Center of Functionally Integrative Neuroscience
& MIND*Lab*

ANNUAL REPORT 2014

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Heading home from conference
The Department of Clinical Medicine at Aarhus University's car all packed and ready to return to Aarhus after the Neuroscience of Music Conference in Dijon, France, in May 2014.
Music in the Brain researchers Maria Witek, Rebeka Bodak, Line Gebauer and Bjørn Petersen ready for 'take off'.
Photo: Henriette Blæsild Vuust

Introduction - 2014 in words

by Leif Østergaard

2014 was the final year of the funding period for the prestigious MIND*Lab* UNIK grant, awarded in 2008 to Aarhus University to found an interdisciplinary neuroscience and cognition hub that integrates research activities across Aarhus University and Aarhus University Hospital. MIND*Lab* has been tremendously productive in terms of scientific output and new collaborations, both nationally and internationally. Across Aarhus University, the grant helped generate 536 publications and 6 patents. The project involved 52 senior investigators, 23 postdocs, and 48 PhD students across all AU former and current Faculties, and helped bring in additional external funding far in excess of the 120 DKK million Government grant. MIND*Lab* set out to reach other tangible goals: New educations, new technologies to study the human brain and its diseases, and spin-out companies to help bring these innovations into the diagnosis and management of patients. In recent years, we have reported on exciting new technologies being developed by MIND*Lab* researchers to detect and diagnose new aspects of brain disorders, and last year on the COMBAT Stroke company. Adding to the Master program in Neuroscience and Neuroimaging at the Sino-Danish Center in Beijing already coordinated by CFIN / MIND*Lab* researcher Kim Ryan Drasbek, CFIN / MIND*Lab* and Interacting Minds Center affiliated researchers Mikkel Wallentin, Kristian Tylén, Ethan Weed, and Riccardo Fusaroli established a Bachelor program in Cognitive Sciences in 2014, opening its doors to Danish and international students in 2015. Meanwhile, plans are underway to establish programs within integrative neuroscience, building on the unique knowledge and research approaches that have emerged from CFIN / MIND*Lab* over the years. The UNIK grant period ends on a long and sour note in terms of the embedment of MIND*Lab*'s successful activities, as we still lack a sustainable funding model to secure key scientists and running costs associated with our neuroimaging facility. We hope that dialog may help secure this critical part of our activities in the near future.

Joyful notes filled CFIN / MIND*Lab* in October 2014 as the Danish National Research Foundation announced its decision to fund the Music in the Brain (MIB) Center, to be established at Aarhus University from 2015. Peter Vuust has led the development of a unique and immensely successful research approach to the study of music, combining knowledge and methods from across musicology, psychology, and neuroscience to examine the fundamental brain mechanisms associated with the processing of music – with a special emphasis on the anticipatory aspects of both brain function and music. The Music in the Brain Center is joined by an impressive range of leading international researchers: From Helsinki, Elvira Brattico: an expert on the cognitive and affective neurosciences of music and the relation between brain plasticity and musical expertise. From Oxford, Morten Kringelbach: an expert on pleasure and on the emotional aspects of music and other auditory stimuli. And from London, Lauren Stewart: an expert within the neuroscience and neuropsychology of music, with a special emphasis on disorders of musical processing and on learning and plasticity in relation to musical training. We are proud to share offices and infrastructure with the MIB Center as it grows – and look forward to exciting interactions with its researchers!

Recognition in science comes in many forms: In 2014, Maria Witek from the MIB group was awarded the *Adam Krims Memorial Prize*, and MIB researcher Niels Christian Hansen an *EliteForsk travel scholarship*. Nina Kerting Iversen was awarded one of the prestigious *Sapere Aude Research Talent awards*, and Chris and Uta Frith received the prestigious 2014 *Jean-Nicod Prize*. Morten Overgaard was recognized by the World Economic Forums *Young Scientist Award* and I was honored to receive the *Danish Alzheimer Associations Research Prize*. More importantly, CFIN / MIND*Lab* researchers got highly competitive grants as a token of their creative ideas, allowing them to carry out the exciting research that will become news - and perhaps awards - in the years to come. The success of CFIN / MIND*Lab* is felt in other ways as we struggle to squeeze more scientists into every office, and have to limit desk-access in our offices in the Danish Neuroscience Center. We are grateful for the patience of our researchers, for whom 'close interdisciplinary interaction' is taking on a whole new meaning right now – and thank those who help us explore solutions as the anticipated expansion of our activities seems to outgrow the space allocated in the future Aarhus University Hospital in Skejby.

With the CFIN / MIND*Lab* leadership, I thank you for your support, your collaboration and interest, and hope you enjoy the reports from some of our researchers in this Annual Report.

On behalf of the CFIN / MIND*Lab* group leaders,

Leif Østergaard
CFIN / MIND*Lab* director

NEUROPHYSICS

by Sune Nørhøj Jespersen & Brian Hansen

The main advantages of magnetic resonance imaging as compared to other imaging techniques, is its noninvasiveness and its versatility. However, being based on magnetic properties of tissue, the relation to neurobiology and physiology is somewhat indirect. In the neurophysics group, we work towards establishing a clearer connection between contrast in the MRI images and the underlying biological properties. This involves a combination of biophysical and mathematical modeling, and subsequent validation using e.g. disease models and comparison to traditional histology and stereology. A longer-term goal is then to translate these methods to a clinical setting. This, in turn, entails the design of robust and rapid acquisition and estimation strategies.

To aid in our comparisons of diffusion MRI to tissue histology, Lundbeck postdoc Ahmad Raza Khan has developed a new 3-D methodology to quantify local fibre directionality from confocal microscopy. The method is a generalization of 2-D image analysis methods, where great care must be taken to correct for different sources of bias in the third (through plane) direction. The result is a procedure for rapid quantification of tissue properties, in a manner appropriate for comparison to MRI. Figure 1 illustrates local neurite orientation anisotropy acquired using Ahmads method along with confocal tissue microscopy sections. His work is currently in press with NeuroImage[1].

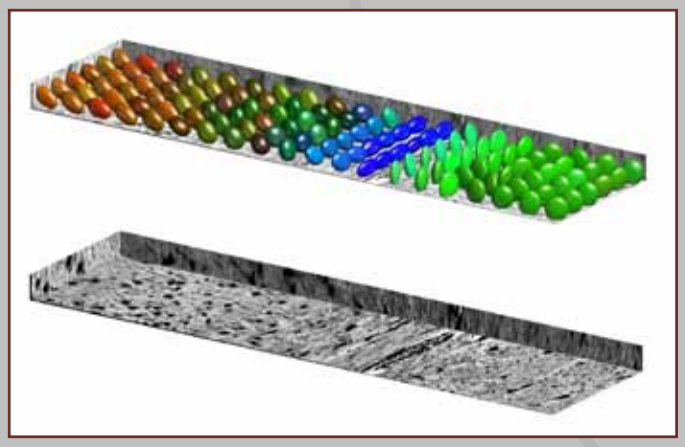

Figure 1
The direction and colours of the ellipsoids indicate the mean direction of fibers in the neighbourhood, identified using 3-D structure tensor analysis of DiI stained tissue sections (monkey hippocampus).

Ahmad now directs his efforts towards the study of tissue microscopic changes as a result of mental stress. He works in close collaboration with research assistant Andrey Chuhutin. This project is supported by close collaborations with Ove Wiborg (Translational Neuropsychiatry Unit), Jens R. Nyengaard (Stereology), and Christopher D. Kroenke (Oregon Health and Science University). Chronic mild stress (CMS) is one of the leading known causes of depression. However, the lack of sensitive and noninvasive methods to study tissue changes represents a significant challenge before we can hope to better understand the disease and develop new treatment regimens. In this project, fixed brain tissue from rats exposed to chronic mild stress investigated with our neurite model of diffusion weighted MRI[2,3], the kurtosis sequence[4,5], and histology in order to identify and map tissue changes in anhedonic and resilient animals. The preliminary results from this work have shown changes in prefrontal cortex and were accepted for presentation at ISMRM 2015.

Diffusion Kurtosis Imaging (DKI) is an extension of Diffusion Tensor Imaging[5], and aims to approximate the Diffusion Weighted Signal in a more precise manner by accounting for major non-Gaussian diffusion effects. In DKI imaging studies, a wide range of different gradient strengths (b-values) is used. This however is known to affect the estimated diffusivity and kurtosis parameters[6]. Hence there is a need to assess the validity of the DKI signal equation and the accuracy of the estimated parameters as a function of b-value. The purpose of an analytical project carried out by Andrey Chuhutin is to examine the error in a mean kurtosis parameter with respect to the ground truth, using a biophysical model[2] with parameters determined from real data and to explore practical ways of reducing the effect of this error. The results identified a rather high degree of deviation between true mean kurtosis values and the experimentally acquired ones (as a function of b-value), suggest caution when relating kurtosis parameters acquired with current standards to tissue structure, and when using them in efforts to build reliable neural tissue models. We previously developed a pulse sequence for rapid acquisition of diffusion kurtosis[4], a metric which is receiving increasing interest in the diffusion community. It has been found to be a sensitive marker of various brain tissue pathologies, and we have observed a strong association to neurite density in experiments. We are advising groups that are interested in implementing the sequence, and the first applications have already been published[7,8]. In reference 8, medical doctor and PhD student Anna Tietze applied the fast kurtosis protocol in glioma patients and found that mean

kurtosis was able to distinguish high-grade from low-grade tumors, in contrast to mean diffusivity. Likewise, research assistant PhD Birgitte Kjølby found mean kurtosis superior in identifying the fibrotic tissue in mouse kidneys, and her results were accepted for presentation at ISMRM 2015.

In parallel efforts, Brian Hansen is pushing our abilities to measure neurite density under clinical conditions. Using powder averaging techniques in combination with modelling, he identified a reduced set of diffusion images capable of extracting approximate neurite density in a fixed rat brain. His results, which will be presented at ISMRM 2015, show close agreement using the full model in combination with extensive data sets.

Other work devoted to developing new diffusion pulse sequences and metrics was also continued in 2014. Specifically, Sune Jespersen identified new directional schemes and analysis methods for double diffusion encoding procedures (9,10), which were tested on model systems and collaborations with the diffusion groups at Hvidovre Hospital and University of Manchester. These metrics are sensitive to e.g. cell shapes, and can also be used to disentangle confounding microscopic contributions to fractional anisotropy. This is potentially useful in the diagnosis and characterization of cancer, and also for interpreting changes in FA which are notoriously unspecific. This work has been accepted for an oral presentation at ISMRM 2015.

PhD student Hugo Angleys' work on modelling the effects of capillary flow heterogeneity on oxygen extraction in the brain was accepted for publication in the Journal of Cerebral Blood Flow and Metabolism late 2014, and he is now extending his work to study glucose extraction and metabolism. This is a different situation than oxygen, due to different metabolic and kinetic pathways of glucose, and different compartmentalization. His work is of great importance for understanding the balance of oxygen and glucose uptake in the brain, the energy budget of the brain, and how it may affected by capillary blood flow heterogeneity, which may become disturbed in various diseases. This is a work in close collaboration with the functional hemodynamics group, led by Leif Østergaard.

Four physics Master students graduated in 2014 with excellent results. Sarah Garney implemented intensive computer simulations of molecular diffusion in spiny dendrites, and found a characteristic signature in terms of the time dependence of

FACTS

Group members, students and collaborators:

- Sune Nørhøj Jespersen
- Brian Hansen
- Hugo Angleys
- Astrid Krabbe
- Sarah Garney
- Lise Trier Nielsen
- Louise Rydtoft
- Leif Østergaard
- Birgitte Kjølby
- Søren Haack
- Ahmad Khan
- Peter Mondrup Rasmussen
- Torben Ellegaard Lund
- Ryan Sangill
- Mikkel Bo Hansen
- Kennet Thorup
- Mads Hartmann Jensen
- Chris Kroenke
- Tim Dyrby
- Henrik Lundell
- Casper Kaae Sønderby
- Andrey Chuhutin

Conferences and research visits:

- ISMRM 2014
- EU CONNECT CLUB
- Brian Hansen: Research visit at the McKnight Brain Institute, Gainesville, FL, USA. (October 2014)
- Jeremy Flint (UFL) visited CFIN for a week in summer 2014.

Invited lectures and Awards (Sune N. Jespersen):

- Brian Hansen, Magnet Lab, Tallahassee, FL, USA.
- Sune Nørhøj Jespersen, Universitätsklinikum Hamburg-Eppendorf, Hamburg.
- Sune Nørhøj Jespersen, EU CONNECT CLUB meeting, Champery, Switzerland.
- Sune N. Jespersen was awarded a Distinguished Reviewer certificate from Magnetic Resonance in Medicine.

Committees:

- Brian Hansen: Elected member of NHMFL users advisory committee.
- Brian Hansen: PhD opponent on a diffusion MRI thesis at Oslo / NTNU, Norway.
- Sune N. Jespersen is secretary in the ISMRM diffusion study group Governing Committee.
- Sune N. Jespersen is a member of PLOS ONE Editorial Board.

Teaching:

- Sune N. Jespersen taught MR courses on Biomedical Engineering and in China for SDC, and a course in Neurophysics at Dept. of Physics and Astronomy.
- Brian Hansen taught MR courses on Biomedical Engineering and was a censor for SDC.

the diffusion coefficient. Her results indicate that in principle spine density in principle could be probed using for example time-dependent diffusion tensor spectroscopy sensitized to intracellular metabolites. In collaboration with scientists from iNANO Lise Trier Nielsen built and tested a grey matter model system ("phantom") made of electro spun fibers. Such a sample can help us test new diffusion sequences and analysis methods in well controlled model systems. Johan Kruse Mortensen implemented a collection of microstructural diffusion models and applied them to a large diffusion data set obtained in deceased human brains, and compared the images to clinical diagnoses and tissue pathologies identified by microscopy. One goal was to identify new imaging biomarkers of Alzheimer's disease, and it was found that specific parameters in white matter and in grey matter showed strong correlations with the presence of Alzheimer's disease. Finally, Astrid Krabbe implemented and tested a recently proposed method for detecting causality in time series[11], with the specific aim of investigating the applicability for brain network analysis based on fMRI. She was able to characterize the requirements in terms of SNR and imaging parameters.

NEW FACE at CFIN

Ahmad Raza Khan, M.Sc, Ph.D (Biochemistry) working as a posdoc at CFIN since July 2014 with Sune Jespersen. He received his PhD on the topic of "Radiation induced morphological and biochemical changes in mouse model using NMR Imaging and Spectroscopy" from Jamia Hamdard, Delhi, India.

Ahmad has worked as a visiting scientist of Aarhus University at Oregon Health and Sciences University (OHSU), Portland, USA from July 2013-14 and working on the project entitled "Cellular underpinnings of MR diffusion contrast in Brain Gray Matter" funded by Lundbeck Foundation.

Ahmad is using microscopy and Image processing to validate diffusion MRI based findings, especially gray matter region of the brain through.

Søren Haack handed in his PhD thesis late 2014, and it was defended successfully early 2015. His work has been to investigate the ability of diffusion weighted MRI to assess the effects of radiation therapy in cervical cancer. He found that brachytherapy targets have specific diffusion properties, and he implemented various techniques to reduce the geometric uncertainty inherent in diffusion MRI, especially in the pelvic area. He also implemented objective and user independent tumors segmentation procedures based on diffusion weighted MRI.

Sune Jespersen received funding of 450,000 DKK from the Simon Fougner Hartmanns FamilieFond. The money will be used on two advanced imaging courses to further improve the team member high field MRI qualifications. The first of these courses was given in the fall of 2014 (see photo page 7), and the next will follow in April 2015. The remaining money was spent on the acquisition of specialized imaging coils for the Bruker high field system.

Our collaboration with the Blackband microscopy group at University of Florida continues. Their imaging facility (Advanced MRI and Spectroscopy, AMRIS) is one of three sites of the US National High Magnetic Field Laboratory (NHMFL). In 2014 Brian Hansen was elected member of the NHMFL Users Advisory Committee to serve from 9/1/2014 through 6/30/2017. This committee advises the NMR/MRI and AMRIS facilities on matters relating to their NSF-funded user program and serves as external reviewers for external user proposals. The committee meets annually. This is a great opportunity to interact with some of the world's leading experts on MR microimaging and magnet technology.

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Thomas Basse from Bruker (left) instructs Neurophysics group members Ahmad Khan, Birgitte F. Kjølby, and Andrey Chuhutin on high field imaging techniques.
Photo: Brian Hansen

FACTS

Funding:

Apart from funding from CFIN / MI*NDLab* the group has received funding from Simon Fougner Hartmanns Familiefond, The Lundbeck Foundation, NIH, and Kornings Foundation.

Selected research projects:

Sune Jespersen, Tim Dyrby, Henrik Lundell, Casper Sønderby: New microstructural metrics from double pulsed field gradient diffusion MRI.

Brian Hansen, Torben Lund, Ryan Sangill, Jurgen Finsterbusch, Sune Jespersen: Fast diffusion kurtosis imaging in humans.

Hugo Angleys, Leif Østergaard, Sune Jespersen: Modeling oxygen and glucose extraction.

Sune Jespersen, Brian Hansen, et al.: Cellular underpinnings of diffusion weighted magnetic resonance image contrast in brain gray matter.

Brian Hansen, Sune Jespersen: Clinically feasible imaging of neurite density.

Master's projects:

Sarah Garney: Influence of dendritic spines on time-dependent diffusion coefficient.

Astrid Krabbe: fMRI network identification with convergent cross mapping.

Johan Kruse Mortensen: Diffusion model comparisons in humans.

Lise Trier: Brain tissue phantoms from electro-spun fibers.

NEUROPHYSICS

Mean Diffusion Kurtosis in glioma patients

by Anna Tietze, Sune Jespersen, and Brian Hansen

Mean Diffusion Kurtosis in glioma patients – initial results with a fast imaging method in a clinical setting

Background

Diffusion kurtosis imaging (DKI)[1] is a technique that improves the sensitivity of MRI to investigate tissue microstructure. This is expected to have wide clinical utility, but lengthy acquisition times have so far limited the use of DKI to experimental radiology. One important imaging biomarker is mean kurtosis (MK), which has been shown to provide improved lesion outline in stroke[2] and improved sensitivity to pathology in other brain diseases (see review in[3]). In 2013, CFIN's neurophysics group published a method for fast MK estimation[3], which allows the implementation of DKI in clinical protocols. The potential of this method has since been validated in an animal stroke model by others[4]. Here, we outline results from our first clinical study, in which we investigate the technique's ability to distinguish between glioma grades in patients. The study is in press with American Journal of Neuroradiology.

Gliomas are a heterogeneous group of primary brain tumors, divided into low-grade (LGG) and high-grade (HGG) tumors with different histopathological features, such as cellularity, the presence or absence of necrosis, and the development of new tumor vessels. MRI is a cornerstone in evaluating glioma patients, monitoring their treatment, and diagnosing disease progression. MK is thought to correlate with tumor cell proliferation and necrosis, both indicators of highly malignant tumors. DKI may therefore be a valuable technique to characterize gliomas and to diagnose disease progression earlier than conventional MRI methods allow.

We have evaluated our new and rapid technique in untreated glioma patients and compared our results with those from the literature, obtained with traditional DKI sequences[5,6]. Moreover, we compared MK with the mean diffusivity (MD), acquired by diffusion-weighted MRI, a widely used method to estimate cellularity in tumors.

Material and Methods

MK and MD were measured in the tumor and in normal brain tissue of 34 patients (22 HGG, 12 LGG). The DKI data acquisition took 166 s and post-processing of the data 3 – 5 s. MK values in different grades were compared to literature values. The diagnostic accuracy of MK and MD to differentiate HGG from LGG was quantified by the area under receiver operating characteristics curves (AUC).

Results and discussion

Typical examples of a LGG (upper panel A) and a HGG (lower panel B) are shown in Figure 1. Note the areas with increased MK (bright signal) and decreased MD (dark signal) in the HGG, whereas MK is low and MD high in the LGG case. MK is elevated in areas with high tissue complexity, typical for highly aggressive tumors. Accordingly, MD is low in rapidly growing lesions, possibly due to their high cell density.

The mean value of MK in the tumor of all patients was significantly higher in HGGs compared to LGGs ($p = 0.028$), unlike the traditional cellularity measure MD. MK values in the tumor and in normal white and grey matter were comparable to those from the literature.

The AUC for the discrimination between HGG and LGG was higher for MK (AUC = 0.731) than for MD (AUC = 0.595). The diagnostic accuracy to identify the most aggressive HGG, a glioblastoma multiforme, was similar for MK (AUC = 0.842) and MD (AUC = 0.876).

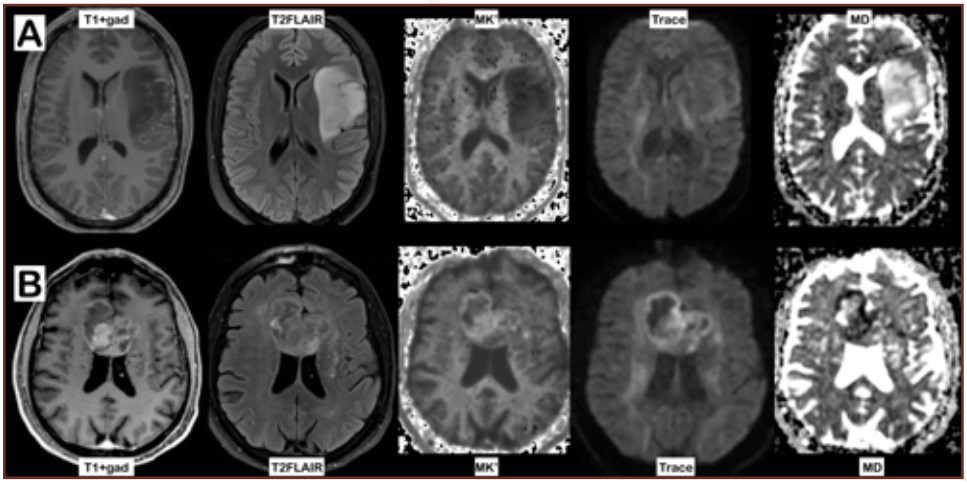

Figure 1

Our study showed that MK is a valuable tool for glioma grading and that our fast DKI method provides robust measurements comparable to those from the literature. This opens up for a larger scale implementation of DKI in clinical studies, allowing the investigation of its utility in treatment evaluation or detection of recurrent disease. Moreover, imaging with a rapid DKI technique in clinically unstable patients, as after a stroke or trauma, has the potential to give new insights into the pathophysiology and the longitudinal progression of these diseases.

NEW FACE at CFIN

Andrey Chuhutin, MSc (Biomedical Engineering), research assistant, starting his PhD in summer 2015.

Andrey has done his BSc in Technion (Haifa, Israel) and his MSc in Tel Aviv University, both in Biomedical Engineering. During his Master's he worked on the evaluation of the changes in the pattern of the water molecules movement in the neural tissue during the epileptic activity. The studies were performed using advanced diffusion weighted imaging modalities: double Pulsed Gradient Spin Echo (dPGSE) and Oscillating Gradients Spin Echo (OGSE).

Andrey started working in CFIN in August of 2014 and since he has been involved in the research related to the neurite density and kurtosis measurement of Chronic Mild Stress (CMS) rat model and an analytical project that was aimed to evaluate the relation between the 'true' diffusive kurtosis of the tissue and its values estimated by the conventional fit procedures as a function of gradient strengths and signal to noise ratio.

Andrey's PhD project entitled "Developing new MRI biomarkers for Multiple Sclerosis" that was submitted in January 2015, will be performed under supervision of Sune Nørhøj Jespersen and Brian Hansen in collaboration with Professor Trevor Owens of Syddansk Universitet and a team of researchers from Washington University in St Louis.

