011
- Situating Mental Illness. Berlin, Germany. 28-29 April 2011
- Technologies of the Mind: Methods and Research Design, Aarhus, Denmark. 11-12 May 2011
- Copenhagen colloquium on children and religion, Copenhagen, Denmark. 18-19 May 2011
- Megaseminar 2011: Reconsidering Ethnographic Comparison,Sandbjerg Manor, Sønderborg, Denmark (Organizer and participant). 31 May-1 June 2011
- BRAIN GEAR – Discussing the design and use of neurodevices in neurosocieties, Groningen, Holland. 16 September 2011
- European Stakeholders' Meeting, Mind & Life Institute, Paris, France. 2-4 November 2011
- Cooperation, Coordination, Joint Intentionality: Developmental Issues, Paris, France. 4 November 2011

Peter Vuust:
- The Neurosciences and Music – IV. Edinburgh, Scotland, UK. 9-12 June 2011
- Organizer of: Music and Language in the Brain, Aarhus, Denmark. 26-27 May 2011

Leif Østergaard:
- Brain 2011, Barcelona, Spain. 26-28 May 2011
- Forskningsledernetværket FL1, Qeqertarsuaq, Greenland. 24-29 June 2011
- ESMRMB, Leipzig, Germany. 6-8 october 2011

Other CFIN researchers:
- Risto Näätänen: XI International Conference on Cognitive Neuroscience (ICON XI), Palma, Mallorca, Spain. 25-29 September 2011.
- Martin Dietz. 17th Annual Meeting of the Organization for Human Brain Mapping, Quebec City, Canada. 26-30 June 2011
- Riccardo Fusaroli. Organizer of: Methods workshop on measuring and testing the temporal unfolding of cognitive processes. Aarhus, Denmark.11 May 2011
- Riccardo Fusaroli. Organizer of: Sequence Alignment Methods Inspired by Dynamical Systems: Symbols in Time. Aarhus, Denmark. 8 December 2011
- Riccardo Fusaroli. Organizor of: Hands-on workshop on Symbolic recurrence, Aarhus, Denmark. 9 December 2011
- Niels Trusbak Haumann. Music and Language in the Brain, Aarhus, Denmark. 26-27 May 2011
- Niels Trusbak Haumann. The Neurosciences and Music – IV. Edinburgh, Scotland, UK. 9-12 June 2011
- Sune Nørhøj Jespersen. Organizer of: Mini Symposium on NMR in complex media, Aarhus, Denmark. 16 August 2011
- Kaare Mikkelsen. The Brain Prize Meeting, Hindsgavl Slot, Denmark. 6-8 October 2011
- Uffe Schjødt. CogSci 2011, Boston, USA. 20 July 2011
- Uffe Schjødt. Organizor of: RCC feat. Granqvist, Aarhus University, Denmark. 8-9 September 2011
- Kristian Tylén. Empirical Methods in Cognitive Linguistics (EMCL), Freiburg, Germany. 6-11 March 2011
- Kristian Tylén. Language as Social Coordination, SALC III, Copenhagen, Denmark. 14 June 2011
- Ethan Weed. Organizer of: What's hidden under the curve? Advanced methods for ERP analysis, Aarhus, Denmark. 30 November 2011

Radio / TV / newspress

CFIN researchers have participated in the following in 2011:

Eduardo A. Garza Villarreal:
- *Den musiske smertelindring*. Information.dk, 14 March 2011
- *Aftenshowet*. DR, 17 March 2011
- *Musik er smertestillende medicin*. Videnskab.dk, 17 March 2011
- *Musik kan lindre smerte effektivt - og uden bivirkninger*. Politiken, 10 April 2011
- *Musikk er smertestillende medisin*. Forskning.no, 28 March 2011

Morten Kringelbach:
- *"Smil" and the brain.* TryghedsGruppen, WeLovePeople, 1 February 2011
- *Vi kender ikke hjertet i hjernen* (Rikke Carlsen), AUgustus, 1 April 2011
- *At skrive er at genkalde sig fremtiden* (Anne Winther), Børsen, 1 April 2011
- *Futureproof*, Newstalk, Ireland (Jonathan McCrea). 17 May 2011
- *Lykke* (Mette Volander), JyllandsPosten, 30 october 2011
- *Det er nydelse, der driver værket.* (Annemette Schultz Jørgensen), DJØF bladet, 1 December 2011
- *Sexlyst er tabu* (Mette Volander), JyllandsPosten, 31 December 2011
- *Lysten er i skammekrogen* (Mette Volander), JyllandsPosten, 31 December 2011

Jakob Linnet:
- *Spillefugle tilbydes et helt nyt behandlingstilbud.* TV2 Østjylland, 16 May 2011
- *Milliarder på spil.* DR Magasinet Penge, 25 May 2011
- *Poker task og kognitive fejlslutninger ved ludomani*. Berlingske Tidende, 2011
- *Tænk hvis du vandt*. Radiodokumentar, DR, 2011
- *Stor lotto udtrækning.* TV-Avisen and DR update, 28 December 2011

Morten Overgaard:

- *Morten Overgaard udnævnt til professor i neuropsykologi.* Nordjyske.dk, 22 February 2011
- *EEG finds consciousness in vegetative state*, New Scientist, 10 November 2011
- *EEG finds consciousness in vegetative state*, HealthDay, 10 November 2011
- *EEG can identify awareness in those thought to be in permanently vegetative state.* Medical News Today, 10 November 2011
- *Hypnose gør det lettere at multitaske.* Videnskab.dk, 5 october 2011
- *Hypnose gør det lettere at multitaske.* www.dr.dk, 5 October 2011
- *Hypnose gør det lettere at multitaske.* www.berlingske.dk, 5 october 2011

Andreas Roepstorff:

- *Samarbejd ikke med idioter.* DR, P1. 14 June 2011
- *Den digitale hjerne.* Interview, Kristeligt Dagblad. 12 july 2011
- *Building common ground: New study records impact on the heart and brain.* Monographic issue of the Lego Serious Play gazette. (Newsletter), with Andreas Roepstorff, Kristian Tylén, Riccardo Fusaroli. 30 September 2011
- *Ny teknologi - nye tanker.* Interview in Kolon: 2: 11, Issue on Digital Learning. 21 october 2011
- *Læring og hjernen.* Interview for Radioavisen, DR P1, P2 and P4 (Narcisa Vucina). 23 October 2011

Uffe Schjødt:

- *Blær og luksus er nødvendig for at overleve.* Magasinet SYSTIME, 15 March 2011
- *Viden Om: horoskoper - fup eller fakta.* DR2, 12 April 2011
- *Blær er det hele værd.* JyllandsPosten, 19 May 2011

Peter Vuust:

- *Er musiksmag medfødt?* Videnskab.dk, 3 January 2011
- *Apropos .... lyd*. DR P1, 10 January 2011
- *Håb for tonedøve X Factor-deltagere.* www.kpn.dk (Kultur På Nettet), 15 January 2011
- *Jeg lytter - altså er jeg*. DR P1, 13 February 2011
- *Musikere på stuegang.* Aarhus Stiftstidende, 1 March 2011
- *Skadeligt for hørelsen at arbejde i tøjbutik.* Horsens Folkeblad, Radio Horsens, 26 March 2011
- *Talentfuld eller tonedøv?* Horsens Folkeblad, Fredensborg Amts Avis, Holbæk Amts Ventreblad, Kalundborg Folkeblad, Nordjyske Stiftstidende, Midtjyllands Avis, Dagbladet Køge/Ringsted/Roskilde, 29 April 2011
- Det Gode, Det Sunde og Det Virk´lig Sjove. DR P4, May 2011
- *Musik rammer hjernerne forskelligt.* Politiken, 15 May 2011
- *Tango hjælper som terapi mod Parkinsons.* Politiken, 22 May 2011
- *Musik er kontorets nye vægge.* Frederiksborg Amts Avis, Nordjyske Stiftstidende, Midtjyllands Avis, Dagbladet Køge, Herning Folkeblad, 30 May 2011
- *Musik er de nye vægge.* Nordjyske Stiftstidende, 5 June 2011
- *Michael Jackson*. DR P7, 25 June 2011
- *Træn din hjerne.* Helse.dk (Familiens Lægemagasin), 27 June 2011
- *Martin og Ketil går klassisk*. DR P2, 3 July 2011
- *Er din hjerne til Gaga eller Grieg.* Femina, 18 August 2011
- *Mønstre*. DR P7, 2 October 2011
- *Når unge henter et fix i cyperspace.* Politiken, 9 October 2011
- *Musik giver motivation.* Aarhus Stiftstidende, 24 November 2011
- *Derfor hænger musikken ved.* Kristeligt Dagblad, 25 November 2011
- *Musik erstatter specialundervisning.* Magasinet Frie Skoler, 12 December 2011
- *Hvad giver et julehit?* Videnskab.dk, 13 December 2011
- *Last Christmas: Et sikkert julehit anno 1984 - og se lige siden.* Videbskab.dk, 23 December 2011