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NEW FACE at CFIN

Birgitte Fuglsang Kjølby, MSc, PhD was employed as an assistant professor, starting from August 2014. She has been working in the field of MRI since 2002 and will now be working in the high field MRI lab in CFIN's preclinical imaging facility.

Birgitte is responsible for setting up methods for *in vivo* scans and will assist researchers with both imaging and data analysis. She is already deeply involved with a number of exciting projects.

As part of Birgitte's position she also coordinates the three MR courses under the Master's program in biomedical engineering at Aarhus University. Furthermore, she teaches MRI as part of the Sino-Danish Neuroscience education in China.

FUNCTIONAL HEMODYNAMICS

by Leif Østergaard

ARCADIA – Year 1

The Functional Hemodynamics group was honored and grateful to receive funding from the VELUX Foundation in 2013 to establish the Aarhus Research Center for Aging and Dementia - ARCADIA.

This grant has permitted us to pursue the exploration of the capillary dysfunction phenomenon in age-related disorders – partly through the acquisition and development of equipment and methods to detect capillary flow and tissue oxygenation, and to undertake specific research projects on the topic. With the help of other CFIN / MIND*Lab* and ARCADIA staff, talented junior researcher Eugenio Gutierrez Jimenez made impressive progress on the development of a two-photon microscopy (TPM) based method to quantify capillary transit-time heterogeneity (CTH), the parameter we use to quantify functional shunting (or more accurately: high end-capillary oxygen tension, as pointed out by Timothy Secomb during our annual CTH workshop) as capillary flow control is lost. In 2015, the ARACADIA grant will permit us to implement optical coherence tomography (OCT) as a complementary method to quantify CTH based on individual erythrocyte velocities across multiple capillaries. In these efforts, and in our implementation of oxygen sensitive TPM, we are grateful to our close collaborators at the Optics Division at the Athinoula A. Martinos Center at Massachusetts General Hospital (MGH). Here, David Boas, Sava Sakadzic, and Jonghwan Lee, who pioneered the development of TPM- and OCT-based methods that are crucial to our future work, have been an immense support by welcoming our junior staff to their lab, and by helping us to test and implement methods. We now work together to develop efficient data analysis tools for these methods.

ARCADIA was joined in 2013 by PhD student Hugo Angleys, a bright young physicist educated in Paris. In 2014, he extended the original biophysical model of CTH effects[1] to include the effects of tissue metabolism, and examine the model's sensitivity to specific transit time distributions[2]. He will now move on to study the effects of CTH on glucose extraction, to get a fuller view of how capillary flow patterns affect cerebral ATP production. Hugo discovered an important, theoretical distinction between the hemodynamics associated with low tissue oxygen tension, and those associated with low oxygen availability. This finding may prove important in neurointensive care. Meanwhile, postdoc Peter Mondrup Rasmussen analyzed whether the effects of capillary flow dynamics on neurovascular coupling allow us to better explain the dynamic relation between blood flow and blood oxygenation – providing the first evidence that CTH effects may be crucial in understand the blood oxygen level dependent (BOLD) contrast changes used in human brain mapping[3]. Combined, Hugo and Peters work is crucial for our modeling of the experimental data that emerge as TPM, OCT, and magnetic resonance imaging (MRI) based measurements of CTH and blood oxygenation are made possible by the ARACADIA grant.

Following up on last year's hypothesis paper on the role of capillary dysfunction in the development of angiographic vasospasms after subarachnoid hemorrhage (SAH)[4], another bright young PhD student, Maryam Anzabi who received her MD in Tabriz, Iran, received a Faculty stipend to pursue the development of a mouse model of subarachnoid hemorrhage

Funding from Velux Foundation

In 2014 CFIN researcher **Rasmus Aamand** received DKK 2.944.840 from the VELUX Foundation for his research project: "Sund aldring med nitrat"

Currently, no preventive treatment against Alzheimer's disease (AD) exists and the cause of sporadic (non-inherited) AD is unknown. In a new hypothesis on the cause of sporadic AD, we have argued that disturbed capillary flow patterns may play an important part in the development of AD. Based on this theory, we have proposed that dietary nitrate may be able to normalize capillary function and consequently help to prevent AD. Our current project is based on a crossover study involving participants with the apolipoprotein E (APOE) ε3/ε4 genotype (high risk of sporadic AD) and participants carrying APOE ε3/ε3 (normal risk of sporadic AD). We focus on cerebrovascular function and capillary flow patterns in ultra-high resolution magnetic resonance imaging (MRI) scans and relate this to the functional importance of nitrate ingestion on cognitive function.

VELUX FONDEN

(SAH) at Aarhus University. With the help of renowned SAH model specialist Nick Plesnila from Munich, she made impressive progress on this challenging project. Another highlight of 2014 was the publication of a reliable and efficient method to determine CTH from dynamic susceptibility contrast (DSC) MRI[5]. Championed by Neuroinformatics group leader Kim Mouridsen, the paper shows evidence of how important CTH changes may be in ischemic stroke. The algorithms of this method also form the basis of the CTH detection method being developed for TPM (above), and they are also being extended to allow analysis of patient cases with contrast leakage. Results obtained by this method are reported elsewhere in this Annual Report – and I predict they may dominate future Annual Reports!

Figure 1
The graphics used to illustrate the normal homogenization of capillary flow patterns during functional hyperemia in our paper on neurovascular coupling after traumatic brain injury (TBI) made it to the cover of the October 2014 issue of Journal of Cerebral Blood Flow and Metabolism.

Traumatic Brain Injury

If one examines the brains of patients who died after severe traumatic brain injury (TBI) under microscope, 90% or so will show evidence of widespread ischemic or hypoxic brain damage – but so far, nobody knows how and when this brain injury occurs[6]. Frustratingly, this number has seemingly remained largely constant for many years, despite efforts invested into guidelines and protocols for pre- and in-hospital management of these patients. Although patients receive what is now considered optimal care from their retrieval at the site of accident and throughout their hospitalization, their mortality remains high, and severe, long-term disabilities are frequent in those who survive. In recent years, it has become clear that even concussions, mild head injuries experienced during sports, and certainly the blast injuries experienced by soldiers sent to combat zones, are sources of long-term cognitive problems, and high morbidity. Yet, the source of tissue injury and disturbed neuronal function after head injury remain largely unknown.

We have previously pointed out that acute changes known to occur in the brain's microcirculation after concussions or more severe traumatic brain injury may impair tissue oxygenation and lead to long-term neurodegenerative changes[7]: Capillary pericytes seemingly take part in the immune response after traumatic brain injury[8] – diverting them from other important tasks, such as controlling blood brain barrier permeability[9] and the transport of toxic substances across it[10], and controlling capillary blood flows[11]. Also, astrocytic endfeet swelling cause dramatic compressions of the capillaries they ensheath, and the mere increase in intracranial pressure (ICP) after head injury seemingly causes a dramatic redistribution of capillary flow patterns.

With a team of neuroanesthesiologists, neurosurgeons, and neuroradiologists, CFIN / MIND*Lab* researchers set out to analyze the possible role og capillary dysfunction after severe traumatic brain injury[6]. The literature reveals several signs of severe capillary dysfunction, other than the structural changes outlined above: Findings that augmented cerebral perfusion pressure may cause tissue oxygenation to deteriorate, rather than improve, and suggestions that hemorheology and attenuation of cerebral blood flow (CBF) seemingly improve outcome, all speak in favor of capillary flow patterns may affect tissue oxygenation in TBI. The paper lists a number of testable predictions on the optimal management of TBI patients, and we hope to examine these in future controlled studies. With generous support from the Lundbeck Foundation, neuroanesthesiologist Klaus Ulrich Koch already set out to examine how specific vasopressors used in neurointensive care medicine, affect CTH and brain oxygenation.

Ischemic Heart disease

Ischemic heart disease (IHD) is the most common cause of death in most western countries. Patients with IHD experience chest pain, angina, mostly in relation to activity, and often shortness of breath as the disease sometimes develops into heart failure. But why is there a section on cardiology within an Annual Report from what claims to be a neuroscience research center? First, neuroscientists, neurologists and cardiologists at Aarhus University Hospital have maintained close collaborations within organ ischemia over the past decade, for example within the protective effects of remote

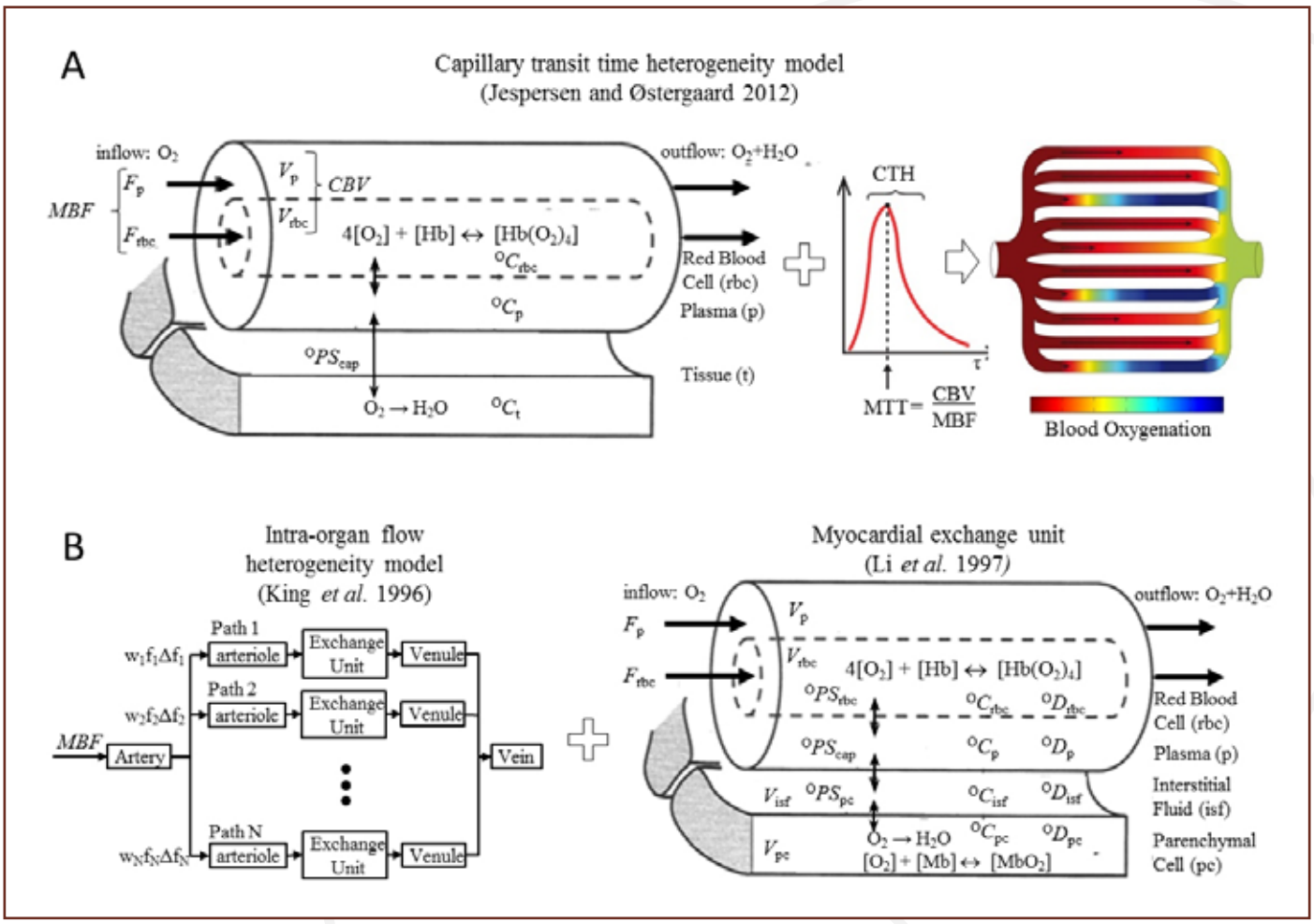

Figure 2

The physiology nerd's overview of our model of tissue oxygenation (A) and previous models (B), from our 2014 paper in Basic Research in Cardiology. Previous state-of-the-art models such as that in (B) cannot explain the increased uptake of oxygen into myocardium as flow and metabolism increases, unless an ad hoc assumption is made that its capillary surface area increase in parallel. Our capillary transit time heterogenity model (A) explains this puzzling discrepancy as an instance of passive redistribution of capillary flows during hyperenmia – not having to assume that capillaries are actively opened during hyperemia in order to fit experimental data.

preconditioning, first discovered in the heart but recently shown to be of benefit in humans stroke in a joint 2014 publication in Stroke[12]. Second, within physiology, the study of solute transport from blood into tissue has evolved in parallel within cardiology and neuroscience for many decades. My own work, for example, is influenced by eminent physiologists such as James B. Bassingthwaighte, Colin P. Rose, and Carl A. Goresky, all of whom modeled and measured tracer transport in the heart. Third, we work hoping that our discoveries may one day benefit patients – irrespective of which organs their ailments affect. With capillaries modifying oxygen and glucose delivery to all parts of our body, this and future Annual Reports will therefore deal with translational research is the sense that the disease mechanisms and methods that CFIN / MIND*Lab* works on affect and apply to other organs than the brain.

'Ischemia' means 'reduced blood supply', and IHD is mostly ascribed to narrowing or blockage of the heart's large blood vessels. Accordingly, IHD treatment aims to prevent vessel wall changes, or to reopen or bypass blocked or narrowed coronary arteries. Some heart patients, however, suffer from chest pain and can't seem to increase blood supply to their heart muscle to the same extent as normal individuals – but display no apparent hindrances in the blood supply to their hearts. In these patients, IHD symptoms are often ascribed to microvascular dysfunction (MVD): Flow hindrances in

myocardial pre-arterioles and arterioles, too small to be visible on normal angiograms. Nevertheless, some patients, for example with hypertension and diabetes, develop symptoms and signs of IHD even before their arterioles show any signs og damage – and at a time where their myocardial blood flow is higher than that of healthy subjects.

With cardiology professor Hans Erik Bøtker, a leading international expert on MVD, and other heart and nuclear medicine specialists, we set out to examine whether early capillary flow disturbances can explain the odd findings and symptoms of some MVD types[13]. Indeed, early hyperperfusion is the predicted hall-mark of mild capillary dysfunction, in which the tissue compensates for a slight reduction in oxygen extraction efficacy by increasing its blood supply – a phenomenon incompatible with a primary, flow-limiting condition. The early myocardial hyperperfusion in diabetes and hypertension can therefore be understood as signs that capillaries are affected first in hypertension and diabetes – while upstream arterioles become affected later on, possibly to augment oxygen extraction in tissue downstream[13]. Importantly the capillary dysfunction phenomenon dissociates tissue ischemia from tissue hypoxia – and therefore 'allows' patients to suffer from angina (a sign of hypoxia) without showing any signs of ischemia. This dissociation, we speculate, may turn out to be critical as we restore myocardial blood flow after myocardial infarctions – while capillary compressions or constrictions still persist and may cause severe capillary flow disturbances: In such cases, restored blood flow may, paradoxically, result in severe myocardial hypoxia and contribute to the puzzling reperfusion injury phenomenon: Myocardial tissue damage that seems to result from the reperfusion of ischemic myocardium itself – a phenomenon known to occur after cerebral ischemia as well[14]. We hope to test these novel hypotheses in future collaborations with our cardiologist colleagues.

Pain

It is often said that the labor pains experienced by women during their first child-birth is among the most painful experiences imaginable. In fact one condition is more painful – but fortunately also much more rare – namely complex regional pain syndrome, or CRPS. Unlike labor pains, the pain experienced by patients with CRPS and neuropathic pain conditions is chronic – in some with little hope of cure or relief. My father, who underwent multiple operations to remedy failed hip replacement surgery, and my nephew who sustained back injuries in a car accident, are my personal reminders of the loss of quality-of-life severe chronic pain can inflict. Within the neuroscience community, we were recently reminded that subjects, who suffer from such excruciating, permanent pain, unsurprisingly, in some cases become depressed or even consider suicide. Neuropathic pain after knee injury and subsequent surgery thus claimed the life of one of the Worlds most gifted and respected neuroscientist, Jon Driver, at a young age.

CRPS usually develops after injury or trauma to a limb (arm, leg, hand, or feet), such as fractures, sprains/strains, soft tissue injury (burns, cuts, or bruises), or surgical or medical procedures. For some unknown reason, normal healing fails, and tissue instead develops excessive swelling and redness of the skin. Blood vessels are seemingly involved

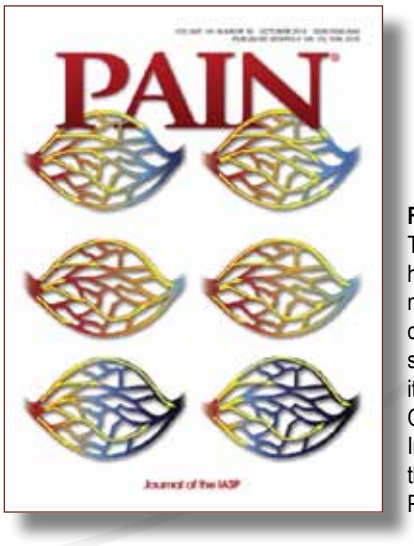

Figure 3
The graphics used to illustrate how tissue injury and pain may become chronic and cause complex regional pain syndrome (CRPS) made its way to the cover of the October, 2015 issue of the International Association for the Study of Pains Journal, Pain®.

Figure 4
After its on-line publication in mid-june 2014, our paper, which proposes capillary dysfunction as a central mechanism in the development of CRPS, has attracted considerable attention. The graph displays Pain®'s record of article views since then

in this abnormal response as they dilate and leak fluids into surrounding tissue. The underlying tissue and muscle may become starved of oxygen and nutrients, causing muscle and joint pain and damage. In some instances, blood vessels may constrict instead and cause cold, white, or bluish skin. CRPS seemingly cause the peripheral and central nervous systems to malfunction – causing prolonged or excessive pain, swelling, and changes in skin color and temperature. The condition cannot be predicted, although it rarely develops in preschoolers or in the elderly, and it is somewhat more common in women. CRPS symptoms vary in severity and duration. Luckily, most cases are mild and patients recover gradually with time. In more severe cases, individuals may not recover and suffer long-term disability.

Working with the Danish Pain Research Center (DPRC) scientist and CRPS specialist Astrid J Terkelsen, CFIN/ MIND*Lab* researchers analyzed the disease mechanism underlying CRPS. We were particularly interested in the transition from the 'triggering' acute inflammation and tissue injury, to the chronic CRPS condition[15]. It appears that tissue is particularly prone to hypoxic and oxidative injury during acute inflammation: The swelling caused by local extravasation of fluid and increased interstitial pressure tends to compress soft tissue capillaries, while the local recruitment of inflammatory cells is known to cause shunting of oxygenated blood through the microcirculation. The natural inflammatory response is thus a delicate balance between natural tissue repair mechanisms and severe tissue hypoxia. Oxidative stress is high under such conditions, partly as an intrinsic mechanism to maintain sufficient oxygen extraction. We speculate that protracted swelling may cause permanent oxidative damage to the microvasculature, and hence irreversible capillary dysfunction - but also that deficient or dysfunctional vascular control is an important culprit in the paradox, 'reperfusion injury'- like (See above) state of tissue hypoxia and high perfusion that initially dominates tissue CRPS. While hypoxia and ATP depletion can cause pain, the subsequent changes in central processing of these pain stimulus probably drive the subsequent, chronic pain condition. We hope to test these hypotheses in future studies with our DPRC colleagues.

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International MIND*Lab* meeting:
Self-awareness – An emerging field in neurobiology
Organized jointly wih Gitte Moos Knudsen, Cimbi, Copenhagen University

17 - 19 September 2014 - Royal Danish Academy for Sciences and Letters, Copenhagen, DK

The last two decades have seen a remarkable effort to include self-awareness and conscious experience as topics for the natural sciences. Neuroscientists, philosophers and psychologists share the goal of trying to understand how the mind relates to the brain. The effort represents a gathering conviction that a fruitful convergence of disciplines is timely.
The symposium aimed to address the fundamental limitations of interpreting experimental results: To which extent can experimental findings provide insights into causal mechanisms behind the "emergence" or "creation" of conscious experience, and to which extent do theony represent correlations only? Similarly, the symposium discussed how empirical data best inspire, improve, and be incorporated in theoretical models of mind-brain relations in this field.

PROGRAM

- **Dan Zahavi**, DK: *Awareness and self-awareness*
- **Anthony Jack**, USA: *Finding the Mind in the Brain: The opposing domains hypothesis*
- **Patrick Haggard**, UK: *Action and self-awareness*
- **Hugo Lagercrantz**, SE: *Awakening of the newborn*
- **Josef Perner**, AT: *Development of metacognition*
- **Axel Cleeremans**, BE: *Prediction-driven interactive loops between self-awareness and theory of mind*
- **Andreas Roepstorff**, DK: *The self and others*
- **Chris Frith**, UK: *Social aspects of metacognition*
- **Jonathan Smallwood**, USA: *That's me in the spotlight: The role of self-generated thought in understanding who we are*
- **Morten Overgaard**, DK: *What is the fundamental empirical basis for self-awareness research?*
- **Shaun Gallagher**, USA: *Seeing without an I: Disturbances in minimal self-awareness*
- **Troels W. Kjaer**, DK: *Paralimbic activity in minimal and extended self-awareness*
- **Kai Vogeley**, DE: *Detecting and evaluating social information*
- **Morten L. Kringelbach**, UK/DK: *Self-awareness, emotions, and reward*
- **Shihui Han**, Peking University, CN: *How does a molecule affect self-reflection?*
- **Steve Fleming**, UK: *The frontal lobe and metacognition*
- **Andrea Eugenio Cavanna**, UK: *Precuneus and self-awareness*
- **Leif Østergaard**, DK: *Neurovascular coupling and the decoding of brain states: Is less more?*
- **Joachim Gross**, UK: *Brain oscillations and human behaviour*
- **Peter Uhlhaas**, UK: *Neural oscillations and predictive mechanisms in schizophrenia: Relevance to self-disturbances?*
- **Vikaas S. Sohal**, USA: *Interneurons, gamma oscillations, and cognition*
- **Julian P. Keenan**, USA *The Evolution of Self-Awareness*
- **Martin Ingvar**, SE: *Reprogramming of the self - teachings from placebo*
- **Gitte Moos Knudsen**, DK: *The neurochemical substrate for the actions of hallucinogens*
- **Hans C. Lou**, DK: *From correlation to causality – Implications for pathophysiology*

MIND*Lab*

Results of an ambitious grant scheme

by Leif Østergaard

The MIND*Lab* UNIK grant was the result of an ambitious grant scheme where Universities were given 120 million DKK by the Danish Government to initiate interdisciplinary projects at a highly competitive international level. Similar large-scale network- and center grants have been pursued in other countries, the German Excellence Initiative being a notable example.