Mikkel Wallentin:

- *Formiddag på 4'eren.* DR P4 (national), 1 February 2011
- *Hjernen og Google.* TV2 News, 16 July 2011
- *Forsøg med frygt.* Politiken, 10 August 2011
- *Hjernen lader os lide med den grimme ælling.* www.au.dk, 10 August 2011

Other CFIN researchers:

- Jonas Lindeløv. *Høj hjerneaktivitet er ikke lig med skarp hjerne.* Videnskab.dk, 22 November 2011
- Leif Østergaard. *En ny strategi for Arktis*. Med Nils O. Andersen, Ole Fejerskov, Marie Louise Nosch, Lars Quortrup, Ole Steen Andersen, Karen Edelmans, Jørgen Staunstrup. Politiken, 22 August 2011.

The meeting room at Sandbjerg Manor. CFIN & MIND*Lab* Retreat, August 2011
Photo: Alejandra Zaragoza Scherman

Boards / Committees / Editorials

CFIN researchers are involved in the following:

Uta Frith:
- Elected Foreign Member of the Royal Society of Arts and Sciences in Göteborg, Sweden. 1 January 2008 →
- Elected Member Deutsche Akademie der Naturforscher Leopoldina, Germany. 1 january 2008 →
- Honorary Fellow, Newnham College, Cambridge, UK. 1 January 2008 →

Morten Kringelbach:
- Associate Editor, *Social Neuroscience*. Joined editorial board of psychological journal. 2010.
- Board member, Medical Research Council Board Advisory Group, UK. High level strategic advice on scientific plans for obesity and metabolic medicine.

Risto Näätänen:
- The Royal Swedish Academy of Sciences 2008 →
- International Steering Committee of the Centre of Behavioural and Health Sciences, University of Tartu, Tartu, Estonia. Member 2001 →
- The Bergen Mental Health Research Center, University of Bergen, Norway. Member of the Scientific Advisory Board. 2005 →

Andreas Roepstorff:
- Programkomiteen for Strategiske Vækstteknologier. Member. 2011 →

Peter Vestergaard-Poulsen:
- Faculty Member, Biomedical Engineering, Aarhus University

Peter Vuust:
- Forskningsudvalget ved Det Jyske Musikkonservatorium. Chairman. 1 August 2005 →
- Kulturministeriets forskningsudvalg. Member. 1 January 2008 →
- Music in the Brain. Coordinator. An interdisciplinary research network, Founding institutions: Royal Academy of Music, Center of Functionally Integrative Neuroscience, Department of Psychology (Aarhus University), Department of Music (Aarhus University), 1 August 2007 →

Leif Østergaard:
- Akademiet for de Tekniske Videnskabers Tænketank. Member. 10 June 2009-10 January 2011.
- Danmarks Forskningspolitiske Råd. Member. 3 July 2010-March 2012.
- Det Kongelige Danske Videnskabernes Selskab. Member. 30 September 2008 →
- Forskningsledernetværket FL1. Member. 15 December 2007-15 December 2011

Research stays abroad

- Daniel Campbell-Meiklejohn, Visiting Researcher. New York University, 1 January 2011-1 January 2013
- Brian Hansen, McKnight Brain Institute, April 2011
- Risto Näätänen, Laboratory for Human Brain Dynamics, Nicosia, Cyprus, 19 February - 5 March 2011
- Morten Overgaard, City University New York, USA, July-August 2011

Scholarships & awards

- Daniel Campbell-Meiklejohn. Sapere Aude - Elite Researcher, Danish Ministry for Science and Technology. 1 January 2011
- Line Gebauer. Danish Agency for Science Technology and Innovation, EliteForsk Travel Scholarship.
- Brian Hansen. Kornings Foundation, 20.000 DKK for participation in ISMRM 2011 in Montreal, Canada.
- Sune Nørhøj Jespersen. 2 million DKK from the Lundbeck foundation for the project *Cellular underpinnings of MR diffusion contrast in brain gray matter*.
- Sune Nørhøj Jespersen. 30,000 DKK from Familien Hede-Nielsens foundation for *MR metode til neurit arkitektur i grå substans*.
- Sune Nørhøj Jespersen. 15000 DKK from Korning's foundation for participation in ISMRM 2011, Montreal, Canada.