During the five-year funding period, MIND*Lab* researchers attracted highly competitive grants. Professor Eva Vedel Jensen (Science & Technology), initially leader of the New Neuroimaging Methods MIND*Lab* stream, obtained center-of-excellence grants from Villum Kann Rasmussen in 2009 and again in 2014 (DKK 55 million total), Professor and MIND*Lab* co-director Andreas Roepstorff (Joint position with Arts and Health) obtained an internal Aarhus University IDEAS grant (DKK 25 million) to found the Interacting Minds Center, Dorthe Berntsen (Business and Social Sciences) and Peter Vuust (Health and Royal Academy of Music) both obtained Danish National Research Foundation (DNRF) Center-of-Excellence grants, while Morten Overgaard (Health) and Morten Kringelbach (Health and Oxfords University) were awarded ERC Starting and Consolidator grants, respectively. In addition to these, numerous grants from the Danish Council for Independent Research and from private research foundations (VELUX foundation, Lundbeck Foundation) have been awarded to both junior and senior MIND*Lab* scientists.
In total, we estimate that MIND*Lab* affiliated researchers were awarded over DKK 292 million DKK from competitive, external sources during the 5½ year UNIK grant period, and over DKK 30 million DKK from competitive internal grants, including strategic grants from the Aarhus University IDEAS initiative and from the Aarhus University Research Foundation.
The scientific output of MIND*Lab*-affiliated researchers late 2014 was 536 peer-reviewed articles, 45 working papers and article-size peer-reviewed conference proceedings, and 45 books/book chapters. The delay from the completion of a project until its results reach final publication is usually 1-2 years. MIND*Lab*s scientific production is therefore expected to increase as for example PhD projects are completed and results published in the coming year.

Impact of MIND*Lab* research

Bibliometric analysis is inherently difficult when it comes to quantifying scientific production across disciplines with different publication patterns and -traditions: Within the humanities, research is often communicated in books and book chapters, whereas results within medical and natural sciences are traditionally communicated through peer-reviewed articles. In most cases, citations of books, book chapters and articles by scientific peers represent the best index of the impact and importance of research results – but this information may only reveal impact decades after publication.

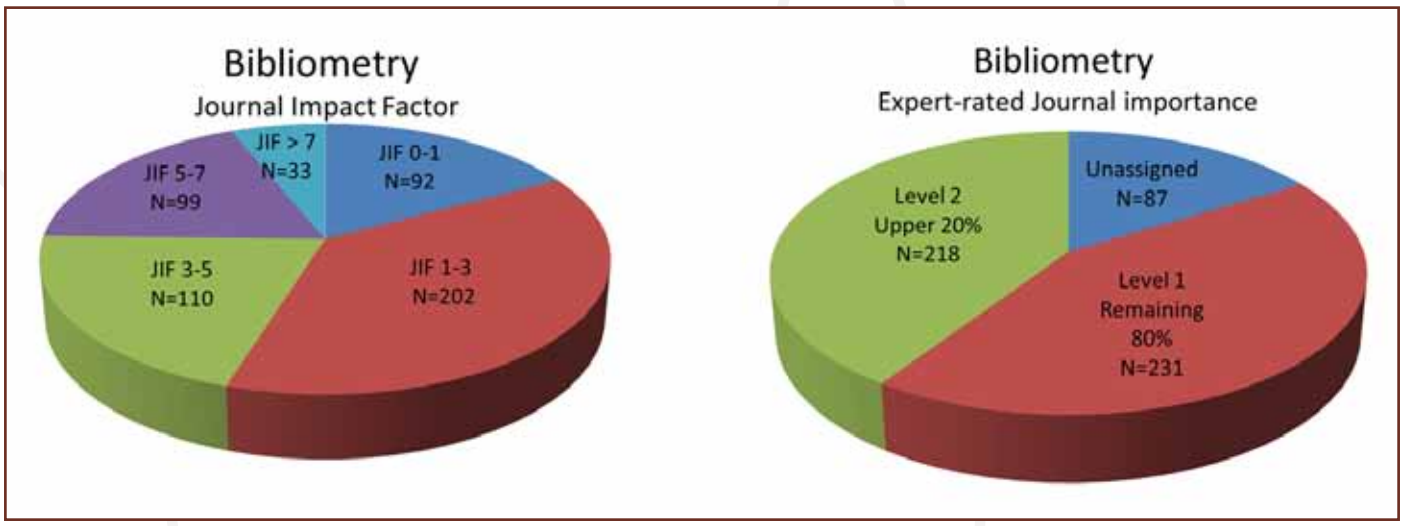
The Journal Impact Factor (JIF) reflects the average number of citations to recent articles published in a given journal, and is often used as a proxy for the relative importance of a journal within its field. Journals with higher impact factors are hence deemed to be more important than those with lower ones. The figure below displays the distribution of MIND*Lab* articles according to JIF.

However, JIFs cannot be compared across fields, and much less across disciplines, For example, within psychology, top-journal JIFs are comparable to those of medium-influence neuroscience journals, whereas top neuro-rehabilitation journal JIFs are comparable to those of lower-ranking neuroscience journals.

Multidisciplinary journals such as Science and PNAS, and general medicine journals such as Lancet and Nature Medicine, publish exceptional research from broader fields while also having high impact factor (JIF>10). MIND*Lab* research was indeed published in these journals and in prestigious review series. So far, MIND*Lab* scientists thus published 18 papers with JIF > 10.

The Ministry of Education and Research has developed a bibliometric tools that assess research productivity and quality across disciplines: Authority Lists. Scholars identify the top 20% journals (Level 2 journals) within their respective disciplines and fields. In this way, quality can be compared across disciplines, fields, and laboratories by means of the percentage of publications published in Level 2 journals. 'Average performance' of a research group would thus be expected to result in in 80% of articles being published in Level 1 journals, and the remaining 20% in Level 2 (top) journals.

The figure shows that roughly half of MIND*Lab*s scientific papers appeared in journals considered by our peers to rank among the top 20% journals in their field.



Some journals are too new to have received JIF or have been ranked for the authority lists. They were included as 'Unassigned' and 'JIF 0-1', respectively.

The future of the MIND*Lab* collaboration

MIND*Lab* researchers have formed several, strong centers-of-excellence during the grant period, and MIND*Lab*-related research therefore continues at an even greater scale as the UNIK grant expires. The Interacting Minds Center, led by Andres Roepstorff and situated in the Nobel Park, will expand the strong 'Cognition and Culture' research themes within MIND*Lab*, maintaining close ties and collaborations with the 'Neuroimaging' and 'Integrative Neuroscience' themes, centered at nearby Aarhus University Hospital where CFIN / MIND*Lab* now struggles to find space for its activities in the Danish Neuroscience Center. The 'Cognition and Memory' theme continues in the Con Amore center, lead by Dorthe Berntsen, who recently received funding from the DNRF until 2019. The 'Language and Music' themes continue their work within the newly founded DNRF Music in the Brain Center, and in close collaborations with the Interacting Minds Center. Less secure is the core of many MIND*Lab* collaborations, namely the 'democratic' access to advanced neuroimaging equipment and methods, and to consult experts who can guide researchers less accustomed to the physics, statistics, and computer skills that neuroscience and neuroimaging at times require. The Aarhus University leadership decided that part of this crucial infrastructure must be financed in part via direct external grant support in the future. While we do attract grants – and overhead – to our Institution very successfully, we experience that both private and public funding bodies are, at best, reluctant to fund project planning and pilot studies (which may turn out unsuccessful) and equipment running costs. The fact that 'embedded' staff positions are contingent on direct external funding obtained by fellow researchers therefore represents an explicit threat to the long-term job security of key MIND*Lab* staff, and we share the international UNIK expert panels deep concern over this decision. We remain hopeful that with time, this crucial part of our activities will be secured as laid out by the UNIK grant agreement – and funded through the overheads and activity MIND*Lab* research generate instead. We are grateful to the Institute for Clinical Medicine and the Head & Heart Center at Arhus University Hospital for their willingness to listen and help through what has been two extremely difficult years for MIND*Lab* staff in view of our troubled embedment.

The MIND*Lab* grant provided the means for what is perhaps the most central 'tool' for interdisciplinary interaction: The odd opportunity for junior, senior and foreign researchers to meet and discuss new ideas and thoughts across disciplines. Easy as it sounds within a University with all Faculties present, this source of inspiration takes intellectual 'nudging', time, and opportunity. The MIND*Lab* Sandbjerg Retreats, the many topical workshops, and the talks and 'master-classes' by visiting scholars during the grant period, have been unique vehicles for MIND*Lab*s success, and a source of inspiration to staff at Aarhus University Hospital and Aarhus University in general. We have yet to find support to continue these activities, but we hope the spirit of collaboration and interdisciplinary exploration built from these past events will fuel future collaborations and innovative ideas – especially those not visible from our traditional, disciplinary approaches to science and medicine.

Neuroscience in China

by Kim Ryun Drasbek

CFIN / MIND*Lab* remains a driving force in the master programme in Neuroscience and Neuroimaging being offered to Danish and Chinese students in Beijing, China as part of the Sino-Danish Center for Education and Research (SDC). Researchers from CFIN / MIND*Lab*, with colleagues from the Danish neuroscience community, are committed to the SDC initiative and work towards the success of the project. They travel to China to teach a range of specialized courses, to participate in workshops and seminars, and to meet with Chinese scientific collaborators.

The master programme in Neuroscience and Neuroimaging was among the first four 2-year master educations in the SDC collaboration to admit students in September 2012. In the summer of 2014, all 15 Danish and Chinese students from this class graduated and obtained degrees from both Aarhus University and University of Chinese Academy of Sciences. Several of the Chinese graduates have continued their studies as Chinese PhD students and one of the graduates, Kaibin Xu, obtained SDC support for a 6-months visit to Aarhus University to work with Morten Overgaard and Thomas Alrik Sørensen. Two of the Danish students started their PhD studies in 2014/15 working on Danish-Chinese collaboration projects. Jan Ole Pedersen is working with DTU and Institute of Biophysics, Beijing, while Carsten Gleesborg is a PhD-student at CFIN / MIND*Lab* and Institute of Psychology, Beijing in a project supervised by Arne Møller, Raymond Chan, Poul Videbech, and Morten Kringelbach.

In November and December 2014 the first Chinese SDC student visited Denmark. Yanhua Xu visited CFIN / MIND*Lab* and the PET-center as part of her Chinese master project to work with micro-PET which is not available in China. Since then the Chinese university has allocated money for travel grants for their Chinese students to visit Denmark during their master education to give them the opportunity to experience Denmark and Danish neuroscience research.

The second annual SDC Neuroscience and Neuroimaging Symposium took place in Beijing the 13th and 14th of January 2014. The first day was dedicated to project presentations from the 2nd year master students. This gave them the opportunity to present the progress of their master projects and get valuable feedback from their fellow students, supervisors, and both Chinese and Danish neuroscientists. All students gave informative and well-formulated talks. The talks provided opportunity for students to train scientific presentation, but also represent the first step towards the Chinese master degree which will be granted in conjunction with the master degree from Aarhus University after their final exam during the summer.

The second day was reserved for a workshop for the Chinese and Danish professors to facilitate scientific collaborations. The scientific workshop was successful and was a step towards future collaborations between Danish and Chinese research groups.

Several smaller and larger adjustments to the master programme have successfully been implemented, and the Chinese contribution to the teaching has been increasing. As the master programme is moving into a more stable operating situation, more time can be spent on scientific collaborations.

2nd Annual SDC Neuroscience and Neuroimaging Symposium
Photo: Liu Yuan, SDC/UCAS, China

List of CFIN / MIND*Lab* researchers involved in SDC

Arne Møller
Birgitte Fuglsang Kjølby
Chris Bailey
Dora Ziedler
Jens Kjærgaard Boldsen
Jørgen Scheel-Krüger
Kim Mouridsen
Kim Ryun Drasbek
Louise Rydtoft
Peter Mondrup Rasmussen
Simon Eskildsen
Sune Jespersen
Thomas Alrik Sørensen
Torben Lund

2nd Annual SDC Neuroscience and Neuroimaging Symposium
Photo: Liu Yuan, SDC/UCAS, China

SDC students

Carsten Gleesborg, SDC PhD student at CFIN / MIND*Lab*:

One of the very great things of getting to do an SDC PhD is the cross-cultural element. Also, there are certain advantages for doing some of the PhD project in China due to the fact that everything is large scale in China making it a splendid opportunity to find participants that live up to the criteria in my research project. As an example of the larger scale in China, the subway net in Beijing transports as many people as the entire Danish population each day. As if that was not impressive enough, the size of the Beijing province is only about the size as Fyn. On top of this I am also very happy to have the chance to combine the expert knowledge of my supervisors, learning from specialists from both East and West.

I took my master in China with the SDC. It gave me a great education, lots of memorable experiences and I met and fell in love with my fiancée Huahua. Obviously this means there is a certain personal element in wanting to go work in China for some time during my PhD. I'll get to practice my beginner-level Chinese and experience more of the intriguing far-east culture and delicious food.

Huahua (Xu Yanhua), master student at SDC in Beijing:

It has been a very new and great experience to be in Denmark and work in a Danish laboratory that is very organized compared to Chinese laboratories. For example, in China it can be difficult to find out how to dispose of laboratory waste and gain access to the right equipment so I am used to being more dependent on my colleagues in order to work in the laboratory. While I was in Denmark I could work with very little supervision because of the high level of organization.

I also experienced this planning and organization in the spare time of Danish people, playing football, going to the gym or going out. I am used to things being more spontaneous in China. If you want to go out for dinner or go for a walk in the forest park you just call up some friends and arrange it.

I really liked going out to see the Danish nature, especially the ocean and the sky is very pretty. I missed the Chinese food the most, but I stayed with Carsten so luckily we could cook some ourselves. Overall being in Denmark has given me a new perspective on life in China, and it has made me appreciate the closeness we have in the workplace and family in China.

Photos from Xu Yanhua's research visit in Denmark in November and December 2014

APPLIED IMAGING AND MODELLING

by Simon Fristed Eskildsen

The Applied Imaging and Modelling (AIM) group engages in interdisciplinary collaborations within neuroimaging research using various acquisition modalities, primarily MRI. Our focus is on image processing, statistical modelling, and prediction. The AIM group is involved in a number of projects with internal and external partners, ranging from optimizing cortical thickness measurements in monkeys, over characterizing abnormal brain structure in psychiatric disorders, to measuring changes in cerebral perfusion in Alzheimer's disease (AD). Imaging biomarkers of AD is one of the main interests of the group, and in 2014 our research efforts within this field was strengthened by a grant from the Danish Council for Independent Research. With this grant we were able to enroll Rune Bæksager Nielsen as a PhD student. His PhD project is entitled "Magnetic resonance imaging biomarkers in Alzheimer's disease: investigating capillary dysfunction and neurodegeneration for diagnosis and prediction."

Alzheimer's disease and mild cognitive impairment

The AIM group collaborates with Professor David Brooks and PhD candidate Peter Parbo in their efforts to recruit individuals with mild cognitive impairment (MCI) as well as individuals with normal cognition. The amnestic MCI project, which was initiated in 2013, continued the acquisition of patients in 2014 and we now have 21 MCI subjects and 12 healthy controls with completed baseline investigations (neuropsychological testing, PiB PET, PK11195 PET and MRI). The aim is to reach 50 MCI patients at the end of 2015. The MRI data from these patients will form the basis for Rune Nielsen's PhD project and enable us to address the capillary dysfunction hypothesis of Alzheimer's disease (AD) (Østergaard et al., 2013) as well as investigating potential new imaging biomarkers based on perfusion and diffusion MRI.
Perfusion MRI data from a study on the effect of the long-acting GLP-1 receptor agonist liraglutide on AD patients (Egefjord et al., 2012) was analyzed in 2014. We found that normalizing the transit time heterogeneity by the mean transit time gives rise to a much more sensitive measure of flow disturbance at the capillary level. The results support the idea of capillary dysfunction in AD and give promises of a new MRI based perfusion biomarker.

Similarly, data from a previous study on dementia supported the notion of a capillary flow component in the pathogenesis of AD. In this study we found a correlation between the flow-normalized capillary transit time heterogeneity and cognitive test scores in 13 patients suspected of AD (Figure 1) (Eskildsen et al., 2014b).

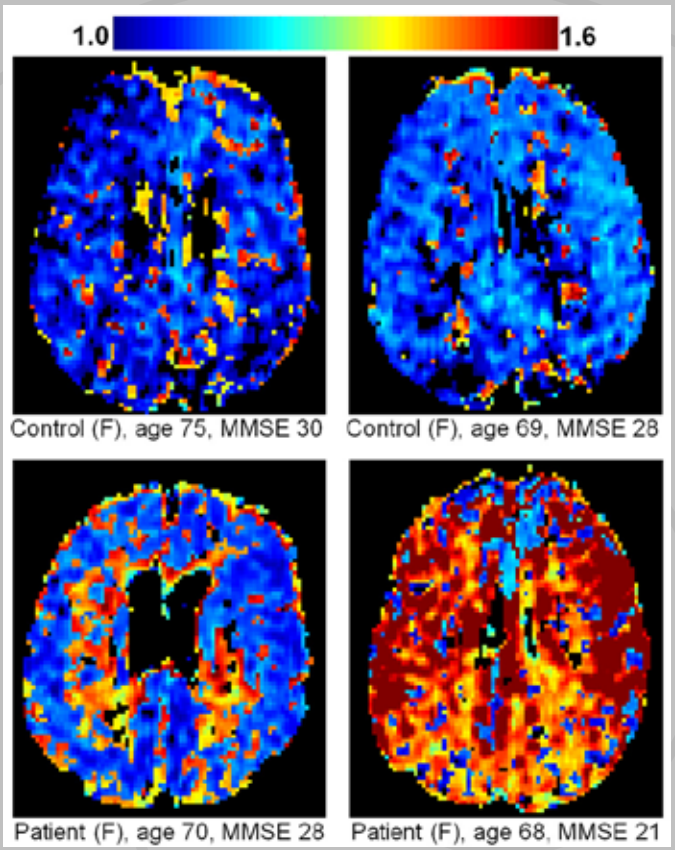


Figure 1
Example maps of capillary transit time coefficient of variance (CoV) in two patients (bottom row) and two controls (top row) (Eskildsen et al., 2014b).

Classification of Alzheimer's patients – a challenge

Predicting the progression from MCI to AD is a topic that receives a lot of attention these years. This increasing interest is primarily driven by the need to improve the power of disease modifying clinical trials by more efficient recruitment and by higher power to detect treatment effects. However, prediction accuracies have been disappointing. This is partly due to the complexity of the symptoms, resulting in improper patient stratification. MCI spans a highly diverse group of patients, spanning the continuum between healthy subjects and clinical AD, as well as dementias and cognitive disorders. Nevertheless, many groups have proposed MRI-based methods that seemingly predict conversion to AD with accuracies around 75%. The problem is to compare these

methods because their inclusion criteria, data acquisition, and data analysis vary greatly. In general, it is unclear how the methods and algorithms perform on "virgin" data, and thus, how they would perform in clinical practice when there is no opportunity to adapt the algorithm to the data at hand.

To address this comparison problem, a grand challenge on computer-aided diagnosis of dementia (CADDementia) was proposed in the spring of 2014. The CADDementia challenge aims to objectively compare algorithms for classification of AD and MCI based on a clinically representative multi-center data set. The AIM group collaborates internationally on developing algorithms for predicting AD, so this challenge could not be ignored. We teamed up with collaborators from McGill University and Université de Bordeaux and set out to address the challenge by applying our previously developed algorithms (Coupé et al., 2012; Eskildsen et al., 2013). The task was to automatically classify structural 3D T1-weighted MRI images into three classes: AD, MCI, and normal controls. The data set originated from three medical centers; two in The Netherlands and one in Portugal. In total, 384 subjects were included. Only 30 were provided with diagnostic information. We trained our algorithms on data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database and tested on the 30 images with known labels. In testing we obtained overall accuracies of 77% (Eskildsen et al., 2014a). A workshop was organized at the 17th International Conference on Medical Image Computing and Computer-Assisted Interventions (MICCAI) where all participating teams (15 in total) presented their methods and the performances on the 354 images with unknown labels were revealed. In general, results on the small training data set did not hold for the larger test set. Our team obtained an accuracy of 52%, which placed the us among the best performing algorithms (the best algorithm achieved 63% accuracy, while the worst performing algorithm only got 32% correct classifications, which is similar to random classification). The results are reported in a recent article (Bron et al., 2015). The results demonstrate that there is still room for improvement if fully automatic classification algorithms are to become useful in clinical practice – for recruitment to clinical trials and for diagnostic support. In retrospect, the challenge data was criticized for not being representative – especially compared to ADNI data. Thus, local adaptation of algorithms will most likely improve performances.

FACTS

Core and affiliated group members

- Simon Fristed Eskildsen
- Rune Bæksager Nielsen
- Leif Østergaard
- Torben Ellegaard Lund
- Sune Nørhøj Jespersen
- Brian Hansen
- Kim Mouridsen
- Jesper Frandsen
- Irene Klærke Mikkelsen
- Mikkel Bo Hansen
- Lars Ribe
- Jakob Udby Blicher
- Erhard Trillingsgaard Næss-Schmidt
- Anna Tietze

National & International collaborators:

- Professor David Brooks, Positron Emission Tomography Center, Department of Clinical Medicine, Aarhus University.
- Professor Louis Collins, McConnell Brain Imaging Center, Montreal Neurological Institute, McGill University.
- Dr. Pierrick Coupé, Laboratoire Bordelais de Recherche en Informatique, Unité Mixte de Recherche CNRS (UMR 5800), Bordeaux, France.
- Professor José Manjon, Instituto de Aplicaciones de las Tecnologías de la Información y de las Comunicaciones Avanzadas (ITACA), Universitat Politècnica de València, Valencia, Spain.
- Dr. Rikke B. Dalby, Centre for Psychiatric Research, Aarhus University Hospital, Risskov, Denmark.
- Professor Ron Kupers, Department of Neuroscience and Pharmacology, University of Copenhagen.
- Dr. Tim Dyrby, Diffusion Imaging Group, Danish Research Centre for Magnetic Resonance
- Professor Pedro Rosa-Neto, Translational Neuroimaging Laboratory, McGill Centre for Studies in Aging, McGill University, Montreal, Canada.
- Professor Marc Vérin, Institut des Neurosciences Cliniques de Rennes, Université Rennes, France.
- Professor Lars-Olof Wahlund, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet, Stockholm, Sweden.

International research visits:

- Dr. Florence Le Jeune and Dr. Gabriel Robert from Université Rennes visited CFIN/AIM, 20-22 January 2014.
- Oskar Hansson, Petter Sjölin, Tomas G. Olsson from Lund University visited CFIN/AIM, 25 February 2014.

Invited oral presentations:

- Simon Eskildsen: BRAINlab mini-symposium: Alzheimer's disease: mechanisms, diagnosis and prognosis, 15 July 2014, Panum Institute, Copenhagen
- Simon Eskildsen: Aarhus CTH meeting 2014, 17 December 2014, Aarhus University Hospital

Conferences:

- Simon Eskildsen: Organization for Human Brain Mapping 2014, Hamburg, Germany
- Rune Nielsen and Simon Eskildsen: Alzheimer's Association International Conference 2014, Copenhagen, Denmark

Talks, teachings and media storms

The AIM groups ongoing investigations of capillary dysfunction in AD were presented at the Alzheimer's Association International Conference (AAIC), and among other things we were invited to give talks on the subject at a symposium in Copenhagen in July and later at the CTH meeting in Aarhus in December.

One of our group's primary goals is to bridge the gap between research and clinical practice. One way to achieve this is by disseminating the research and knowledge to future practitioners. The benefit of this is twofold. First, young clinicians become aware of the advanced methods and techniques in imaging and the value of having this in their toolbox. Second, by increasing the research interest among students, innovations and new ideas may be stimulated, and the field as a whole will benefit. In 2014, the AIM group became involved in teaching at the Neuroscience Bachelor track at the medical education. The undergraduate students are taught basic methods in neuroscience and neuroimaging is part of their curriculum. The AIM group happily accepted the invitation to teach and supervise students within the neuroimaging topic and the chance to disseminate their research to young students. The course runs on both fall and spring semesters.