Completed PhD dissertations, 2011

- Niels Buhl. *Diffusion on Networks and Diffusion Weighted NMR of the Human Lung*. 15 August 2011.
- Eduardo Adrian Garza Villarreal. *Cognitive and Emotional Processing of Music and its Effect on Pain*. 15 March 2011.
- Ivana Konvalinka. *Interacting minds, brains, and bodies: behavioural, neural, and physiological mechanisms of joint action in social interaction*. 20 June 2011.
- Bjørn Petersen. *Advances in Music and Speech Perception after Cochlear Implantation*. 14 March 2011.
- Kristian Sandberg. *Measuring consciousness*. 17 January 2011.
- Joshua Charles Skewes. *Agency: A Philosophical Concept in Psychological Science*. 31 January 2011.
- Ethan Weed. *Getting the Message Right: Social Cognition, Pragmatic Impairement, and Right Hemisphere Damage*. 3 May 2011.

Completed Master theses, 2011

- Brian Broman Petersen: *Tids- frekvens kohærens analyse af dual-EEG i meditationspraksis.* Masters thesis, Biomedical Engineering, Aarhus University

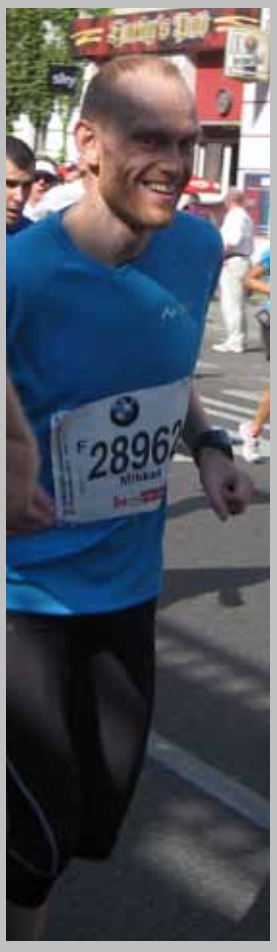
CFIN and MIND*Lab* Retreat 2011

The annual CFIN and MIND*Lab* Retreat was held at Sandbjerg Manor 22-24 August 2011. This year's program was:

- Double keynote: Katja Wiech, Nuffield Department of Clinical Neurosciences and FMRIB Centre, University of Oxford, *The neurobiology of cognitive-affective pain modulation* and *Decision-making in the context of pain*.
- Informal discussions and socializing within groups and across groups
- ***What if…? Thinking outside the box***:
  Leif Østergaard, *Neurocapillary Coupling. An important paradigm in brain mapping and neuropsychiatric disorders?*
  Chris Frith, *Thinking inside the box. On the importance of proper experimental control.*
- Groups:
  How to do experiments on really interesting questions?
  Modeling the mind
  Measuring neurocapillary coupling
  Neurocapillary coupling in the normal and diseased brain
- Groups: Presentations of discussion highlights to the other groups
- Keynote: Hans Lou, *GABAergic interneuron regulation of conscious experience – a hypothesis*.
- CFIN groups and MIND*Lab* streams:
  Internal meetings
  Plans for the next year
- Keynote: Uta Frith, *Mechanisms in social cognition. Do human beings have a trick up their sleeves?*

CFIN on the RUN
Every Thursday the CFIN running team starts the day with a run in the forrest. Here Irene K. Mikkelsen, Captain of the team Mikkel Wallentin, Andreas Højlund Nielsen, and Michael Nygaard Pedersen pose to show the new official CFIN running shirts.
Photo: Søren Møller Madsen

DHL stafet 2011 - Mikkel Wallentin.
Photo: DHL



VI LØBER MED VIDEN (running with knowledge) ... Captain of the CFIN running team, Mikkel Wallentin during the Berlin Marathon 2011, 25 September 2011.
Photo: Henriette Blæsild Vuust

2011 Publications

Peer reviewed articles:

Aamand R, Skewes J, Møller A, Fago A, Roepstorff A. Enhancing effects of acetazolamide on neuronal activity correlate with enhanced visual processing ability in humans. Neuropharmacology, 2011; 61: 900-8

Alawneh JA, Jones PS, Mikkelsen IK, Cho T, Siemonsen S, Mouridsen K, Ribe LR, Morris RS, Hjort N, Antoun N, Gillard JH, Fiehler J, Nighoghossian N, Warburton EA, Østergaard L, Baron J. Infarction of 'non-core–non-penumbral' tissue after stroke: Multivariate modeling of clinical impact. Brain, 2011; 134: 1765-76

Allen M, Williams G. Consciousness, plasticity, and connectomics: the role of intersubjectivity in human cognition. Frontiers in psychology, 2011; 2: 20

Alstrup AKO, Simonsen M, Landau AM. Type of anesthesia influences positron emission tomography measurements of dopamine D2/3 receptor binding in the rat brain. Scand J Lab Anim Sci, 2011; 38: 195-200

Bahrami B, Frith C. Interacting Minds: A Framework for Combining Process- and Accuracy-Oriented Social Cognitive Research. Psychological Inquiry, 2011; 22: 183-6

Bahrami B, Olsen K, Bang D, Roepstorff A, Rees G, Frith CD. Together, slowly but surely: the role of social interaction and feedback in the build-up of benefit in collective decision-making. Journal of Experimental Psychology: Human Perception and Performance, 2011; 38: 3-8

Becchio C, Skewes J, Lund TE, Frith U, Frith CD, Roepstorff A. How the brain responds to the destruction of money. Journal of Neuroscience, Psychology and Economics, 2011; 4: 1-10

Bjornerud A, Sorensen AG, Mouridsen K, Emblem KE. T_1- and T_2*-dominant extravasation correction in DSC-MRI: part I-theoretical considerations and implications for assessment of tumor hemodynamic properties. Journal of Cerebral Blood Flow and Metabolism, 2011; 31: 2041-53

Bubandt NO, Roepstorff A, Willerslev R. Email-trialog: Hvordan vil (og bør) antropologien se ud i fremtiden? Antropologi, 2011; 63: 167-77

Bulbulia J, Schjødt U. Toward an evolutionary social neuroscience of religion. Religion, Brain, and Behavior, 2011; 1: 220-2

Campbell-Meiklejohn D, Cooke J, Wakeley J, Herbert V, Scollo P, Ray MK, Selvaraj S, Passingham RE, Cowen P, Rogers R. Serotonin and dopamine play complementary roles in gambling to recover losses. Neuropsychopharmacology, 2011; 36: 402-10

Carrera E, Jones PS, Alawneh JA, Mikkelsen IK, Cho T, Siemonsen S, Guadagno JV, Mouridsen K, Ribe LR, Hjort N, Fryer TD, Carpenter TA, Aigbirhio FI, Fiehler J, Nighoghossian N, Warburton EA, Østergaard L, Baron J. Predicting infarction within the diffusion-weighted imaging lesion: does the mean transit time have added value? Stroke, 2011; 42: 1602-7

Changeux JP, Lou HC. Emergent pharmacology of conscious experience: new perspectives in substance addiction. FASEB J, 2011; 25: 2098-108.

Christensen KR, Wallentin M. The locative alternation: Distinguishing linguistic processing cost from error signals in Broca's region. NeuroImage, 2011; 56: 1622-31

Damholdt MF, Østergaard K, Borghammer P, Larsen L. The Parkinsonian personality and concomitant depression. Journal of Neuropsychiatry and Clinical Neurosciences, 2011; 23: 48-55

Emblem KE, Bjornerud A, Mouridsen K, Borra RJH, Batchelor TT, Jain RK, Sorensen AG. T_1- and T_2*-dominant extravasation correction in DSC-MRI : part II-predicting patient outcome after a single dose of cediranib in recurrent glioblastoma patients. Journal of Cerebral Blood Flow and Metabolism, 2011; 31: 2054-64

Frith CD. Consciousness is for sharing. Cognitive Neuroscience, 2011; 2: 117-8

Frith CD. What brain plasticity reveals about the nature of consciousness: commentary. Frontiers in Psychology, 2011; 2: 87