Figure 2
Dr. Alexander Lebedev's Ph.D. defense in Stavanger. Left to right: Professor Roald Omdal (acting dean), Professor Anders Fjell (first opponent), Dr. Alexander Lebedev (candidate), Assoc. Prof. Simon Eskildsen (second opponent), and Professor Elisabeth Farbu (chairman). Title of the thesis: "Cognitive impairment in neurodegenerative diseases: insights from computational neuroimaging".

The international interest of the AIM group's research led to an invitation to evaluate a PhD thesis at University of Bergen. The defense stood in early September and Dr. Lebedev successfully defended his thesis entitled "Cognitive impairment in neurodegenerative diseases: insights from computational neuroimaging" (see photo from the defense, Figure 2).
The work of the AIM group has also kindled the media's interest. Expert opinions of the group have been requested on several occasions, which bring into focus the research at CFIN and Aarhus University as a whole. A small media storm developed when we were asked to comment on a study demonstrating that flavanols (compounds naturally found in cocoa) could improve memory and possibly delay dementia symptoms in at-risk subjects. The study was picked up by the international media and the AIM group provided their expert opinions to videnskab.dk (see http://videnskab.dk/krop-sundhed/kakao-forbedrer-aeldres-hukommelse), the Norwegian forskning.no, and the radio program P1 morgen (live in DR's studio). What spurred the media's interest was the story that chocolate can improve memory. Unfortunately, one has to consume 1 kilogram of dark chocolate per day to achieve the levels of flavanols administered in the study. This cannot be recommended!

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FACTS

Selected research projects:

Rune B. Nielsen, Simon F. Eskildsen, Leif Østergaard: Magnetic resonance imaging biomarkers in Alzheimer's disease: investigating capillary dysfunction and neurodegeneration for diagnosis and prediction.

Simon F. Eskildsen, Pierrick Coupé, Vladimir Fonov, Louis Collins: Prediction of Alzheimer's disease progression using structural MRI.

Rune B. Nielsen, Lærke Egefjord, Simon F. Eskildsen, Arne Møller, Hans Brændgaard, Jørgen Rungby, Leif Østergaard: Capillary flow changes in Alzheimer's disease.

Peter Parbo, Simon Eskildsen, Michael Winterdahl, Nicola Pavese, Leif Østergaard, David Brooks: The relationship between Aβ, inflammation and capillary dysfunction in amnestic mild cognitive impairment.

Rikke B. Dalby, Simon F. Eskildsen, Poul Videbech, Leif Østergaard: Cerebral perfusion in patients with late-onset major depression.

Ron Kupers, Simon F. Eskildsen, Maurice Ptito: Altered neuroanatomical structure in congenitally deaf and congenitally blind subjects.

Simon Hjerrild, Simon F. Eskildsen, Leif Østergaard, Poul Videbech: Cerebral cortical thickness and perfusion in non-cirrhotic patients with hepatitis C.

Simon F. Eskildsen, Henrik Lundell, Tim Dyrby: Cortical thickness in the Vervet monkey brain.

Florence Le Jeune, Simon Eskildsen, Gabriel Robert, Claire Haegelen, Louis Collins, Marc Vérin: Structural and metabolic correlates of apathy induced by subthalamic stimulation.

Tormod Fladby, Ole Andreassen, Dag Årsland, Clive Ballard, Leif Østergaard, Lars Nilsson, Atle Bjørnerud: Pre-clinical genotype-phenotype predictors of Alzheimer's disease and other dementia.

Per Qvist, Steffen Ringgaard, Simon F. Eskildsen, Anders Børglum: The implication of the schizophrenia-associated gene, BRD1, in behavior, cognition and brain development in genetically modified mice.

Selected publications:

Structural imaging biomarkers of Alzheimer's disease : predicting disease progression. / Eskildsen, Simon Fristed; Coupé, Pierrick; Fonov, Vladimir S; Pruessner, Jens C; Collins, D Louis; Alzheimer's Disease Neuroimaging Initiative. Neurobiology of Aging, 2014.

Detecting Alzheimer's disease by morphological MRI using hippocampal grading and cortical thickness. / Eskildsen, Simon Fristed; Coupé, Pierrick; Fonov, Vladimir; Collins, D. Louis. MICCAI 2014.

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Capillary transit time heterogeneity in the cerebrum correlate with cognitive decline in AD. / Eskildsen, Simon Fristed; Gyldensted, Louise; Nagenthiraja, Kartheeban; Hansen, Mikkel; Dalby, Rikke; Frandsen, Jesper; Rodell, Anders; Gyldensted, Carsten; Jespersen, Sune Nørhøj; Mouridsen, Kim; Brændgaard, Hans; Østergaard, Leif. AAIC 2014.

NEUROINFORMATICS

Adrenoleukodystrophy

by Kim Mouridsen

Introduction - 2014 in Neuroinformatics

Last year we presented a novel approach to perfusion imaging, which allows mapping of capillary dysfunction along with measures representing oxygen extraction capacity and maximum supportable metabolism for given flow patterns. During 2014 we have extended this modeling approach to conditions with non-intact blood-brain-barrier such as tumors and sclerotic lesions. Figure 1 compares our perfusion images to currently available software.

During the past year the Neuroinformatics group has been driving implementation of this technology at many international sites for validation and to apply our methods in a wide range of diseases. This has led to interesting and proliferating collaborations and partnerships and extends the research scope of CFIN / MIND*Lab*. As an example of new insights enabled by this perfusion technology through one of our collaborations, we report on results from a study on adrenoleukodystrophy with colleagues from Massachusetts General hospital below.

Further examples of disease applications include carotid artery stenosis with The German Cancer Research Center, hemorrhagic transformation in ischemic stroke with Department of Neurology MGH, CADASIL and stroke with the University of Glasgow, Multiple Sclerosis with Brigham and Women's Hospital, Harvard Medical School as well as Department of Diagnostic Radiology and Intervention, UMC Hamburg Eppendorf.

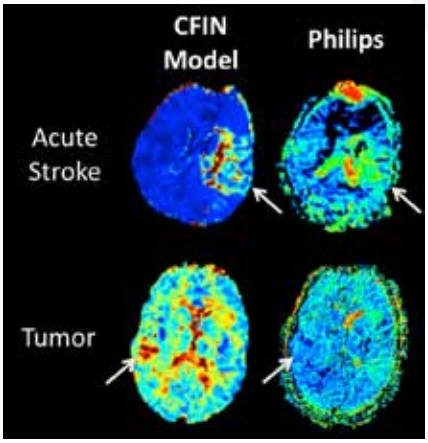

Figure 1
Maps of mean capillary transit time derived with our algorithm compared to Philips implementation as available on the workstation. The acute stroke lesion is clearly distinguishable from surrounding unaffected tissue with the novel algorithm compared to the Philips image. Meanwhile no pathology could be seen in the image generated with Philips software while substantial hyperperfusion is seen in the tumor case with our recent methodology.

by Mikkel Bo Hansen, Anna Tietze, Kim Mouridsen

The disease

Adrenoleukodystrophy (ALD), also known as Lorenzo's oil disease, is an X-linked genetic disease, which affects the nervous system and the adrenal glands. There are three clinically relevant types of ALD: childhood cerebral ALD, adreno-myeloneuropathy (AMN), and Addison's disease, of which we will focus on the childhood cerebral form (CCALD), while referring to Berger, Forss-Petter et al. (2014) for a recent review on ALD in general.

The incidence of ALD is a mere 1:16,800, and the Center for Rare Diseases documents just two new cases per year in Denmark. What the disease lacks in volume, however, it makes up for in severity. CCALD typically debuts in 4-10 year old boys, starting with learning and behavioral problems, followed by vision problems and poor coordination, and then progresses rapidly, ultimately leading to a vegetative state or death within 3-5 years.

The pathophysiology originates from a mutation in a gene coding for a membrane protein responsible for the transportation of very-long chain fatty acids (VLCFA) into the peroxisome, where VLCFAs are normally metabolized. The mutation renders the transporter non-functional resulting in accumulation of VLCFA. In CCALD, this accumulation drives an inflammatory process in the white matter, which results in severe tissue damage. Figure 2 represent a progressed case,

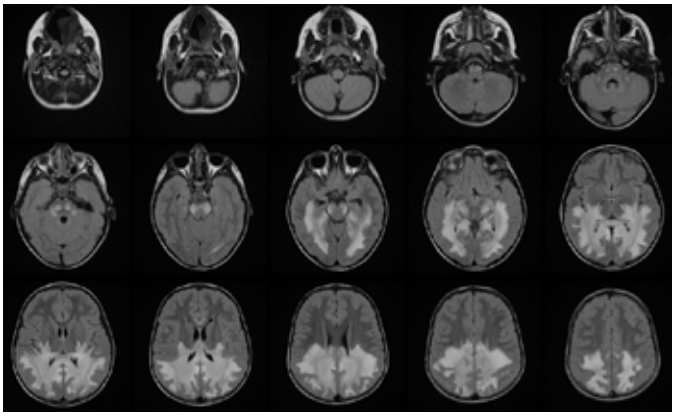

Figure 2
T2FLAIR image of a progressed CCALD case. The profound bilateral confluent lesion (hyper-intense on the T2FLAIR image) is typical in the severe state of the disease and corresponds to non-functional scarred tissue where the disease has run its course. Image courtesy: Eichler, MGH.

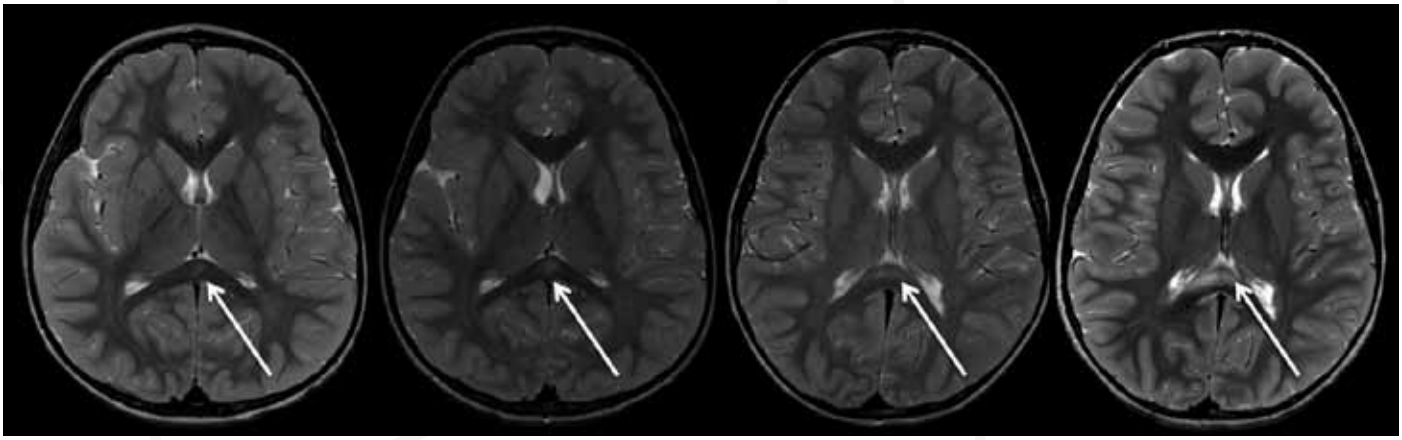

Figure 3
T2 MRI images of a typical CCALD progression. The lesion shows up as a slight hyperintensity at the first timepoint and grows over time (see the arrow heads). The images are sampled every two weeks, emphasizing the aggressiveness of the progression. Image courtesy: Musolino and Lauer, MGH.

and illustrates the severe nature of the disease, whereas MRI images of a typical early progression of the disease are shown in Figure 3.

Treatment and patient selection

Currently, methods for removing VLCFA via drugs or other means are lacking. One treatment, which has been shown to have an effect on CCALD, is haematopoitic stem-cell transplantation (HSCT). Initial evidence indicates that the transplantation must be performed at an early state of the disease in order to have the best chance of success (Musolino, Rapalino et al. 2012, Musolino, Lund et al. 2014). HSCT has a high rate of complications and given that only a subset of ALD patients develops the childhood cerebral form, selection of patients for treatment is crucial. MRI is a sensitive marker for this task, and enhancing regions in T1-weighted post-contrast images, which highlight blood-brain-barrier (BBB) breakdown, are currently used to identify the characteristic of 'leading edge' CCALD. The existence of enhancement is a marker of a progressive CCALD (Musolino, Lund et al. 2014).

New insights from fore-front research at CFIN in perfusion MRI

A joint collaboration between the neuroinformatics group at CFIN, pediatric neurologists at the Massachusetts general hospital (MGH), and the Martinos center at MGH and Harvard Medical School uses T2-weighted dynamic susceptibility contrast (DSC) perfusion MRI to assess the vascular status of the patients. The hope is that new insights into the pathophysiology of the disease and methods for its earlier detection, may emerge from this collaboration.

Traditional DSC MRI assumes that the contrast agent is confined to the vasculature. This hampers the traditional models used, since breakdown of the BBB is a central characteristic of the disease, which results in contrast agent leaking into the extravascular space. Researchers at CFIN have developed a method for robustly estimating vascular parameters despite contrast agent leakage. The algorithm enables estimation of parameters in the capillary transit-time model (Jespersen and Østergaard 2012, Mouridsen, Hansen et al. 2014), but extends the model to correct for BBB disruption. The algorithm has recently been tested in simulated data and cerebral tumors and found to perform well (results not yet published).

Initial results

In Figure 4, we present sample perfusion images along with results from our initial analyses. There are observed significant reductions in the Ktrans parameter (b and e), significant elevation of CTH (c and f), and significantly elevated OEC (d and g), immediately beyond the contrast enhancement (zone C on Figure 4a). This is interesting since the currently accepted marker of CCALD is the existence of enhancement on T1 post-contrast images (zone B), which appears later in the disease progression. Hence, the detection of vascular abnormalities appearing before contrast enhancement is very encouraging and may enable early diagnosis of progressive CCALD. This encouraging finding, in turn, may enable earlier

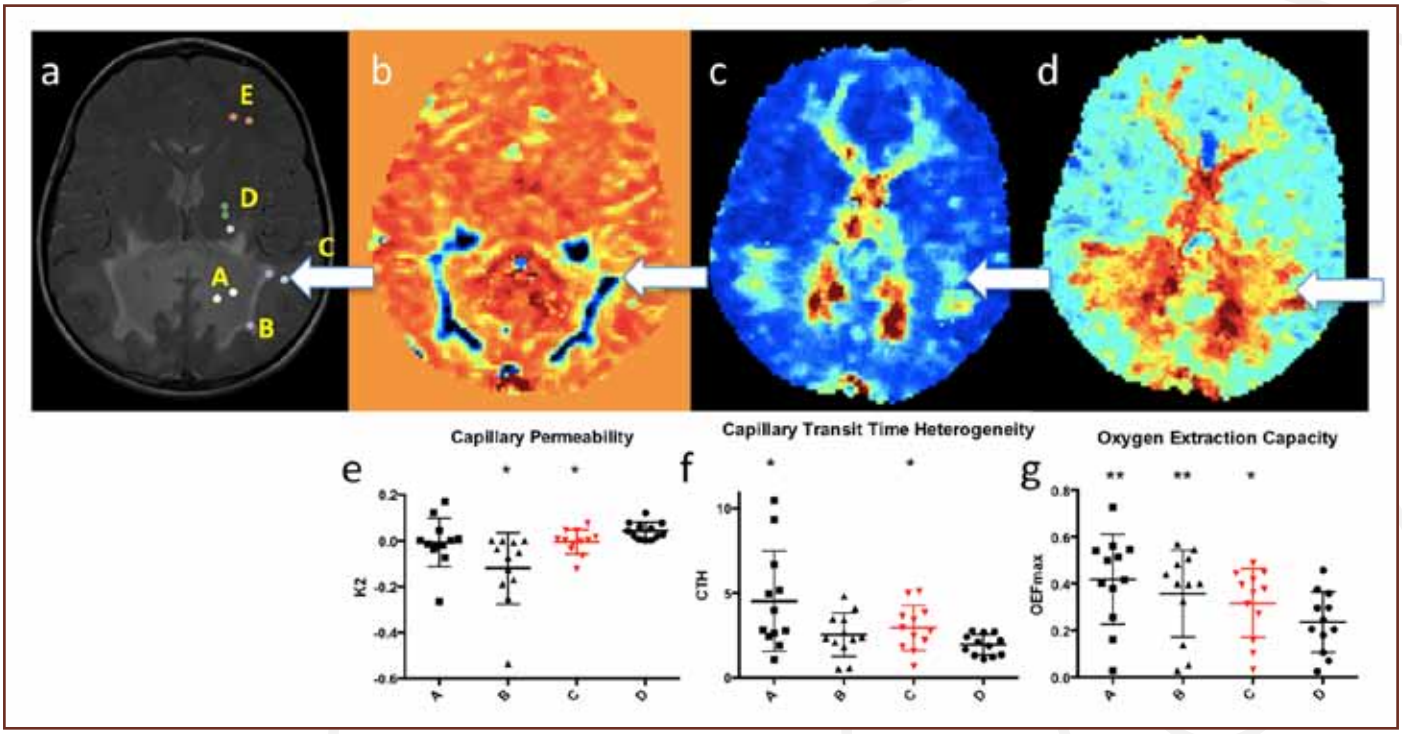

Figure 4
Illustration of perfusion maps from a CCALD patient. The images under lowercase letters a-d represent T1 post contrast, leakage, CTH, and oxygen extraction capacity, respectively. The whisker plots denoted e-g shows the results obtained for the perfusion markers for Ktrans, CTH, and OEC, respectively. The zones denoted A-E on the T1-post contrast image are characteristic for the disease, see (Musolino, Rapalino et al. 2012, Berger, Forss-Petter et al. 2014) for details.

intervention and ultimately result in better prognosis and outcome for this group of patients in the future.

Perspetives

ALD, and in particular CCALD share some characteristics with the much more common multiple sclerosis (MS). In particular, MS patients often present with contrast enhancing white matter lesions, which are known to originate from an inflammatory process. The insights learned from the CCALD study have already spawned interest from the MS community, with a new collaboration currently being established with the Brigham and Women's hospital in Boston, the primary referral hospital for MS patients under Boston's Partners Healthcare.

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Aarhus CTH Meeting 2014

15 - 17 December 2014 - Danish Neuroscience Center (DNC), Aarhus, DK.

The Aarhus CTH Meeting 2014 brought together experts from within neuroscience, vascular physiology, neurovascular coupling, neurovascular diseases, acoustic and optical imaging, modeling of the microcirculation, neurology and neuroimaging to discuss the role of capillaries in the coupling of hemodynamics to the metabolic demands of tissue, and in disease.

SPEAKERS / TALKS

- **Leif Østergaard**, CFIN, AU: Capillary Dysfunction - Update on a hypothesis
- **Richard Buxton**, UCSD: Modeling Neurovascular Coupling and the BOLD signal
- **Aaron Simon**, UCSD: Challenges in measuring blood flow and oxygen metabolism dynamics in humans
- **Jozien Goense**, University of Glasgow: Neurovascular coupling and the BOLD signal across cortical layers
- **Sava Sakadzic**, MGH/HMS: Large arteriolar component of oxygen delivery implies safe margin of oxygen supply to cerebral tissue
- **Clare Howarth**, University of Sheffield: Hypercapnia-evoked cerebral blood flow responses: a role for astrocytes and glutathione
- **Tess Kornfield**, University of Minnesota: Regulation of Blood Flow in the Retinal Trilaminar Vascular Network
- **Roland Pittman**, VCU Medical Center: Regulation and oxygen transport in the microvasculture
- **Timothy Secomb**, University of Arizona: Network hemodynamics and oxygen diffusion in the brain
- **Axel Pries**, Charité Berlin: Oxygen sensing
- **Patrick Jenny**, ETH Zurich: Network hemodynamics, oxygen advection and diffusion
- **Martin Lauritzen**, University of Copenhagen: Brain energy supply and metabolism in aging
- **Eszter Farkas**, University of Szeged: Blood flow and oxygenation during global and focal ischemia
- **Jens Dreier,** Charité Berlin: Neurovascular coupling during Cortical Spreading Ischemia
- **Cenk Ayata**, HMS/MGH: Neurovascular coupling during cortical spreading depolarizations
- **Turgay Dalkara**, Hacettepe University: Cortical spreading depression and migraine
- **Tomas Strömberg**, Linköping University: Assessing the microcirculation by diffuse reflectance spectroscopy and conventional laser Doppler flowmetry
- **Jonghwan Lee**, HMS/MGH: Assessing the microcirculation by optical coherence tomography
- **Janine Berkholz**, Charité Berlin: The endothelial surface layer
- **Hans Vink**, Maastricht University: Physiological and pathophysiological properties of the glycocalyx
- **Fiona Moreton**, University of Glasgow: CADASIL: A neurovascular perspective
- **Simon Eskildsen**, CFIN, AU: Capillary dysfunction in Alzheimer's Disease
- **Franck Ploraboue**, IMFT Toulouse: Tumor microcirculation
- **Anna Tietze**, CFIN, AU: Capillary transit time heterogeneity in primary brain tumors and peritumoral edema

All photos: Kim Ryun Drasbek

NEUROTRANSMISSION

2014 in words

by Arne Møller & Hans Lou

The neurotransmission group develops and applies innovative methods to study the chemical signaling among neurons during normal brain functions, and in a range of neurological disorders. Working with neuropharmacologists, neurologists, and radiochemists, we develop tracers with favorable affinities to the many receptors involved in neurotransmission. To study the uptake and binding of these chemical compounds, we often start with demanding *in vitro* and *in vivo* studies in laboratory animals. For receptor ligands with promising properties, we move on to conduct human positron emission tomography (PET) studies, first to describe their kinetic properties in various parts of the brain, and then in collaborative studies that are designed to unravel key aspects of human behavior and specific neurological disorders. The knowledge we may gain from 'successful' ligands is enormous – and so is the work and the costs of developing one. We are therefore grateful to our many collaborators and to the financial support we have received for our efforts.

In 2014, we witnessed considerable progress in the development of a new PET-radioligand to study GABAergic neurotransmission: The GABA A receptor ligand [^{11}C]Ro15-4313 was approved for use in humans, and has been tested in both human and preclinical studies – with great success. In the sections below, we briefly describe our preclinical work with this tracer in models of epilepsy and addiction, and professor Hans Lou then gives an account of how this knowledge of neurotransmission – and the use of this tracer – is key to our understanding of fundamental aspects of human cognition.

Preclinical work with the [^{11}C]Ro15-4313 GABA A receptor ligand

Our preclinical work with the [^{11}C]Ro15-4313 GABA A receptor ligand has involved both in *in vivo* and *ex vivo* studies:

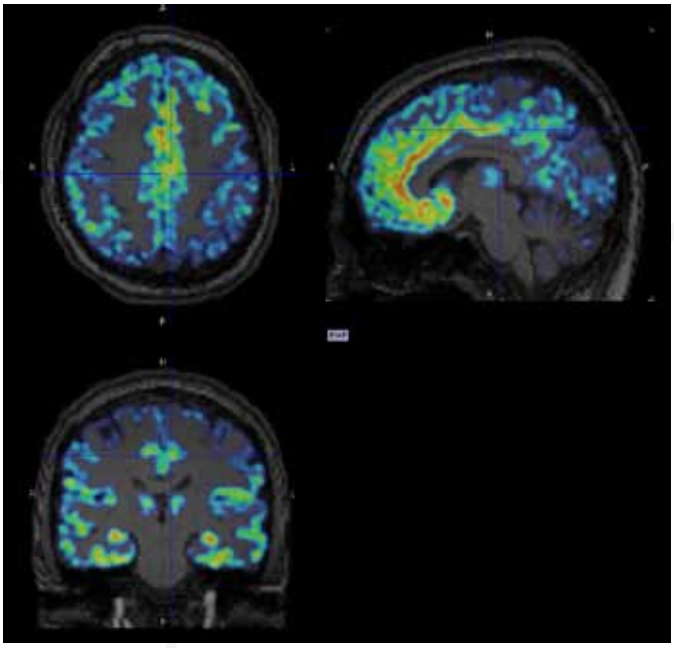
Research year student Majken Borup Thomsen from Anne M. Landaus group has used [^{11}C]Ro15-4313 in *ex vivo* studies. Using autoradiograhy, she studied changes in GABA A alpha 5 receptors in limbic brain regions of rats, applying the domoic acid model of epilepsy. Professors R. Andrew Tasker, University of Prince Edward Island (UPEI), Canada and Gregers Wegener, Translational Neuropsychiatry Unit (TNU) , Aarhus University are both close collaborators in this study.

The [^{11}C]Ro15-4313 ligand has also been used in *in vivo* microPET/MR studies of amphetamine addiction, using a rat model and working closely with Ove Wiborgs group at TNU. Yanhua Xu, master student at the Sino-Danish-Center (SDC) in Beijing was the first Chinese SDC neuroscience student to visit Denmark as part of her master program. During her two month visit, she was part of the research team involved in this study of how neurotransmission is altered in addiction.

The molecular regulation of self-awareness and metacognition

Since our discovery of dopamine release during meditation – with David Brooks' group, then at the Hammersmith in London – it has become apparent that dopamine may participate in the regulation of conscious experience[1]. We provided direct evidence for this hypothesis by demonstrating that dopamine enhances confidence and accuracy in identifying rapidly presented words[2]. More recently, we found direct evidence for dopamine regulation of self-awareness and metacognition through the medial prefrontal cortex[3]. In parallel studies we found that the medial prefrontal and medial parietal cortices, which represent major hubs in the paralimbic network of self-awareness, interact causally with recurrent 40Hz gamma oscillations. Such oscillations are generated in mice by GABA-ergic fast-spiking interneurons by intermittently inhibiting pyramidal cells[4]. Using optogenetic methods to selectively modulate distinct circuit elements it was shown that inhibiting such interneurons did indeed suppress gamma oscillations reversibly[5].

Given the decisive role of interneuron GABA neurotransmission in the generation of pyramidal cell synchrony in mice, and the causal effects of dopaminergic stimulation on paralimbic synchrony and self-awareness in humans described above, we hypothesized that dopamine may exerts its activity on gamma oscillations and self-awareness through release of GABA. To test this prediction, we set out to examine GABA receptor occupancy induced by dopamine challenge vs. placebo in ten normal young men, and, for comparison, in young men with insufficient self-monitoring (pathological gambling), using the GABA receptor PET-ligand [^{11}C]Ro15-4313. The ligand binds selectively to the alpha 5 subtype GABA-receptor, which is abundant in limbic and paralimbic structures. This binding is rapid and reversible, and is sensitive to synaptic GABA fluctuations in animal and human studies[6]. The distribution of the tracer is very promising, in that our preliminary PET images show



strong signals in frontal cortex and in limbic and paralimbic structures, and much less in motor and premotor cortex (see figure above). The yellow and red areas correspond to tissue with high binding of the tracer, whereas the brain MRI is visible in areas with low or no tracer binding.

The first PET-scans were performed in June 2014, and we expect to have finalized all fourty scans within a year. The research team involved in this program are: Hans Lou, Peter Parbo, Kim Vang Hansen, Jakob Blicher, David Brooks, and Arne Møller.

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13th Annual OAK Meeting - 13-14 June 2014

At the Annual OAK Meeting MSc student Mette Marie Busck won the Best Talk Prize - a Nikon camera - for her talk on: *The effect of chronic mild stress on pyramidal cell number in four subfields of the rat hippocampus – a stereology and MR spectroscopy study on the CMS model of depression*

Depression is known to cause hippocampal atrophy. MRI studies have shown a marked decrease in hippocampal volume in humans following severe depression, and studies on rats exposed to chronic mild stress (a validated model of depression), have shown reduced neurogenesis in the dentate gyrus, and alterations in hippocampal shape, kurtosis parametres and metabolism. Remarkably, CMS resilient rats differ in several of these parameters from both CMS sensitive and non-stressed control rats. The aim of this study is to use stereology and magnetic resonance spectroscopy (MRS) to further elucidate the differential effect of chronic mild stress on the rat hippocampus. Using the optical fractionator the pyramidal neuron number is estimated in four subdivisions of CA and compared between the three experimental groups: CMS sensitive, CMS resilient and non-stressed controls. Neuron number estimates will then be compared to local concentrations of the neuronal marker N-acetyl-aspartate (NAA) as measured by MRS. A positive correlation could provide a non-invasive method for measuring neuronal densities, and thus allow longitudinal studies into the effect of stress and the mechanism of resilience. Preliminary stereology data shows approximately 20% more neurons in the ventral CA1 of the resilient rats compared to the other groups.

Best Talk Prize
MSc student Mette Marie Busck receiving the Best Talk Prize at the Annual OAK Meeting in Aarhus. From left: Pia Weikop (Rigshospitalet), Mette Marie Busck, Anne M. Landau (CFIN/PET), and Bente Finsen (SDU)

MIND*Lab* - Interacting Minds

Trails of meaning in mind, brain, and environment

by Kristian Tylén

We humans are the cultural species. Unlike even our closest primate relatives, we extensively shape, and exploit our material environment to construct cultural and cognitive niches (Clark, 2006; Laland, Odling-Smee, & Feldman, 2000). In other words, as a defining trait, we humans are characterized by our elaborate engagement of material objects and technologies. While many material inventions consist in sophisticated tools for instrumental and pragmatic engagement of the environment, the broad class of cultural artifacts does its work by virtue of meaning. Objects such as national flags, religious symbols, artworks, road signs, pictorial representations etc. are imbued with social significance as they are developed, negotiated and engaged in a variety of cultural practices.

MIND*Lab* researchers Kristian Tylén, Riccardo Fusaroli, Johanne Stege Bjørndahl, and Andreas Roepstorff were interested in the complex cognitive and neurocognitive processes involved in the creation and understanding of cultural artifacts. How do we coordinate and negotiate social meanings? How do we come to rely on cultural artifacts? Which neuro-cognitive processes are involved?

In order to bring such complex cultural processes into a more controlled lab setting, they devised a two-day composite experiment. On the first day, participants were assigned to groups of 4 – 6 and instructed to individually and collectively build their understanding of a number of abstract concepts such as "justice" and "responsibility" using LEGO bricks. In order to tap into qualities of the interactive dynamics in the individual groups, the building sessions were video recorded and the participants' heart rates were monitored. Furthermore, the LEGO models were photographically documented and at the end of the sessions, a questionnaire was administered targeting participants' experiences of the collaboration.

Figure 1
Experimental setup for the LEGO construction activity.

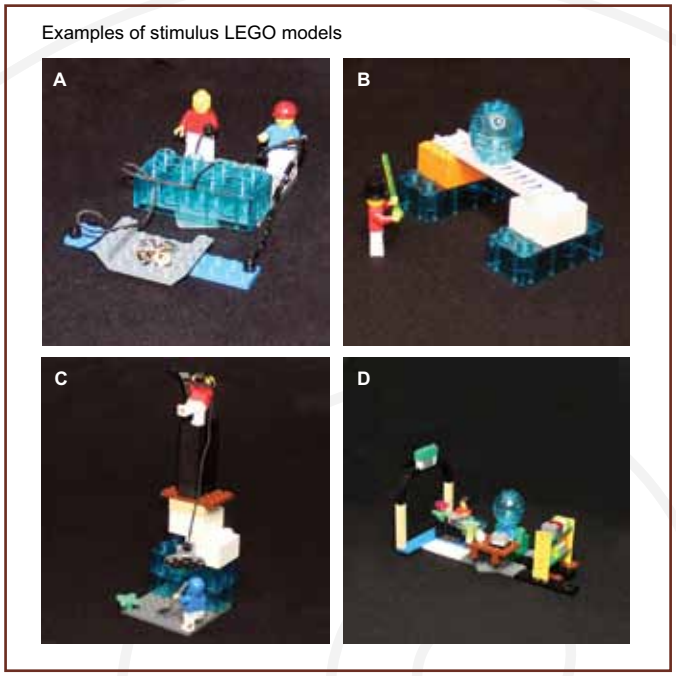

Figure 2
Examples of stimulus LEGO models. A: Collective model illustrating "Collaboration". B: Collective model illustrating "Justice". C: Collective model illustrating "Responsibility". D: Collective model illustrating "Knowledge".

On the following day, participants were invited back for an fMRI brain imaging session. In the scanner, they revisited pictures of LEGO models that they had made themselves individually or with their group, and models that other participants from other groups had made. For each image, they were asked to rate meaning properties (how well the models represented the target concept) and physical properties (the fragility of the model).

The elaborate experimental setup enabled the researchers to ask a number of foundational questions concerning collective meaning construction and cognition. In two studies (Johanne Stege Bjørndahl, Fusaroli, Østergaard, & Tylén, 2014; J.S. Bjørndahl, Fusaroli, Østergaard, & Tylén, In Press), the researchers carefully inspected the video materials from the LEGO construction sessions to investigate how participants arrived at joint creative solutions for the task. Collective

reasoning in the groups widely relied on manipulation and explorations of the material properties of LEGO bricks, as well as on various forms of positive and negative feedback between participants. In another study (Fusaroli, Bjørndahl, Roepstorff, & Tylen, Submitted), the researchers were interested in the coordination dynamics between group members building LEGO models together. They found that variability in speech and building coordination predicted the level and dynamics of physiological entrainment (heart rate) between group members as well as how they rated their feeling of relatedness to fellow group members and their collective performance in the task. Finally, the researchers (Tylén, Bjørndahl, Roepstorff, & Fusaroli, Submitted) investigated patterns of brain activation involved in assessing the LEGO models in the scanner. They found that when participants attended to the bare physical properties of the models, areas of fusiform gyrus and the motor cortex, often associated with object recognition and manipulation, were activated. In contrast, when participants attended to meaning related aspects of the models, areas of the medial prefrontal cortex (mPFC), temporo-parietal junction (TPJ) and inferior frontal gyrus (IFG), normally associated with social cognition and semantics, were activate. Interestingly, these activation patterns were modulated by whether the participants participated in the construction of the models and whether it was an individual or collective model.

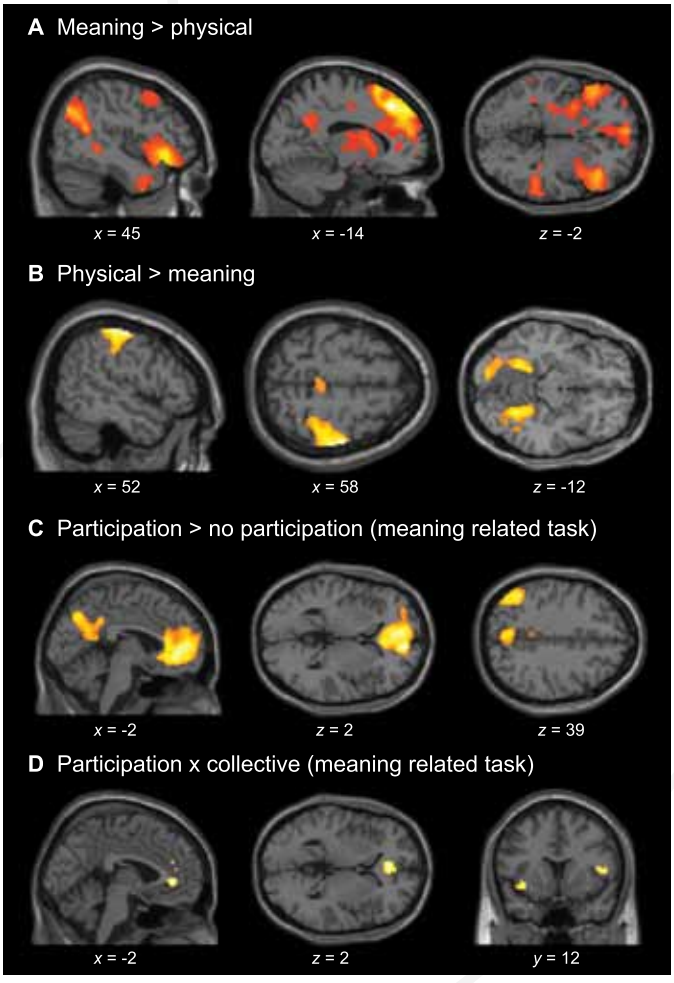

Figure 3
fMRI activation sites. A: main effect of meaning related task > physical property task. B: main effect of physical property task > meaning related task. C: Main effect of participation > no participation (meaning related task). D: The interaction effect 'collective > individual * participation > no participation'.

Together, these studies inform discussions on the hybrid nature of human cognition, which extend far beyond its biological boundaries. Our interactions and cultural practices leave trails in our material environment (e.g. in objects like LEGO models, road signs, symbols and flags), which in turn come to mediate cultural meanings, cognition and brain processes.

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IMC
INTERACTING MINDS CENTRE

CFIN / MINDLab

New Cognitive Science Masters Program at Aarhus University

by Mikkel Wallentin

Cognitive Science is the study of the human mind and how it shapes and is shaped by our experiences and interactions. The new Masters programme at Aarhus University in Cognitive Science will introduce the students to the basic cognitive processes underlying our conscious and unconscious perceptions and actions; how we make decisions; how we use language to communicate, share emotions, and interact socially with others. This involves learning scientific theories, as well as engaging in practical exercises to learn to design and carry out investigations of the human mind, the brain, and human behavior.

An interdisciplinary endeavor

The mind is hugely complex and no single discipline can hope to exhaustively understand it. Cognitive Science combines theories, methods and insights from a range of disciplines such as neuroscience, philosophy, linguistics, anthropology and psychology in a coordinated effort to investigate the human mind and behavior. The study program in Cognitive Science thus includes a broad range of subjects from cognitive neuroscience and computational modelling to consciousness, and cognitive approaches to communication and culture. The students will learn how to argue as a philosopher, experiment like a psychologist, analyse communicational exchanges like a linguist, and program like a computer scientist. The new program is taught in English to promote an international study environment, and to prepare students for the international job market.

Everyday life in the Cognitive Sciences

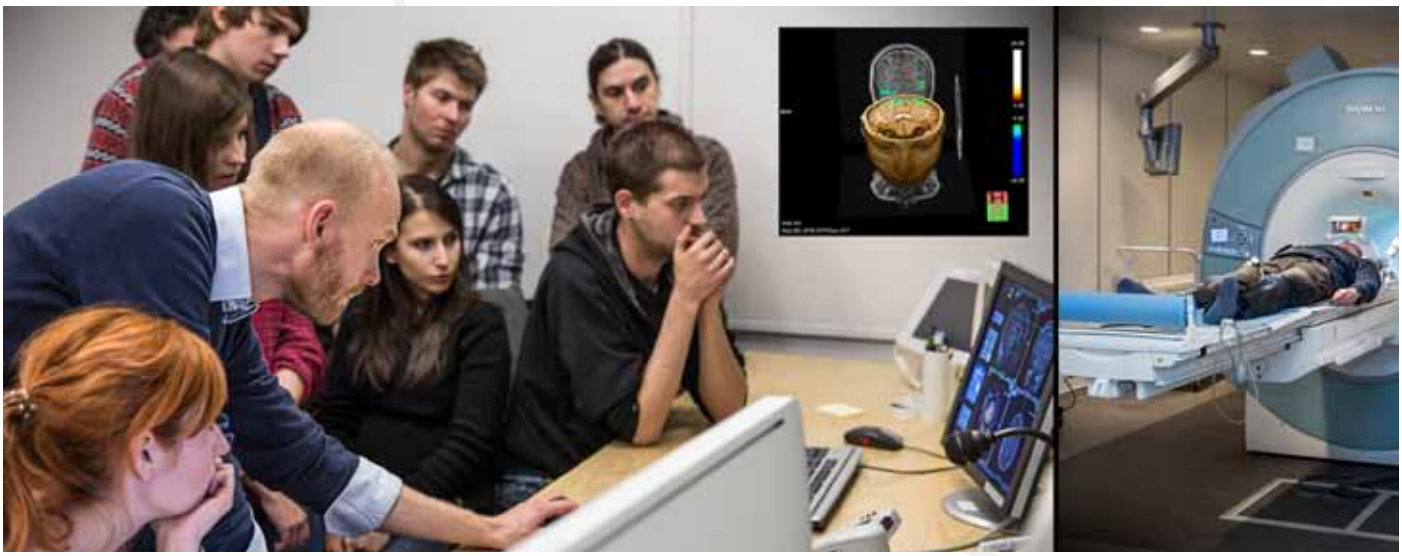
Teaching in Cognitive Science is organised around lectures and group sessions with discussions, presentations, and individual work in study groups. The students will also be involved in practical lab-work, analyse data from brain scans, from behavioral experiments, and large text databases. The Cognitive Science program is embedded in a rich research environment surrounding the Center of Functionally Integrative Neuroscience, the Interacting Minds Centre and the Center for Semiotics at Aarhus University, where students can attend research seminars and learn about interesting new findings.

Career opportunities

With a Bachelor's degree in Cognitive Science the students can choose among a range of masters programs offering specialisation in topics such as Neuroscience, Information Studies, or Corporate Communication. The interdisciplinary profile of the program, combined with concrete skills in data acquisition and analysis, make candidates in Cognitive Science attractive to employers from a wide range of industries, including IT development, product design, neuroscience, and management.

First application round

During the first application round in the spring of 2015, the new Masters programme in Cognitive Science topped the list of educations applied for at ARTS, Aarhus University. 329



applicants – 170 of these had the Cognitive Science study as their first priority. This was twice as many applicants as the second most applied education at ARTS. The new programme ended in the top 10 most applied educations throughout Aarhus University only topped by studies in Medicine, Law, Psychology and a few Business Economy educations. There are a total of 60 student places at Cognitive Science – 6 of these are earmarked for quota 2 applicants.

IMC / CFIN researchers go viral with the "Cognitive Science Song"

Four IMC / CFIN researchers, Kristian Tylén, Mikkel Wallentin, Riccardo Fusaroli, and Joshua Skewes performed as rockstars in a music video that was used as an untraditional PR-campaign for the new AU Masters programme in Cognitive Science.

Music and lyrics for the song was written by IMC researcher Kristian Tylén, and four researchers, all involved in the planing and creation of the new AU Masters programme and in teaching new Cognitive Science students, appear in different settings around Aarhus University in the music video that quickly gained lots of views at YouTube and spread via Facebook.

The Cognitive Science Song

Do you often wonder what is going on in people's minds?
Then there's only one solution you should go and study Cognitive Science
We'll strap your boyfriend up with funny electrodes
And stream his thought live down on your mobile phone
Only one solution comes to my mind:
Go study Cognitive Science!

Is God responsible when my neighbor's acting all insane?
Should I blame it on his culture, the genes or firings in his brain?
And do I experience snow as any Eskimo does?
Or is my language shaping up all my perceptions and thoughts?
The only one answer I can find:
Go study Cognitive Science

I guess you get the gist of what I am trying to say
You can study the mysteries of minds in all kinds of ways
All we need is just your hard work and your curiosity
While big money is waiting impatiently out in the industry

I used to think my thoughts are just something going on in my head
So why do I think so much better when I am hooked up on the Internet?
And though I'm sure your heart is very different from mine
They tend synchronize when we share a glass of wine
Only one solution comes to my mind:
Go study Cognitive Science!
This program is just one of a kind:
Go study Cognitive Science!
There is absolutely no doubt on my mind
Cognitive Science!

Watch the untraditional student recruitment video and read more about the new AU Masters programme in Cognitive Science at: **http://bachelor.au.dk/en/cognitivescience/**

CFIN / MIND*Lab*

Magnetoencephalography at CFIN

by Yury Shtyrov

One of the state-of-the-art brain imaging facilities actively developed at CFIN is magnetoencephalography, or MEG. The MEG technique can monitor brain activity with a high temporal resolution (the device installed at CFIN can trace neural activation with sub-millisecond precision), which it does by recording miniscule magnetic fields generated by electric currents in neurons, the brain's main working cells. These tiny magnetic fields are picked up by the so called SQUIDS, super-conductive quantum interference devices, sophisticated miniature sensors, which are distributed around a person's head in a helmet-shaped device and kept at super-low temperatures near the absolute zero, -273°C. As the magnetic fields permeate through human tissues and air, there is no need for a solid conductor between the head and the measuring device, which makes MEG recordings much more convenient and time-efficient for both subjects and researchers. The technique is quiet and non-invasive: the recordings do not involve any currents, fields or substances "injected" into the participant's body, the operation is completely silent with participants seated in a comfortable chair in a spacious magnetically-shielded room. As MEG allows for more direct estimates of electrical activity sources in the brain, it enables analysis of not only the timing but also of the spatial location of neuronal activation, thus showing in real time the complex interplay of various brain areas as they are processing the information coming to our central nervous system. The Triux™ MEG device installed at CFIN is a masterpiece of state-of-the-art technology produced by Elekta Neuromag (Helsinki/Stockholm), an international leader in biomedical technology. It incorporates 306 MEG sensors of different types making it capable of high resolution acquisitions in different spatial dimensions; these are complemented by continuous head position tracking, 124 EEG channels and other data outputs which can together yield the most accurate spatial-temporal image of the brain activity currently possible. CFIN's MEG Laboratory is the first installation of its kind in Denmark and Scandinavia.

During 2014, the MEG Laboratory has seen a lot of new developments. The stimulation and recordings systems have received various upgrades improving their overall quality. Most importantly, we designed a new EEG cap layout to ideally suit the type of studies run at CFIN. Together with specialists at EASYCAP Gmbh (Germany), we optimised the electrode layout for comprehensive coverage of all cortical areas, and combined it with fixed head position identification (HPI) coil locations to expedite subject preparation procedures and minimise localisation errors. EASYCAP has now manufactured the new electrode caps, which we have started to use routinely for combined EEG/MEG recordings, producing high-quality data simultaneously in both of these modalities. Another major upgrade that was decided in 2014 is an installation of a Helium recycler. Weekly refills of liquid Helium, needed to ensure the superconductive properties of MEG sensors, will be replaced by a recycling procedure which will re-use the gas present in the system by extracting gaseous Helium, re-liquefying it on-site and pumping it back into the dewar. This will both cut the costs of Helium supply and reduce the downtime related to the lab maintenance. We look forward to the implementation of this design during the coming year.

A very important activity at the MEG Lab has been a series of seminars and training events dedicated to raising the level of methodological expertise in MEG research at Aarhus University, increasing the awareness of MEG in the Danish neuroscientific, clinical and psychological communities and building stronger international collaborative networks. This included various training workshops dedicated to data analysis, a series of invited talks by international leaders in MEG research, and an international MEG conference held at AU in May 2014. All of these events have been a large success and attracted national and international audience.

Finally, and most importantly, the MEG lab has seen an influx of new users and new experimental and clinical recordings during the past year. Among others, the MEG user group was joined by Dr Alina Leminen, an international scientist working on uncovering language processing mechanisms in the brain, and Dr Eino Partanen, who has done pioneering research in studying human brain development. Both of them are busy collecting MEG data in their new experiments focussed on the brain underpinnings of human learning abilities. New studies have also been started by Parkinson research group (headed by Professor Karen Østergaard, Aarhus University Hospital) who investigate the effects of deep brain stimulation on cortical activity in Parkinson's patients, by the Music In the Brain group (Principal Investigator: Professor Peter Vuust), who use MEG to understand the neural bases of music perception, by our collaborators from Copenhagen investigating plasticity in the brain of blind patients, etc. etc. Ongoing research includes multiple other projects dealing with various cognitive and clinical questions, while the MEG is also routinely used for clinical diagnostic purposes, most importantly for pre-surgical mapping in epilepsy patients.