Frith CD, Frith U. Mechanisms of Social Cognition. Annual Review of Psychology, 2011; 63: 287-313

Frith U, Frith CD. Reputation Management: In Autism, Generosity is its own Reward. Current Biology, 2011; 21: R994-5

Fusaroli R. The social horizon of embodied language and material symbols. Versus. Quaderni di studi semiotici, 2011; 112-113: 95-120

Garza E, Brattico E, Leino S, Østergaard L, Vuust P. Distinct neural generators of the MMN and the ERAN to chord violations: A multiple source analysis study. Brain Research, 2011; 1389: 103-14

Garzón B, Emblem KE, Mouridsen K, Nedregaard B, Due-Tønnessen P, Nome T, Hald J, Bjørnerud A, Håberg AK, Kvinnsland Y. Multiparametric analysis of magnetic resonance images for glioma grading and patient survival time prediction. Acta Radiologica, 2011; 52: 1052-60

Gjedde A, Aanerud J, Peterson E, Ashkanian M, Iversen P, Vafaee M, Møller A, Borghammer P. Variable ATP yields and uncoupling of oxygen consumption in human brain. Advances in Experimental Medicine and Biology, 2011; 701: 243-8

Guidi S, Bianchi P, Alstrup AKO, Henningsen K, Smith DF, Bartesaghi R. Postnatal neurogenesis in the hippocampal dentate gyrus and subventricular zone of the Göttingen minipig. Brain Research Bulletin, 2011; 85: 169-79

Hansen B, Flint JJ, Heon-Lee C, Fey M, Vincent F, King MA, Vestergaard-Poulsen P, Blackband SJ. Diffusion tensor microscopy in human nervous tissue with quantitative correlation based on direct histological comparison. NeuroImage, 2011; 57: 1458-65

Ho YCL, Petersen E, Zimine I, Golay X. Similarities and differences in arterial responses to hypercapnia and visual stimulation. Journal of Cerebral Blood Flow and Metabolism, 2011; 31: 560-71

Hyam JA, Owen SLF, Kringelbach ML, Jenkinson N, Stein JF, Green AL, Aziz TZ. Contrasting Connectivity of the Vim and Vop Nuclei of the Motor Thalamus Demonstrated by Probabilistic Tractography. Turkish Neurosurgery, 2011; 70: 162-9

Iversen P, Keiding S, Mouridsen K, Ott P, Vilstrup H. Transjugular intrahepatic portosystemic shunt does not alter cerebral blood flow. Clinical Gastroenterology and Hepatology, 2011; 9: 1001-3

Jespersen SN, Buhl N. The displacement correlation tensor: Microstructure, ensemble anisotropy and curving fibers. Journal of Magnetic Resonance, 2011; 208: 34-43

Konvalinka I, Xygalatas D, Bulbulia J, Schjødt U, Jegindø EE, Wallot S, Van Orden G, Roepstorff A. Synchronized arousal between performers and related spectators in a fire-walking ritual. Proceedings of the National Academy of Sciences, 2011; 108: 8514-19

Kringelbach ML, Aziz TZ, Green AL. Balancing the brain: Resting state networks and deep brain stimulation. Frontiers in Integrative Neuroscience, 2011; 2: 8

Kringelbach ML, Aziz TZ. Neuroethical principles of deep-brain stimulation. World Neurosurgery, 2011; 76: 518-9

Kudo K, Sasaki M, Østergaard L, Christensen S, Uwano I, Suzuki M, Ogasawara K, Shirato H, Ogawa A. Susceptibility of T_{max} to tracer delay on perfusion analysis: quantitative evaluation of various deconvolution algorithms using digital phantoms. Journal of Cerebral Blood Flow and Metabolism, 2011; 31: 908-12

Landau AM, Chakravarty M, Clark CM, Zis AP, Doudet DJ. Electroconvulsive therapy alters dopamine signaling in the striatum of non-human primates. Neuropsychopharmacology, 2011; 36: 511-8

Linnet J, Møller A, Peterson E, Gjedde A, Doudet D. Dopamine release in ventral striatum during Iowa Gambling Task performance is associated with increased excitement levels in pathological gambling. Addiction, 2011; 106: 383-90

Linnet J, Møller A, Peterson E, Gjedde A, Doudet D. Inverse association between dopaminergic neurotransmission and Iowa Gambling Task performance in pathological gamblers and healthy controls. Scandinavian Journal of Psychology, 2011; 52: 28-34

Lou HC, Skewes J, Thomsen KR, Overgaard M, Lau H, Mouridsen K, Roepstorff A. Dopaminergic stimulation enhances confidence and accuracy in seeing rapidly presented words. Journal of Vision, 2011; 11: 1-6

Lou HC, Joensson M, Kringelbach ML. Yoga lessons for consciousness research: a paralimbic network balancing brain resource allocation. Front Psychol, 2011; 2: 366.

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MIND*Lab* researchers Armin W. Geertz and Jeppe Sinding Jensen at the CFIN & MIND*Lab* Retreat at Sandbjerg Manor, August 2011 Photo: Alejandra Zaragoza Scherman

Guest researcher at CFIN, Francesca Fardo studying the CFIN & MIND*Lab* Retreat participant's posters describing their scientific and personal interests, August 2011. Photo: Alejandra Zaragoza Scherman

CFIN Bibliometry

by Leif Østergaard

CFINs production of peer-reviewed articles in international journals increased by 15 relative to 2010, continuing the general growth in scientific output - See Table 1. The relatively large number of publications in the 'Impact Factor 0-1' category accounted for the more modest growth in CFIN publications gleaned from the box-diagram in Figure 1. When we started bibliometric analysis in 2006, this category often included publications with poor journal impact factor. In recent years, however, this category increasingly include new journals who have yet to receive a journal impact factor from the Thomson Institute of Scientific Information (ISI). In recent years, publication practices have changed, mainly due to the introduction of open source on-line journals. These journals offer rapid and transparent reviews, in addition to article-level metrics indicating how often papers are viewed and downloaded, as well as opportunities to interact directly with readers of one's work. The most successful of these, PLoS One recently celebrated 5 years in operation. The journal publishes manuscripts from all fields of science based on technical soundness alone, and reached impressive increases in publication volume over its first years, as well as an impact of 4.411. Starting next year, table columns and figure bars will occasionally be updated as these new journals obtain journal impact factors.

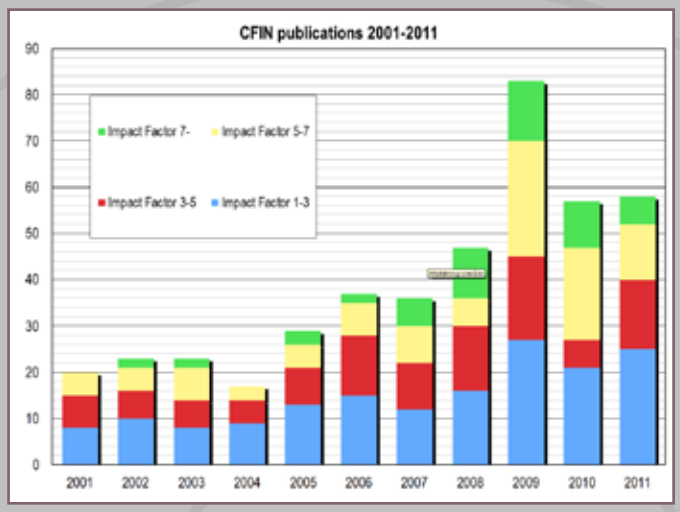

Figure 1
CFIN Publications 2001-2011

Bibliometric research indicators

Future funding of Danish universities will depend in part on the volume and quality of their scientific production. To encourage publication of scientific work in high-impact journals, considerable work has been but into the assignment of so-called 'Authority Levels' to publications sources within all disciplines of research. A range of experts have therefore analyzed over 20.000 publication channels (mainly journals) and assigned them into 'Level 1' and 'Level 2' journals. Within a given research area, 'Level 2' journals are those who experts generally consider to be the leading, international journals within their field, in the sense that they publish the top-20% of the world's scientific production within that area. Meanwhile, 'Level 1' is assigned to journals who publish the remaining 80% of the World's production within the area. This metric has certain advantages when evaluating CFINs scientific production: First, scientist in interdisciplinary research centers often come from fields with different publication strategies and topic-specific differences in typical journal impact factors. By using a common metric which is based on evaluations by expert in various fields, research output quality can therefore be communicated in a way which is less biased by the number of research fields we represent. Secondly, we have a strong interest in communicating the value of our research, not only in terms of scientific and societal impact, to our benefactors and collaborators. By this metric, and the number of books, book chapters, theses and patents we produce, this value becomes tangible in terms of the Government support we bring to Aarhus University.