Aarhus MEG Special 2014

On 13-14 May 2014, DNC and Center of Functionally Integrative Neuroscience (CFIN) organised a workshop dedicated to highlighting the most recent developments in MEG and its integration with other modalities.

The recent advent of whole-brain neuroimaging techniques has revolutionised fundamental brain research and biomedical applications, as it has made it possible to non-invasively study structures and processes in the brain of awake human volunteers and patients. Among the various techniques that can reveal structural (MRI), metabolic (fMRI, PET) or electrophysiological (EEG) properties of the brain, a unique niche is occupied by magnetoencephalography (MEG). The technical complexities and challenges of MEG, which relies on registering minuscule magnetic fields produced by neurons, means that it has fostered an unprecedented level of cooperation between different sciences which involves neurophysiologists, physicists, psychologists, psychiatrists and neurologists, engineers, neurocomputational modellers, neurosurgeons, cognitive scientists, software developers, linguists and many others. Truly, MEG is where the most exciting developments in human neuroimaging are taking place.

Aarhus University is proud to host the first MEG in Scandinavia, and one of the very few in Northern Europe. This latest-generation machine is located at the Danish Neuroscience Centre (DNC), a unique infrastructure that hosts the widest range of neuroscience techniques under one roof: fMRI, PET, 2-photon microscopy, 9T small-sample MRI, EEG, navigated TMS, neurosurgical and wet neurophysiology facilities and many others, all integrated within a research-clinical network of Aarhus University and Aarhus University Hospital.

The program of the Aarhus MEG Special 2014 included a workshop dedicated to current issues in MEG analysis, most importantly state-of-the-art source reconstructions techniques, and a series of keynote talks by international scientists of the highest reputation, each with their unique angle and contribution to the field. Participants, who came from different institutions in Denmark and other countries, also got a general introduction to the MEG and other neuroimaging facilities at the DNC, a lab tour, and the possibility to discuss collaborations and joint projects with the AU MEG group.

Keynote speakers at Aarhus MEG Special 2014:

Professor **Matti Hamalainen**, Harvard University / Massachusetts General Hospital, USA
The Quest for the Philosopher's Stone of Human Brain Imaging

Dr. **Markus Siegel,** University of Tübingen, Germany
Spectral fingerprints of large-scale neuronal interactions

Professor **Joachim Gross**, Glasgow University, Scotland
The functional role of oscillatory phase in coding and communication





Hedonia: TrygFonden Research Group

2014

by Morten L. Kringelbach

In 2006 *Hedonia: TrygFonden Research Group* was founded as a transnational research group and over the last decade we have tried draw on the complementary advantages in Aarhus and Oxford. The main research goal is to understand pleasure in the human brain[1]. Apart from being a lot of fun, this is important since it may offer us novel and more effective ways to treat anhedonia, the lack of pleasure, which is a major component of affective disorders[2].

Our group uses a range of behavioural, neuroimaging, neurosurgical and computational methods to investigate the many facets of pleasure in health and disease. We are interested in the fundamental pleasures afforded by food[3], sex[4,5] and social interactions[6,7], which are central to survival, but we are also interested in higher order pleasures such as music and art[8,9] which have strong links to eudaimonia, the meaningful and engaging life[10].

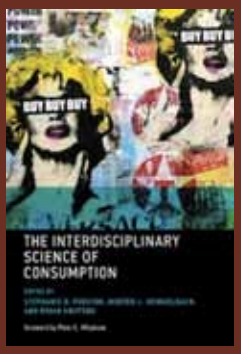
Infants are a focus of our research and especially how their sounds, looks and smells strongly influence the adult brain[6,11]. The ERC is funding a five-year project to map for the first time how this special relationship changes the parent brain. Understanding this is not only exciting and fundamental to understanding the human condition but may also help to shape the way we can intervene when things go awry, e.g. in post-natal depression[12].

Another main focus is understanding and modelling how pleasure systems are fundamental in the dynamic allocation of brain resources[13]. As we have come to understand more of the delicate balance and transitions between different brain states, we can now directly rebalance and recalibrate brain networks through deep brain stimulation[14]. We are also building whole-brain computational models that allows us further probe and understand the human brain in health and disease[15].

When pleasure systems become unbalanced, it can be very difficult to rebalance the brain. One of our main interests is to help advance our understanding of the effects of war and disaster for which we have setup *Scars of War Foundation* at *The Queen's College*. One current project is investigating the brain changes related to post-traumatic stress-disorder in war veterans.

Overall, the time is now ripe for modern neuroscience to study the many faces of pleasure, opening up for new treatments and perhaps even better lives - especially if coupled with early interventions.

New book



Our drive to consume – our desire for food, clothing, smart phones, and megahomes – evolved from our ancestors' drive to survive. But the psychological and neural processes that originally evolved to guide mammals toward resources that are necessary but scarce may mislead us in modern conditions of material abundance. Such phenomena as obesity, financial bubbles, hoarding, and shopping sprees suggest a mismatch between our instinct to consume and our current environment. This volume brings together research from psychology, neuroscience, economics, marketing, animal behavior, and evolution to explore the causes and consequences of consumption.

Contributors consider such topics as how animal food-storing informs human consumption; the downside of evolved "fast and frugal" rules for eating; how future discounting and the draw toward immediate rewards influence food consumption, addiction, and our ability to save; overconsumption as social display; and the policy implications of consumption science.

Taken together, the chapters make the case for an emerging interdisciplinary science of consumption that reflects commonalities across species, domains, and fields of inquiry. By carefully comparing mechanisms that underlie seemingly disparate outcomes, we can achieve a unified understanding of consumption that could benefit both science and society.

About the editors

Stephanie D. Preston is Associate Professor of Psychology at the University of Michigan
Morten L. Kringelbach is Professor of Neuroscience at Aarhus University and Oxford University.
Brian Knutson is Associate Professor of Psychology and Neuroscience at Stanford University.

With a foreword by Peter Whybrow.

New group members

Louis-David Lord is a first-year DPhil student based in Oxford. His research employs cutting-edge network analysis and whole-brain computational modelling to investigate imbalances in the integration and segregation of neural processes in neuropsychiatric disorders. Prior to joining the Hedonia: Trygfonden group, he worked as a Research Assistant in Psychiatric Neuroimaging at Harvard Medical School. He holds a BA (Hons) in Molecular Neuroscience from Bowdoin College (USA) and a MSc in Integrative Neuroscience from Imperial College London.

Alexander Fjældstad is a PhD student currently stationed in Oxford, UK. He has a degree in medicine from AU and his PhD is a collaboration between the Department of Otorhinolaryngology, Aarhus University Hospital, and Hedonia: TrygFonden Research Group. His PhD project focuses on olfaction, with emphasis on olfactory testing and neuroanatomical olfactory connectivity (DTI). The aim is to develop a method to differentiate neurological causes of hyposmia/anosmia.

Marina Charquero Ballester, is a doctoral student with the *Scars of War Foundation,* investigating the functional neuroanatomy of post-traumatic stress disorder in war veterans. Her project aims to deepen the current understanding of the impact that combat-related stress and trauma have on whole-brain structural and functional connectivity by using three highly complementary imaging techniques (MRI, fMRI and MEG). The research will also be important for other groups exposed to trauma, such as refugees and victims of natural disasters.

Carsten Gleesborg, is a PhD student at the AU. His PhD is a collaboration between CFIN and the Risskov Psychiatric Hospital at AUH, Hedonia: TrygFonden Research Group at University of Oxford, and Institute of Psychology at UCAS in Beijing. He will use MEG and DTI to study olfaction in depressed patients undergoing wake-therapy in order to explore the characteristics of treatment outcome.

FACTS

Hedonia TrygFonden Research Group:

Group members, students and collaborators:

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Therese Ovesen
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Selected ongoing research projects::

- Berridge K.C. & Kringelbach M.L. Pleasure systems in the brain.
- Kringelbach M.L. The pleasure of food: underlying brain mechanisms of eating and other pleasures.
- Rømer Thomsen K., Whybrow P. & Kringelbach M.L. Reconceptualising anhedonia: novel perspectives on balancing the pleasure networks in the human brain.
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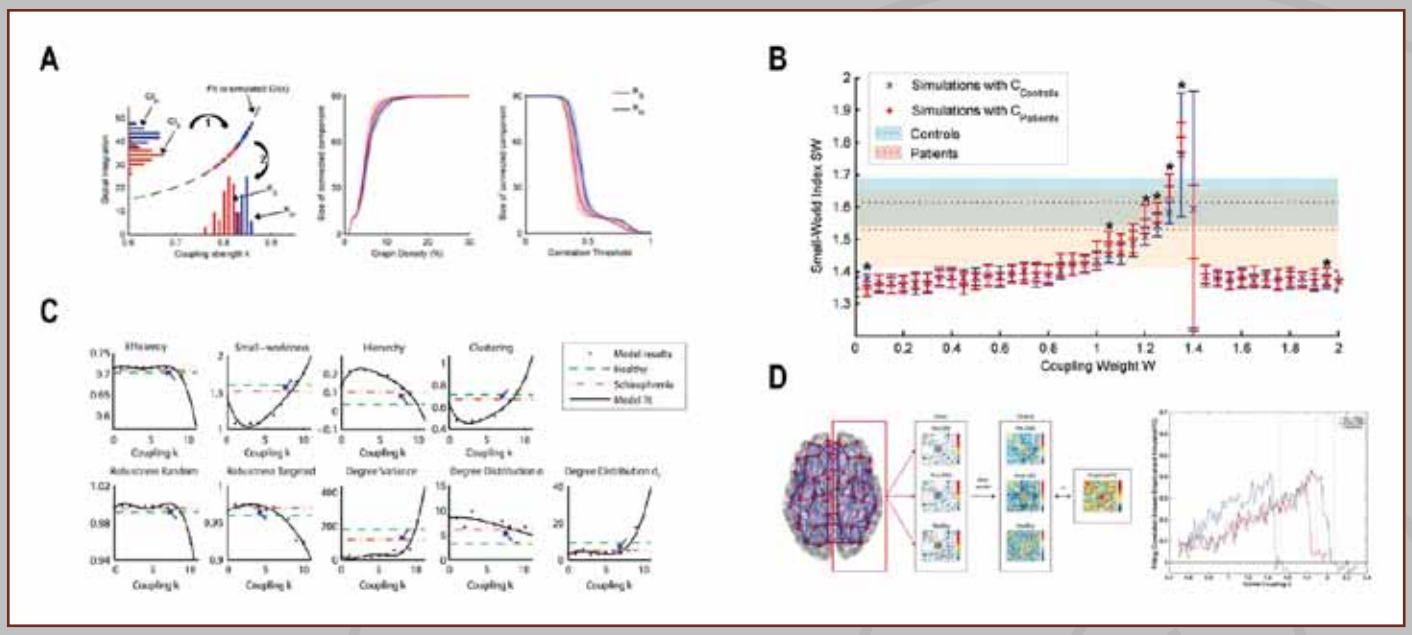

Figure. Examples of whole-brain computational modelling of schizophrenia and Parkinson's Disease.
A) Whole-brain computational modelling was used to simulate functional networks in schizophrenia and health using global integration values reported experimentally. This showed significant fragmentation in the simulated functional networks between the two groups as shown by the number of connected components as a function of graph density and correlation threshold (Cabral et al., 2012a). B) Significant changes small-world index between schizophrenia patients and control patients were found using a whole-brain computational model and varying the global coupling weight (Cabral et al., 2013). C) Similarly, simulations showed that the model predicted well the experimentally observed measures of graph theoretical measures as a function of the coupling strength (Cabral et al., 2012b). D) Whole-brain computer models have also been useful for other neuropsychiatric disorders such as PD, and combined with a therapeutic intervention. This, a computational model using the changes in pre- and six-months post-DBS showed significant recovery of structural network connectivity as a result of using DBS to alleviate the symptoms of PD (Van Hartevelt et al., 2014).

Research during 2014

During the very productive year of 2014, we published 21 papers. Among many other papers on the parent-infant relationship, we published the Oxford Vocal (OxVoc) Sounds Database, which is a validated set of non-acted affective sounds from human infants, adults and domestic animals[16]. We hope this freely available database for probing emotion will become a useful tool to our colleagues.

Together with Professor Peter Vuust, we also published a number of papers on the impact of groove music on the brain[17,18] and in particular how musical training and empathy can positively impact adults' sensitivity to infant distress[19]. In the coming years we are very much looking forward to studying these and other related questions in the new "Music In the Brain" centre funded by the Danish National Research Foundation from June 2015.

Whole-brain computational modelling is another growing area of research in collaboration with Professor Gustavo Deco. The perhaps most exciting publication of the year was our Neuron review on the great expectations for using whole-brain computational connectomics to understand neuropsychiatric disorders[20]. In this paper we focus on the disruption of functional and structural connectivity in neuropsychiatric disorders and how whole-brain computational models can help generate and predict the dynamical interactions and consequences of brain networks over many timescales. We review methods and emerging results that exhibit remarkable accuracy in mapping and predicting both spontaneous and task-based healthy network dynamics. This in turn raises great expectations that whole-brain modeling and computational connectomics may provide an entry point for understanding brain disorders at a causal mechanistic level, and that computational neuropsychiatry can ultimately be leveraged to provide novel, more effective therapeutic interventions, e.g., through drug discovery and new targets for deep brain stimulation.

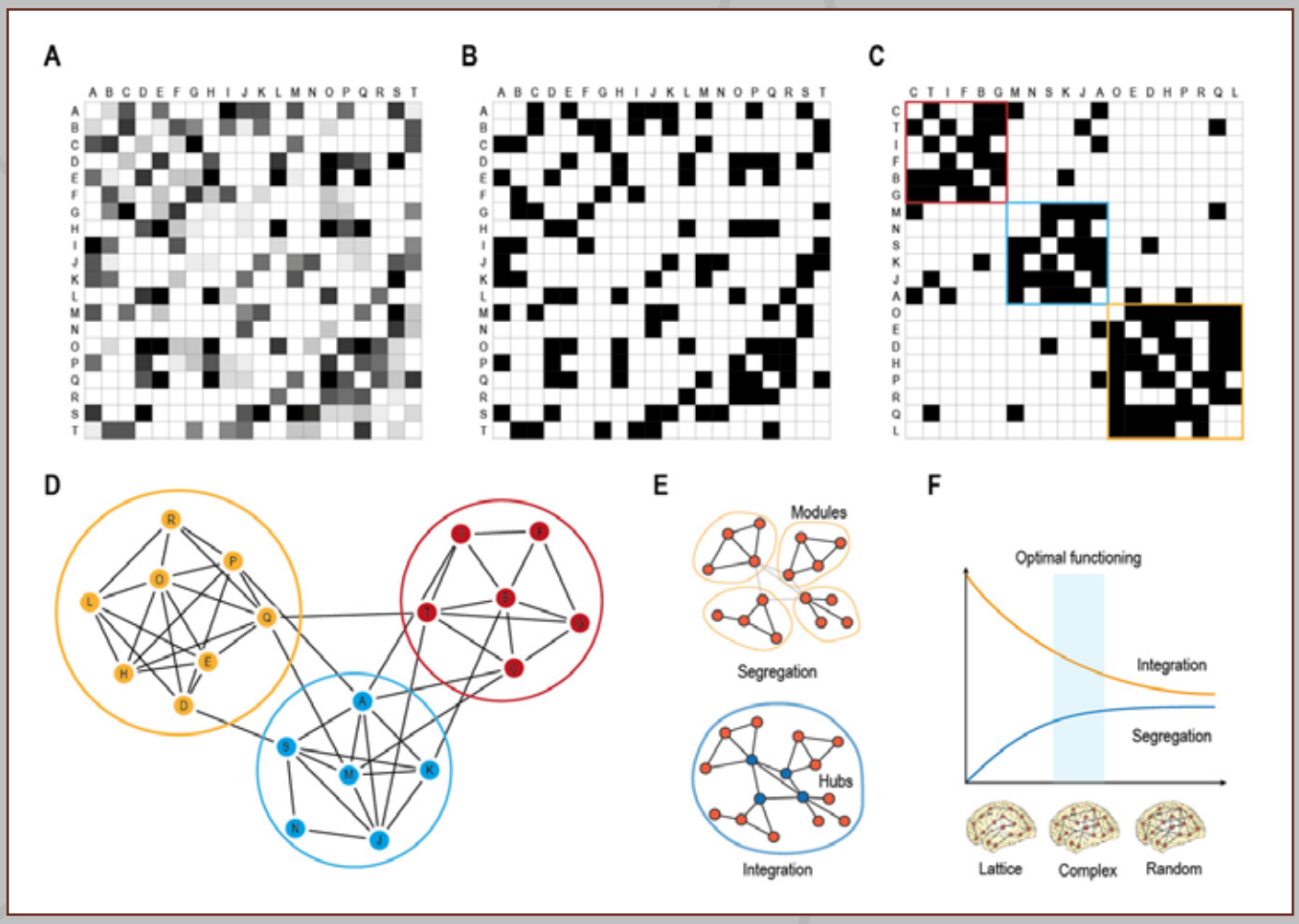

Figure. Network science.
Connectomics is concerned with characterizing the way that different regions connect to each other. A brain network can be characterized using graphs where the nodes are the regions and the edges are the connections between regions. Here, we introduce some of the key concepts in network models. A) The example shows a matrix with the connection strengths (in shades of grey) between twenty brain regions. B) This connectivity can be binarized at a given threshold of connectivity strength (here, we have used 50%). C) This binary connectivity can then be reordered to an optimal modularity partition, with this example having three modules (coloured in orange, blue and red). D) Another way to visualize this network is to use a spring-embedded two-dimensional network diagram, with the three modules circled. E) The topology of networks can be separated into segregated modules and integrative hubs. F) The key issue for optimal functioning for any brain is to balance the amount of spatial segregation and integration. In the example with 20 brain regions, region A is clearly a hub with a high degree (number of connections), betweenness centrality (placed on many of the short paths in the network) and participation coefficient (distributed connections across network modules). In contrast, region A has low clustering given that most of the topological neighbours are mutually unconnected. In contrast, region O has high clustering and region H has low betweenness, while region G has low participation coefficient and region N has low degree. Figures B-D adapted from (Sporns, 2014).

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MUSIC IN THE BRAIN

by Peter Vuust

In 2014, the Music In the Brain group was awarded a DKK 52 million centre of excellence grant from the Danish National Research Foundation of to create The Danish National Research Foundation's Centre for Music In the Brain (MIB). Hence, from 1 June, 2015 MIB will be an interdisciplinary research centre aiming at addressing the dual questions of how music is processed in the brain and how this can inform our understanding of fundamental principles behind brain processing in general. The centre will employ state-of-the-art scanning methods (MR, fMRI, MEG, EEG, PET) and behavioural measures and will be a collaboration between Aarhus University (AU) and The Royal Academy of Music (RAMA), placed at AU .

MIB is based on four strands of research in music and the brain: **Perception**, led by Lauren Stewart: centred around music perception and cognition, **Action**, led by Peter Vuust: centred around the processing of musical rhythms and the interaction between rhythm and motor behaviour, **Emotion**, led by Morten Kringelbach: centred around the relationship between music and emotions and how and why music brings pleasure, **Learning**, led by Elvira Brattico: centred around the effect of music training, expertise and individual traits. The group leaders are acclaimed international experts who conduct ground-breaking research within their designated MIB research areas. Lauren Stewart is an expert in music perception and cognition with a special interest in congenital amusia, a developmental disorder of musical perception. Peter Vuust is an expert within the cognitive neuroscience of music and has earned an international reputation for his research into musical rhythm. Morten Kringelbach is an expert in pleasure widely recognized for his research on the valence of reinforcers, including auditory cues such as baby crying, laughter and music. Elvira Brattico is an expert within the cognitive and affective neurosciences of music, the relation between brain plasticity and musical expertise, and the genetic variations of music-related brain functions.

With a strong foundation in music practice and theory at the highest level, MIB will combine neuroscientific, musicological, and psychological research within music perception, action, emotion, and learning with the potential to test the most prominent theories of brain function and to influence the way we play, teach, use, and listen to music.

One important focus of MIB is that the insights gained from a more refined understanding of the influence of music and musical training on the brain[1-6] is incorporated into clinical practice and research[7-8]. The advent of neuroscientific methods in music has prompted research into demonstrating the beneficial effects of music in a variety of somatic and psychiatric disorders, and into improving general well-being in healthy individuals. This trend was examined by Line Gebauer and Peter Vuust in a white paper[9], which critically reviewed the current state-of-the-art of the clinical applications of music, along with the possible explanatory brain mechanisms. We hope this review will serve as the starting point, and point towards future possible exploitations, of music as a clinical tool. Hence, translating basic research into clinical application was a recurring theme for the MIB research in 2014. The musical multi-feature paradigm which was developed for exploring differences between musician groups with different backgrounds[10] was used in modified versions to investigate atypical processing in cochlear implantees[11-12] and in individuals suffering from autism spectrum disorder. Furthermore, MIB research conclusively demonstrated the beneficial effect of music listening for chronic pain patients[13], of musical training on adults' sensitivity to infant distress[14], along with a number of other clinical studies. These interests contributed to the fact that MIB in collaboration with DTU reached the second round of the Innovation Fund Denmark's 2014 call with the project MiCARE.

MIB has established itself within a strong network of researchers nationally and internationally. This has lead to joint publications and grant applications. In 2014, MIB had a number of presentations on the most important international conferences within the field (e.g. the Neuroscience of Music in Dijon and ICMPC in Seoul), and MIB leader, Peter Vuust, was invited as key note speaker on several international conferences, e.g. in Oslo, Helsinki, Tuebingen, alongside top researchers such as Isabelle Peretz, Stefan Koelsch, Mari Tervianemi, Kenneth Hugdahl and others. MIB also attracted international junior and senior researchers for research positions, shorter stays, and longer sabbatical visits in 2014, MIB hosted a minikonference at the SPOT festival in May, and was prominently featured in the media throughout the year. With the new centre of excellence grant, MIB will be the first research centre of its kind in Europe, positioned as an international hotspot in its field by bringing three internationally acclaimed researchers to Aarhus, to strengthen and extend existing networks and collaborations. This will in turn attract top-level international scientists and the most talented students. MIB will be a unique research training environment with weekly meetings, courses, and summer schools directed by leading international scholars.

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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. Music and Pain.

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

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MUSIC IN THE BRAIN

Music in the deaf adolescent brain

by Bjørn Petersen

Digital hearing

The cochlear implant (CI) is a neural prosthesis that provides deaf individuals with the opportunity to gain or regain the sense of hearing. The implant transforms acoustic signals into electric impulses, which are delivered to an electrode array implanted into the cochlea. The electrodes stimulate intact auditory nerve fibers at different places in the cochlea, thus mimicking the tonotopic organization of the healthy cochlea. The clinical impact of the device is extraordinary, allowing postlingually deafened adults to restore speech comprehension and deaf children to acquire language. Perception of music with a CI is challenging, primarily because CIs are designed to provide recipients with speech comprehension[1, 2, 3]. Nevertheless, neural correlates of residual prerequisites for music perception have been found in postlingually deaf adult CI users and in children with CIs[4, 5].

A new generation

By contrast, little is known about music perception in the new generation of prelingually deaf adolescents who grew up with CIs. Recent studies indicate that, to keep pace with their normal hearing (NH) peers, supplementary measures of aural rehabilitation are important throughout adolescence[6]. Music training may provide a beneficial method of strengthening not only music perception, but also linguistic skills, particularly prosody. To gain new insight and test our hypothesis, we initiated this study, aiming to investigate:

1. The behavioral and neural correlates of music perception in prelingually deaf adolescent CI users
2. The potential effects of an intensive musical ear training program on adolescent CI users' discrimination of music and speech

Participants

The participants were all recruited from Frijsenborg Efterskole (post-school) in the city of Hammel, Denmark. Eleven adolescent CI users signed up for the study. The young CI users had a severe-profound/profound congenital or prelingual hearing loss and had received their CI at different points of time in childhood or adolescence (Mean age at implant = 7.5 years; range: 2.2-14.9 years). The participants committed themselves to two weeks of music training. The program was based on three elements: rhythm training, singing, and ear training. The active music making was supplemented with daily computer based listening exercises. Ten NH peers formed a reference group, which followed their everyday school schedule and received no music training (Table 1).

Group	Girls/ Boys	Mean age at project start	Age range	Mean implant experience (y)	Uni-/bilateral implant
CI grp.	6/5	17.0 (SD 0.9)	15.6-18.8	9.5 (SD 4.2)	(2/9)
NH grp.	2/8	16.2 (SD 0.5)	15.3-17.0	-	-

Table 1
Demographic data for the 2 experimental groups.

EEG and tests

Before (T1) and after (T2) the intervention period, both groups underwent EEG recordings and behavioral tests for perception of music and emotional prosody. EEG was recorded with a musical multifeature MMN paradigm[7], consisting of a standard randomly violated by six musical deviants: 1) pitch deviant 1 (+2 semitones), 2) pitch deviant 2 (+ 4 semitones), 3) guitar deviant, 4) saxophone deviant, 5) intensity deviant (-12 dB) and 6) rhythm deviant (-60 ms) (Figure 1). The MMN was measured as the peak amplitude at the Fz electrode site, within a 40 milliseconds (ms) window centered at the most negative point at 75 - 205 ms. The behavioral tests

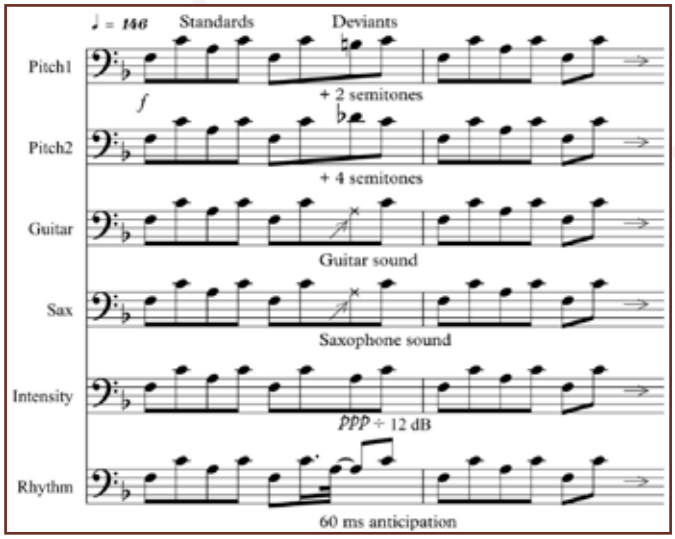

Figure 1
"Alberti bass" patterns alternating between standard sequence played with piano sounds, and a deviant. Deviants were introduced randomly and patterns were pseudorandomly transposed to the keys of G, A or C. Each tone was 200 ms in duration, with an ISI of 5 ms. Comparisons were made between the third note of the standard sequence and the third note of the deviant sequence.

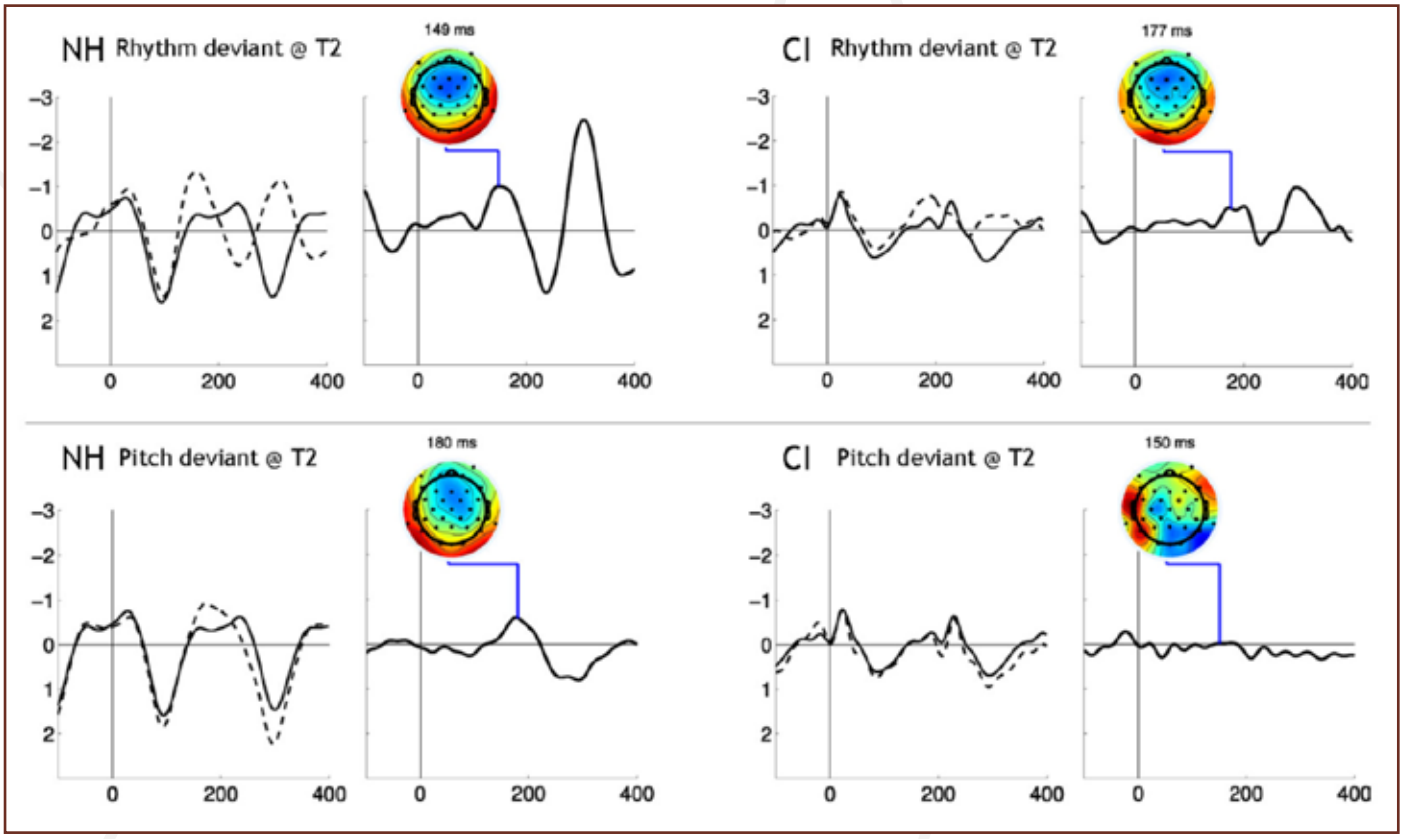

Figure 2
Grand average ERPs and EEG voltage isopotential maps for Rhythm and Pitch deviants in the two experimental groups at T2. For each deviant left panels show responses to the standard (solid line) and to the deviant (dotted line). Right panels show difference waves. Isopotential maps illustrate the differ-ence between the responses to deviants and standards averaged in an interval of ±3 ms around maximal peak amplitudes.

included musical instrument identification, melodic contour identification, rhythmic discrimination, pitch ranking and emotional prosody recognition. Mixed-effects ANOVAs identified main effects of group, time and deviant type, and possible interactions between these effects. The behavioral data were analyzed using the non-parametric Wilcoxon signed rank test.

Results

For the adolescent CI users we found significant and consistent MMNs for guitar, saxophone, intensity and rhythm deviants, but not for pitch. NH listeners produced significant MMNs for all six deviants, which were larger in amplitude than those of the CI users. With regard to MMN latencies we found significantly overall shorter MMN mean latencies in CI users than in the NH participants. We found no effect of training on either MMN amplitude or latency (Figure 2).

NEW FACE at CFIN

Stine Derdau Sørensen, research assistant, is MA in linguistics. Her main interest is how music training can affect language perception in cochlear implant users. She is currently affiliated with the Department of Otorhinolaryngology, Aarhus University Hospital, and works in close cooperation with the Music In the Brain group on developing a fun and motivating music training application for smartphones.

Behaviorally, the CI users improved their discrimination skills within all musical domains after training, resulting in a significant overall progress. In particular, discrimination of melodic contour and rhythm showed a significant progress. The NH group produced significantly higher average scores than the CI group at both sessions (Figure 3). We found no effect of the music training on recognition of emotional prosody.

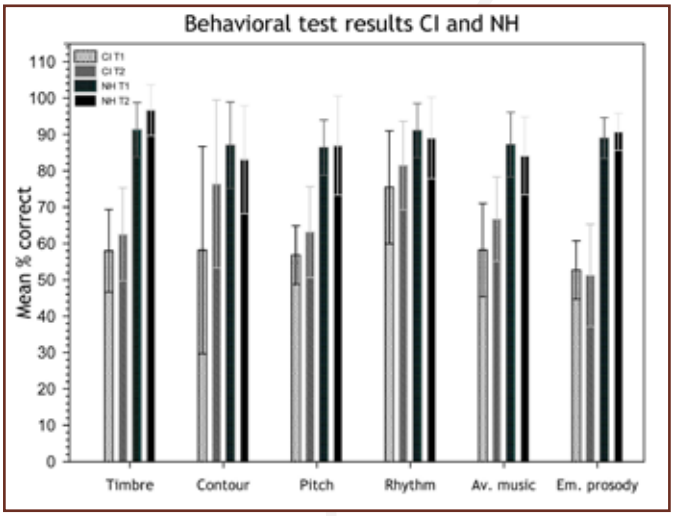

Figure 3
Behavioral scores for the two experimental groups at T1 and T2. Timbre: discrimination of 8 different musical instruments: Contour: identification of the direction of 5-note melodic patterns; Pitch: ranking of 2 pitches; Rhythm: discrimination of rhythm patterns; Av. music: overall music discrimination performance averaged across tests; Em. prosody: recognition of 3 different spoken emotions: happy, sad and angry.

Coda

The findings of this study are intriguing. They indicate residual neural discrimination prerequisites for musical feature change, in prelingually deaf adolescent CI users, who are late implanted and therefore have only experienced the degraded sound from the implant. Moreover, behavioral discrimination of rhythm and melodic contour may be significantly improved by music training, even from short term training, whereas detection of changes in pitch is poor and unaffected.

For most of the young CI users, this project was their first experience with structured and targeted music making and indeed challenging. Nevertheless, they generally responded with great enthusiasm to the different exercises and tasks. In particular, rapping and creation of rap lyrics proved appealing and relevant, and the participants exhibited a marked progress in their performance. Considering that rap is speech, articulated in rhythmic phrases, it seems as an obvious path to follow for young CI users, both as a measure of training and a possible form of artistic expression. Maybe the world will one day see its first profoundly deaf rapper? This would indeed mark the ultimate success of the cochlear implant.

Teenage CI users engaged in rapping
Photo: Bjørn Petersen

This article is based on two studies:

1. Petersen, B., Weed, E., Sandmann, P., Brattico, E., Hansen, M., Derdau, S., Vuust, P: Brain Responses to Musical Feature Changes in Adolescent Cochlear Implant Users; Frontiers in Human Neuroscience, doi: 10.3389/fnhum.2015.00007
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MUSIC IN THE BRAIN

Entropy

by Niels Christian Hansen

Entropy as a model of predictive uncertainty in music cognition, expertise, and learning

Predictive processing underlies key aspects of human cognition, expertise and learning (Bar, 2007; Bubic, von Cramon, & Schubotz, 2010). This includes language comprehension (DeLong, Urbach, & Kutas, 2005), decision making (Hsu, Bhatt, Adolphs, Tranel, & Camerer, 2005), motor behaviour (Wolpert & Flanagan, 2001), visual perception (Egner, Monti, & Summerfield, 2010), and the processing of musical stimuli (Vuust, Østergaard, Pallesen, Bailey, & Roepstorff, 2009). While musical expectations have been studied thoroughly in terms of retrospective behavioural and neural responses to surprising and unsurprising auditory events (Krumhansl, 1990; Pearce, Ruiz, Kapasi, Wiggins, & Bhattacharya, 2010; Tillmann, Bigand, Escoffier, & Lalitte, 2006), the prospective states of uncertainty and certainty preceding such events have thus far received limited attention. In recent years, members of the Music in the Brain Group and international collaborators have embarked on a research programme investigating this lacune using behavioural experiments and computational modelling.

Predictive uncertainty in melodic expectation

Research on statistical learning has shown that transitional probabilities in auditory sequences, e.g. consisting of linguistic syllables (Saffran, 2003) or musical pitches (Saffran, Johnson, Aslin, & Newport, 1999), are learned automatically throughout our lives. These internalised probabilities, in turn, give rise to the subjective percept of expectedness when listening to music (Hansen & Pearce, 2014; Pearce et al., 2010). Drawing on information theory (Shannon, 1948) and studies in other domains demonstrating that entropy offers a cognitively plausible framework for modelling aspects of human cognition (Hale, 2006; Hirsh, Mar, & Peterson, 2012; Swait & Adamowicz, 2001), we hypothesised that predictive uncertainty would depend, not on the probability of individual events, but rather on the entropy of probability distributions characterising multiple possible continuations of a given melody (see Box).

In a recent paper (Hansen & Pearce, 2014), we tested this hypothesis. Two subsets of melodic excerpts were selected from each of two musical corpora: simple English hymns and musically more complex songs by the composer Franz Schubert. Each subset was estimated to generate continuations with either high or low entropy within that particular style of music. Entropy estimates were obtained using the Information Dynamics of Music Model (IDyOM), which is a variable-order Markov model producing conditional probability distributions for each event in a melodic sequence (Pearce, 2005). IDyOM acquires knowledge from the local context as well as from a large predefined database of music through unsupervised statistical learning using multiple viewpoint representations. Thus, the model incorporates the

BOX: What is entropy?

Absolute entropy* (*H*)** quantifies the uncertainty of a probability distribution, ***P (Shannon, 1948). We use this measure to infer predictive uncertainty from the distribution of listeners' expectedness ratings for multiple continuations of a melody.

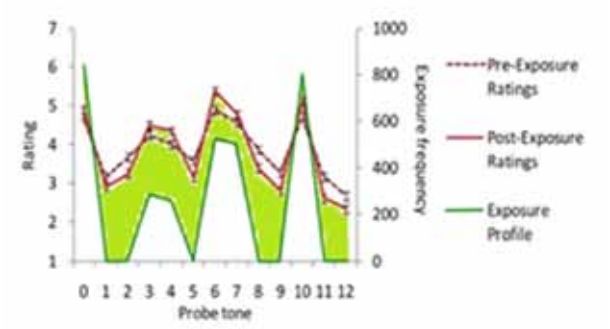
$$H(P) = -\sum_{i=1}^{n} p_i \log_2 p_i$$

Relative entropy **(symD$_{KL}$: symmetrised Kullback-Leibler Divergence)** quantifies the dissimilarity between two probability distributions, ***P*** and ***Q***.

$$D_{KL}(P \parallel Q) = \sum_{i=1}^{n} p_i \log_2 \left(\frac{p_i}{q_i}\right)$$

$$symD_{KL} = \frac{D_{KL}(P \parallel Q) + D_{KL}(Q \parallel P)}{2}$$

Entropy reduction: Musical learning gradually reduces symD$_{KL}$ between **subjective expectedness ratings** and **objective exposure frequencies**.



(Loui, 2012)

scientifically validated principles that musical expectations (a) rely on varying context lengths, (b) govern multiple musical parameters simultaneously, (c) are both schematic (i.e. long-term-memory-based) and dynamic (i.e. local), and (d) arise from a domain-general learning mechanism starting from scratch. Listeners' predictive uncertainty was assessed in terms of explicit ratings and inferred from the distributions of expectedness ratings collected with a version of the probe-tone paradigm optimised for studying this phenomenon. Our first experiment showed that both explicit and inferred operationalisations of predictive uncertainty varied as a function of the Shannon entropy of internalised probability distributions (Figure 1). Furthermore, the extent of this effect, increased with stylistic simplicity and degrees of musical expertise, such that training led to an increasingly accurate predictive model of the world. However, expertise was clearly most beneficial in contexts with objectively low uncertainty. Here, the novice's default high-uncertainty model failed most severely.

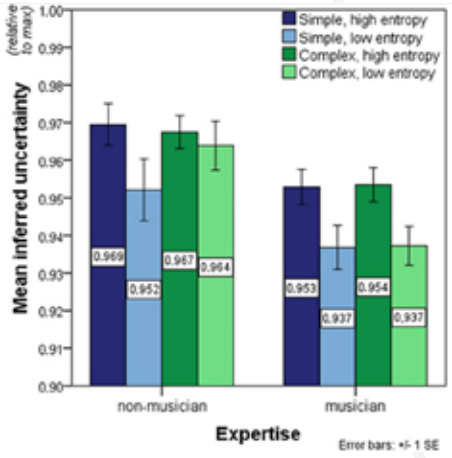


Figure 1
Low-entropy melodies generally generated listener expectations with lower degrees of inferred uncertainty. Overall, musicians were more certain than non-musicians with respect to what the next note would be. The former effect interacted with both expertise and complexity (Hansen & Pearce, 2014).

A role for style-specific expertise

Given the study design of our first experiment, we could not distinguish between general effects of musicianship, which could be related to motivational and attentional factors, and effects specific to a specialised genre of music. We do know, however, that statistical learning is enhanced by attention (Toro, Sinnett, & Soto-Faraco, 2005) and that musicians are sometimes motivated differently from non-musicians in musical listening task (McAuley, Henry, & Tuft, 2011). Thus, we designed a follow-up study where non-musicians as well as professional jazz and classical musicians listened to saxophone solos by the bebop musician Charlie Parker.

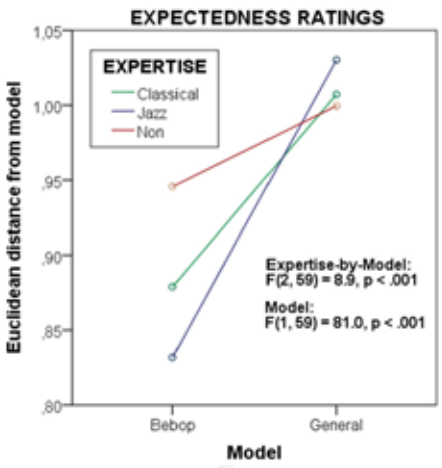


Figure 2
Euclidean distance between expectedness ratings and probability estimates of the two computational models trained to bebop and general tonal music when subjected to multidimensional scaling (distance metric: 1–r). Best correspondence with the bebop model is achieved by jazz and, secondarily, classical musicians.

Two implementations of IDyOM were used to select melodies that were high in entropy within the bebop genre, but low in entropy in the context of more classical tonal music versus melodies that were low in bebop entropy and high in general entropy.

In addition to replicating the findings from our previous study, the follow-up experiment showed that genre-specific jazz expertise predicted the fit to the estimates of the bebop model. Specifically, whereas non-musicians' expectedness ratings correlated weakly with both models, professional musicians significantly followed the bebop model with slightly higher fit in jazz musicians than in classical musicians (Figure 2).

Musical learning as entropy reduction

Now that we had demonstrated that years of musical training led to both optimisation of one's predictive model (Figure 3) and enhancement of the ability to select an optimal model for a given context (Figure 2), we became interested in

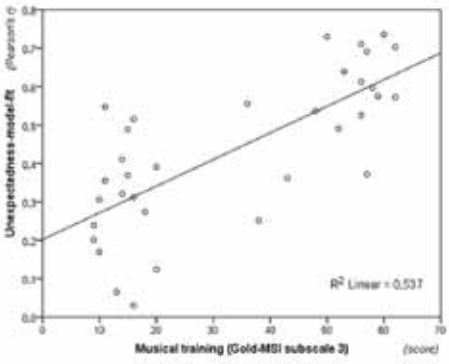


Figure 3
Formal musical training is associated with the extent to which participants' perceived expectedness corresponds to probability estimates of a computational model trained to general tonal music (Hansen & Pearce, 2014).

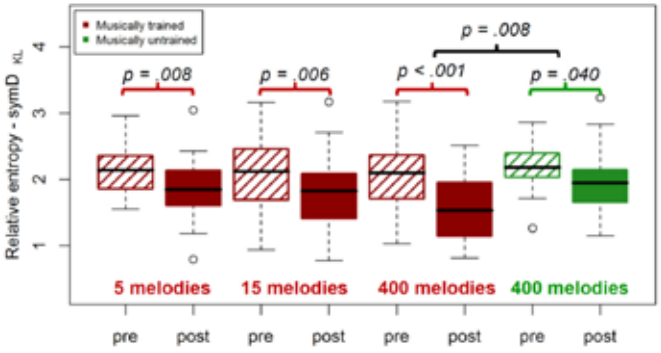


Figure 4
The information-theoretical dissimilarity between subjective expectedness ratings and objective exposure frequencies is reduced after 25-30 mins of exposure to a probabilistically structured, unfamiliar musical system. Generalisability and, to some extent, musical training facilitates this process of entropy reduction.

modelling musical learning on a shorter timescale. Thus, we re-analysed expectedness ratings collected by our colleagues before and after 25-30 mins of passive exposure to melodies composed from finite-state grammars using the unfamiliar Bohlen-Pierce scale system (Loui, 2012; Loui, Wessel, & Hudson Kam, 2010). This analysis demonstrated that musical learning can be understood as a process of reducing the dissimilarity, quantified in terms of relative entropy, between objective probability distributions in the music and subjective expectedness profiles characteristic of a given listener's expertise. Moreover, the extent of relative entropy reduction during exposure increases with generalizability (i.e. with the number of exposure melodies), and this effect tends to be somewhat greater in musicians than in non-musicians (Figure 4).

We have presented a coherent framework for measuring, quantifying, modelling, and theorising about predictive uncertainty in music cognition, expertise, and learning. This work draws on information theory and research on statistical learning and emancipates itself from the traditional musician vs. non-musician dichotomy dominant in most previous music cognition research (Bigand, 2003). Moreover, our approach is consistent with wider theoretical frameworks in cognitive neuroscience–such as predictive coding theory (Huang & Rao, 2011)–which has considerable potential beyond the musical domain.

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CNRU

by Morten Overgaard

Why are we conscious? Why are activations of neural tissue in the brain associated with subjective experience? Such questions about the nature of consciousness are among the oldest ones raised in human intellectual history, yet currently a central topic in many academic disciplines, and, according to Science, it is among the 25 most important areas of investigation for the next 25 years. The various disciplines involved in consciousness research (primarily psychology, philosophy and neuroscience) have, however, not yet delivered a common framework or approach. Instead, the gap between research that attempts to understand consciousness, and research that gathers empirical evidence, appears as wide as ever.

Cognitive Neuroscience Research Unit, or CNRU, has existed since 2007 and has as its primary goal to bridge certain gaps in current scientific understandings of the mind, such as 1) why are we conscious? 2) how can we investigate something that is only subjective? 3) what is free will, and do we have it? 4) how does basic research translate into clinical domains? 5) how can there be a dynamic relation between structure and function (e.g. in neurorehabilitation) alongside functional localization in the brain?