	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011
Impact Factor 0-1	6	4	12	8	8	3	11	9	10	7	21
Impact Factor 1-3	8	10	8	9	13	15	12	16	27	21	25
Impact Factor 3-5	7	6	6	5	8	13	10	14	18	6	15
Impact Factor 5-7	5	5	7	3	5	7	8	6	25	20	12
Impact Factor 7-	0	2	2	0	3	2	6	11	13	10	6
Total	26	27	35	25	37	40	47	56	93	64	79

Table 1
Publication Impact Factor 2001-2011

Table 2 shows the number of Level 1 and Level 2 CFIN publications 2001-2011 according to the '2011 Authority List' from the Danish Agency for Science, Technology and Education. It should be noted that that the scientific production of CFIN over the past ten years has been published in over 220 different journals.

By definition, 'average performance' corresponds to a scientific production where 80% of the production falls in the 'Level 1' category, and the remaining 20% in the 'Level 2' category. We are very pleased that a high proportion of CFIN articles have been published in the 'Level 2' journals within the fields covered by our research. In recent years, more than half of our manuscripts have thus been published in journals considered among the top-20% by our peers.

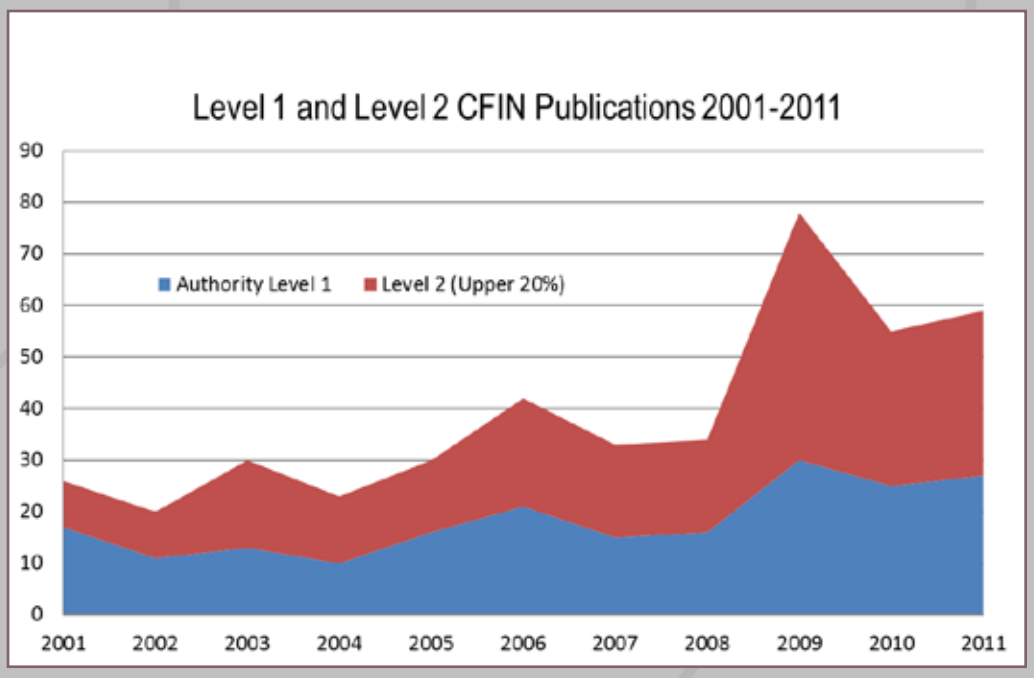

Figure 2
Level 1 and Level 2 CFIN Publications 2001-2011

	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011
Level 1 (Lower 80%)	17	11	13	10	16	21	15	16	30	25	27
Level 2 (Upper 20%)	9	9	17	13	14	21	18	18	48	30	32
Level 2 - Percentage	35	45	57	57	47	50	55	53	62	55	54

Table 2
Number of Level 1 and Level 2 CFIN Publications 2001-2011

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