Methodological issues

One central topic in international consciousness research has been the attempt to isolate neural correlates of conscious experience. To achieve this, however, there are numerous methodological problems concerning how we "objectively" can measure something that is essentially subjectively defined. Over several years, CNRU researchers have developed and refined subjective measures, which we believe to be highly sensitive to even small variations of conscious vision, and which apply to solve various controversies in current consciousness research.

It is typically argued that subjective, verbal descriptions lack the necessary degree of precision and reliability required for scientific measures. If a participant reports a particular experience there is no external way of validating whether that report is given because the participant had that exact experience, or rather because, for instance, the participant was biased to give this report. Such arguments have paved the way for a broad conviction in cognitive science that one should avoid subjective reports as much as possible, and rely on objective measures of correctness or reaction time instead. In consciousness research, however, there are other problems with objective measures. Essentially, if one wishes to study subjective experience, it is not at all clear which objective measure to use. How can we know, for instance, that any measure, such as correct identification or any other measure of performance, is actually about the subjective experience of interest – and more so than the subjective report? It seems the only knowledge we could have comes from a prior correlation with introspective observation and report, and, accordingly, cannot have any higher precision than the introspective observation/report.

CNRU researchers have chosen a different path than most other consciousness researchers as they have attempted to invent and demonstrate ways to systematically use verbal reports. Using such methods, we have shown that other well known methods to investigate consciousness (e.g. the so-called inclusion and exclusion task) do not take vague conscious experiences into account.

Although consciousness research is still far from able to say anything conclusive about neural correlates of consciousness - that is, what they may be and how they may be interpreted - we have taken steps towards such insights. For example, we have been able to tease apart neural correlates of conscious experience, perceptual reversal, and stabilization in a binocular rivalry task. Furthermore, we have found that neural activity related to such experiences can be decoded within and between individuals using MEG, and that this activity is stable for at least 2.5 years.

Voluntary action and control

It is generally believed that being conscious of something makes a difference for the subject and is fundamentally involved in the ability to control one´s own movements. Yet, predominant models of cognitive neuroscience have not been able to conceptually or empirically identify a particular cognitive function (or set of functions) for which consciousness is necessary. In fact, many of these models would seem to imply that the cognitive systems (and the brain) could work without consciousness. That is, according to some influential models of cognitive neuroscience, consciousness is but an epiphenomenon (an accidental by-product of the biological machinery). Such models make it hard to understand how consciousness could at all be important to a subject's control of her own thinking and action.

In one experiment, we showed that people have a better memory for their own movements than for movements induced using transcranial magnetic stimulation - a phenomenon, we named “intentional capture”. We believe that the finding shows that our knowledge of our own movements amounts to more than just a post-hoc confabulation. Or, in other words, that volition is something real.

In another experiment, we have found evidence that “distal intentions” (decisions for future movements) are differently represented in the brain than “proximal intentions” (for immediate actions). Current research on volition makes use of paradigms that operationalize proximal intentions, even though our every-day feelings of having volitions very much relate to distal intentions. We believe that our finding necessitates a new path in volition research: A need to study intentions about future actions.

Clinical applications

CNRU considers it a high priority to bridge basic research in cognitive neuroscience with clinical applications. In 2014 we have investigated neural responses to sounds with varying complexity in patients in coma, vegetative state, and minimally conscious state. We have developed methods to assess and rehabilitate patients with memory and attention-related problems following acquired brain injury or Alzheimers disease. Furthermore, we have investigated metacognition in schizophrenia in order to derive new ways to understand the cognitive background of hallucinations. Examples of such more clinically oriented projects are described elsewhere in this report.

Future perspectives

The major source of funding for CNRU is an ERC starting grant that Morten Overgaard received in 2010. The grant will end in June 2015 and it is currently unknown how CNRU will be funded after this date. There are 17 researchers employed in CNRU, not even counting student helpers.Therefore a reasonably large funding source must be identified, or else restructuring is expected in 2015.

CNRU
Cognitive Neuroscience Research Unit

FACTS

Cognitive Neuroscience Research unit (CNRU)

http://www.cnru.dk/

Group members:

- Morten Overgaard
- Bochra Zareini
- Christian Gaden Jensen
- Daniel Gramm Kristensen
- Daniel Siboska
- Jonas Lindeløv
- Kristian Sandberg
- Lau Møller Andersen
- Lars Evald
- Mark Schram Christensen
- Martin Dietz
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- Mads Jensen
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- Geraint Rees, University College London
- Berit Brogaard, University of Missouri
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- Jesper Mogensen, University of Copenhagen
- Søren Kyllingsbæk, University of Copenhagen
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Collaborators (clinical research)

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- Hammel Neurorehabilitation and Research Center
- Translational Psychiatry Unit, Aarhus University

Selected research projects:

2010-2015: European Research Council Starting Grant (Morten Overgaard): MindRehab - Consciousness in Basic Science and Neurorehabilitation

2012-2015: Danish Council for Independent Research/Humanities: Phenomenal Consciousness and Motor Control

CNRU

Cognitive brain injury rehabilitation

by Jonas Kristoffer Lindeløv

The basic philosophy in CNRU is that research should be philosophically sound, of theoretical interest, and with clinical potential. In our research on cognitive rehabilitation for patients with acquired brain injury, this approach has been particularly fruitful.

We have conducted two randomized controlled trials on brain injured patients. One study on computer-based cognitive rehabilitation was motivated by the fact that research on healthy subjects and brain injured patients so far has proceeded in parrallel with little cross talk. To translate between these populations, we conducted a 2x2 design with 39 in-hospital brain-injured patients at Hammel Neurorehabilitation Center and 39 healthy participants. Each group trained either the N-back task og a closely matched control task for 20 days. Cognitive outcome was measured using a mixture of classical clinical tests and tests from cognitive science. Even though both groups improved on the training tasks (see figure 1), neither groups improved on the outcome measures for neither training condition, indicating that the improvement on the training tasks did not transfer to untrained material. Interestingly, however, the healthy subjects improved much more on the training task than the patients (2.5-5.5 standardized mean differences), indicating that organic brain injury may cause an impaired ability to acquire new specific cognitive strategies. To our knowledge, this is the first longitudinal study to support this finding.

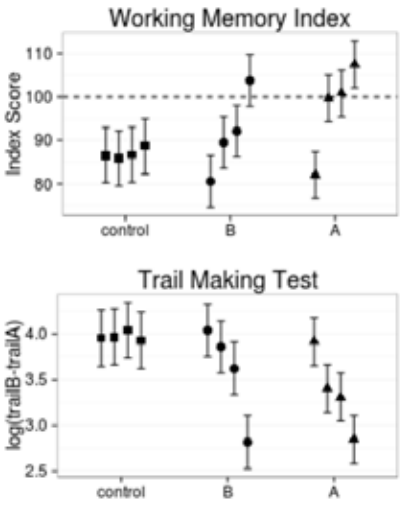

Figure 1
Each panel is the results from a given outcome measure. The control group is stable throughout the experiment. Group A improves from targeted suggestion during phase 1 while group B improves less. Both groups maintain their performance level during the break and group B experiences superior improvement when crossed over to targeted suggestion. The dashed horizontal line is the healthy population average.

To follow up on this finding, we performed a meta-analysis in which we applied the methodological rigorousness from basic sciences to clinical randomized controlled trials on computer-based training and brain injured patients. That is, subjecting the postulated causal relationship between the dependent and independent variable(s) to scrutiny. A total of 30 papers including 1082 patients were included in a meta-analysis. When methodological confounders were included in the statistical model, the true underlying effect size was vanishingly small (0.05 standardized mean differences, 95% credible interval between -0.1 and + 0.2). This suggests that the published studies, reviews, and meta-analyses may have reported effects caused by the experimental design, such as inappropriate control groups or confounded outcome measures, rather than a proper underlying cognitive improvement.

In another study on 68 patients with acquired brain injury in the chronic phase, we used hypnotic suggestion to improve working memory. This study was concieved entierly from the basic sciences literature on expectancy-driven top-down processes. We compared two hypnotic suggestion conditions to a passive control condition, isolating the effect of “working memory directed suggestion”, undirected suggestion, and retest effects respectively. Over the course of just four sessions, patients improved to the population mean on all outcome measures, indicating a normalization of their cognitive function (see figure 2). This effect was sustained after a 7 week break at which they had improved more

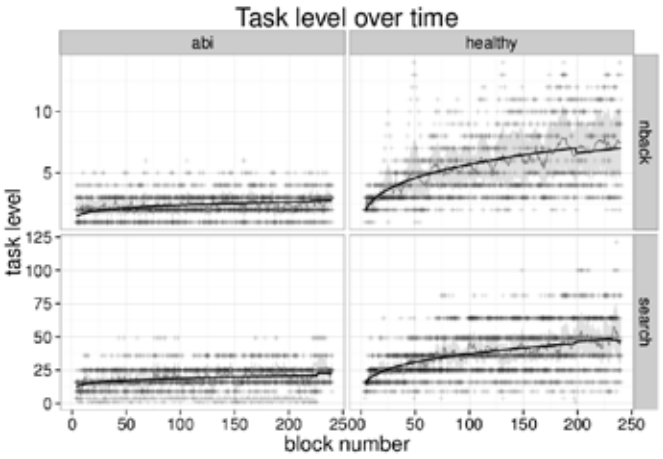

Figure 2
Performance on the training task as a function of time. The solid line is a power function fit to the data while the small dots are individual datapoints. For both tasks, the healthy participants improved much more than the brain injured patients.

than 1.4 standardized mean differences. This experimental interventions is directly translatable to clinical practice. It also feeds back to theory by demonstrating a remarkable residual capacity for information processing in the lesioned human brain.

Bringing intervention research to bear on questions in basic cognitive neuroscience and vice versa is a strategy that we will pursue in future research.

Morten Overgaard receives the Young Scientist Award 2014

Whereas an increasing number of researchers have been working to discover which neural activations that may correlate with conscious experience over the last decades, there are still no clear answers to the underlying question of why consciousness exists in the first place.

Morten Overgaard, Professor and Head of CNRU, has worked on conceptual and methodological aspects of consciousness research since he was a BA student. During the last few years, however, he has set out to develop theoretical models of how mind-brain relations may be understood.

Morten Overgaard has described the outlines for such a theory in a series of recent publications. This work motivated that he was awarded the Young Scientist Award by the World Economic Forum which is given to the 40 most outstanding scientists in the world under the age of 40. Morten received the award at the Annual Meeting of the New Champions organized by The World Economic Forum in Tianjin, China, in September 2014. In a session with the three other award recipients who also held an ERC grant, he described how consciousness seemingly cannot be explained from neuroscientific facts, and that the very attempt to explain consciousness this way may be misguided. He presented an alternative approach according to which consciousness is inherently related to information becoming available for certain actions. The approach is markedly different from many current approaches to understand mind-brain relations as it does not try to reduce the mind to neural events, or even to a "product" of neural events. The idea may lead to the development of a completely novel way to interpret mind-brain relations and, more generally, functional properties of the brain.

About the World Economic Forum Young Scientists Community

Professor Morten Overgaard during the Annual Meeting of the New Champions in Tianjin, China. September 2014

Established in 2008, the Young Scientist community represents the future of science leadership, bringing together the most forward-thinking and advanced scientific minds in the world. The scientists are selected from all regions and a wide range of disciplines. Nominees are pioneers with a proven track record of advancing the frontiers of science, engineering or technology in areas of high societal impact, and are under the age of 40. During their careers, they have exhibited exceptional creativity, thought leadership and high growth potential. Emphasis is placed on individuals with a demonstrated commitment to public service, a deep interest in the global perspective and a strong alignment with the Forum's mission of improving the state of the world. The individuals have actively engaged in playing a transformational role in integrating scientific knowledge into society for the public good. Nominees possess excellent communication skills, a collaborative attitude and an ability to translate their research for a multistakeholder audience of business, political and civil society leaders. They also demonstrate high personal standards and exceptional research ethics.

CNRU

Effective connectivity

by Martin Dietz

Electroencephalography (EEG) and magnetoencephalography (MEG) are non-invasive measures of neuronal current flow. This allows us to characterize post-synaptic activity at the scale of the cortical macrocolumn over the entire neocortex with high temporal resolution (Buzsáki et al., 2012). Although all transmembrane currents contribute to the ensuing voltage differences that create dipoles or n-poles in the extracellular medium, the main contribution to the electromagnetic signal is assumed to be the large populations of pyramidal cells in superficial layers 2/3 and deep layer 5 (Murakami and Okada, 2006). This is because the vertical alignment of their apical dendrites perpendicular to the cortical surface affords a high degree of synchronization. Superficial pyramidal cells are also the sources of feedforward connections that drive activity in a hierarchically higher area, whereas deep pyramidal cells originate feedback connections that are known to modulate the receptive fields of a lower area (Shipp, 2007). Although stellate cells and the synchronous behaviour of inhibitory interneurons generate dipolar patterns of sizeable magnitude, their net contribution to the electromagnetic signal is thought to be less than that of pyramidal cells because of their highly variable dendritic morphology. Nonetheless, their influence on the spectral dynamics of observed MEG and EEG responses is unquestionable, as their local (vertical and horizontal) connections within the cortical column make up the vast majority of connections in the cerebral cortex, with only about 5% giving rise to feedforward and feedback connections between distant areas.

Since the advent of MEG in 2011, human electrophysiological research at CFIN has been concerned with two main issues: anatomical localisation of the currents that generate observed responses and identification of effective connectivity within and between areas of a distributed network. Effective connectivity is defined as the influence one neuronal population exerts on another population at the synaptic level in terms of its excitatory or inhibitory control. This is in contrast to metrics of functional connectivity that operate at the level of data features, such as coherence or Granger causality.

In one study, we used Bayesian source reconstruction to identify the anatomical locations of currents that generated the observed Mismatch Negativity. This analysis revealed activity in bilateral Heschl's gyrus, superior temporal gyrus and inferior frontal gyrus. These regions were then used in dynamic causal modelling (DCM) to identify the relative influence of feedforward, feedback and intrinsic connections. Feedforward connectivity increased selectively throughout this cortical network when there was an unexpected change in the sensory stream. In predictive coding, feedback connections provide lower areas with predictions in the form of prior expectations about states of the world, whereas feedforward connections

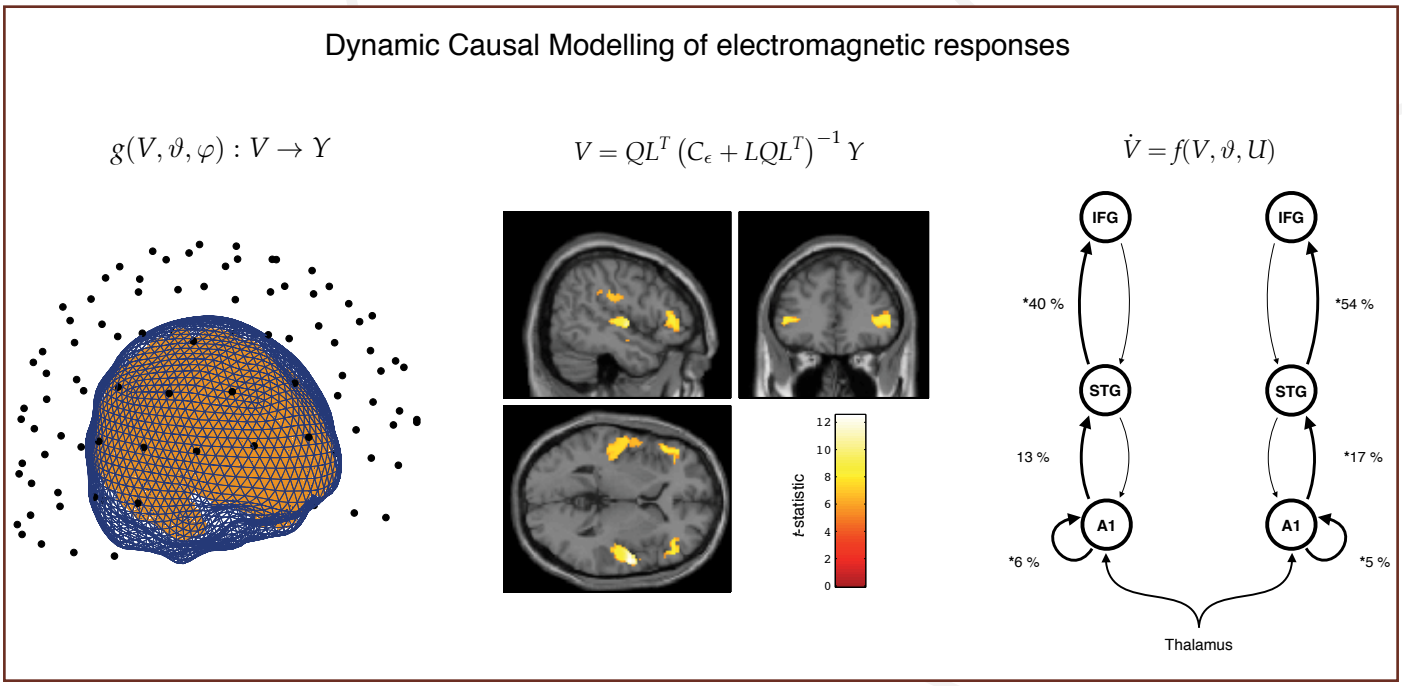

Figure 1
Dynamic causal modelling of evoked responses showing an increase in the strength of feedforward connectivity during the Mismatch Negativity.

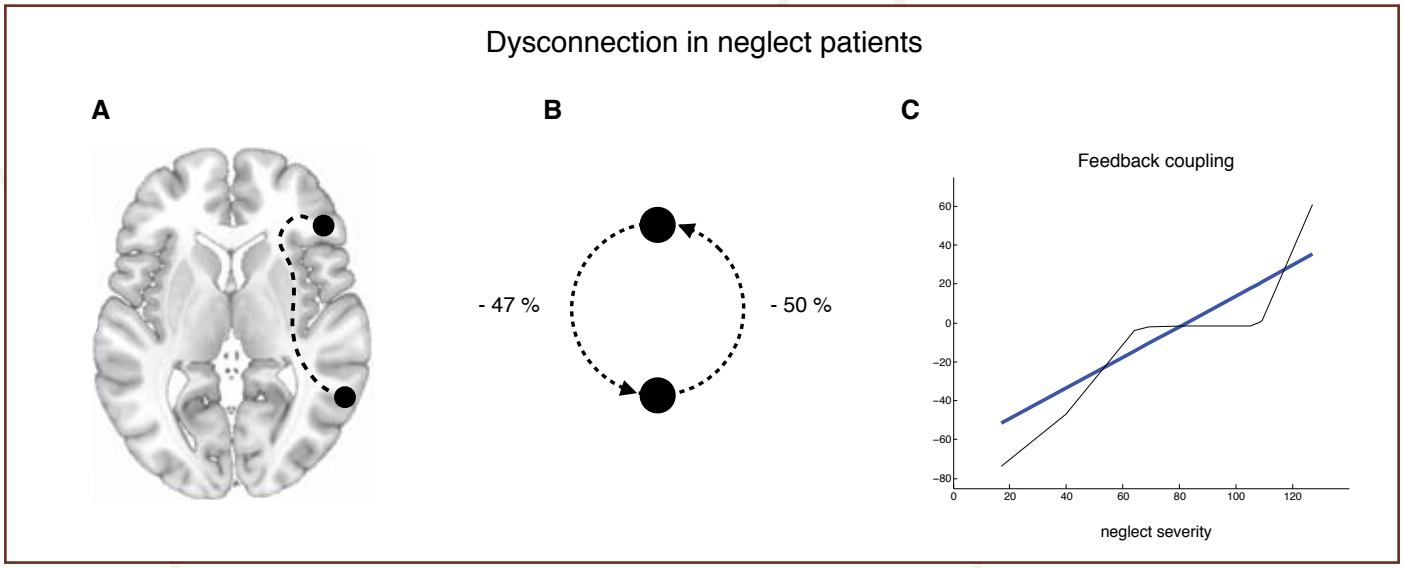

Figure 2
(A) Anatomical architecture showing the connections between the inferior frontal gyrus and the inferior parietal cortex that were significantly weaker in neglect patients compared to healthy controls (B) Dynamic causal model detailing the difference in the strength of feedforward and feedback connectivity between neglect patients and healthy controls (C) Linear correlation between neglect severity and the weakness of feedback connectivity from the inferior parietal cortex to the inferior frontal gyrus.

carry prediction errors that update posterior expectations in higher areas whenever there is a change in sensory input that cannot be explained by prior predictions. Our finding provides evidence that prediction errors are passed from lower to higher areas of the cortical hierarchy via feedforward mechanisms. This has implications for the translational research in Cognitive Neuroscience Research Unit because it allows us to make more detailed inferences about abnormal electrophysiological responses in patients with neurological and neuropsychiatric disorders.

In another study, we therefore investigated the effect of anatomical lesions on the physiology of cortical connections in patients with neglect syndrome. Consistent with our previous findings in the normal brain (Dietz et al., 2014), healthy controls showed a right-hemisphere dominance in feedforward and feedback connectivity with respect to the side of the stimulus. Compared to these age-matched controls, neglect patients showed significantly weaker feedforward and feedback connectivity between frontal and parietal cortex in the right hemisphere when stimuli appeared on the neglected left side. Importantly, the weakness of feedback connectivity correlated with the severity of neglect. This finding support the notion that the neglect syndrome is a consequence of cortical dysconnection between frontal and parietal areas that are thought mediate attentional reorienting to new stimuli in the sensorium.

In a future project, we will use these non-invasive electrophysiological techniques in patients with schizophrenia to elucidate the relative roles of feedforward, feedback and intrinsic connections in the genesis of hallucinations and delusions. Dynamic causal modelling of the brain's spectral responses has the potential to provide insights into abnormalities of the excitation-inhibition balance of glutamatergic and GABAergic interneurons that control pyramidal cell activity and are currently a focus of interest in schizophrenia research.

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The Research Clinic on Gambling Disorders (RCGD)

by Jakob Linnet

The Research Clinic on Gambling Disorders at Aarhus University Hospital is a part of CFIN / MIND*Lab*. RCGD integrates research, treatment and prevention of pathological gambling in an interdisciplinary setting in close collaboration with CFIN / MIND*Lab*. Results from the Clinic are summarized below. The results underscore the importance of evidence based treatment of gambling disorder.

A recent study from the Research Clinic on Gambling Disorders[1] investigated 48 Gambling Disorder sufferers with a 56% completion rate (21 non-completers and 27 completers). The study used age, gender, comorbidity, craving, gambling control and number of days waiting for treatment as predictors of treatment completion.

The results showed that waiting time was a significant predictor of completion rates, $z = -2.44$ ($p < 0.02$) and was the strongest predictor of the variables investigated.

The prediction model had an optimal classification accuracy of 0.729 at the probability threshold of 0.57 (Figure 1A, solid line). The model's optimal probability threshold for classification of treatment completion was equivalent to a waiting period of 22 days (Figure 1B).

Patients waiting fewer than 22 days to speak with a therapist had a 73% chance of full or partial treatment completion, while patients waiting more than 22 days to speak with a therapist had a 27% chance of completing treatment (Figure 1B, dashed line); patients waiting 50 days or more had a 0% chance of treatment completion (Figure 1B, dotted line). Furthermore, Figure 1B shows that patients completing treatment waited significantly fewer days for treatment, $t(27.05) = -2.66$ ($p \leq 0.01$).

Non-completion was not a result of patients seeking treatment elsewhere while waiting for treatment, because the patients had at least one session with a therapist (patients in treatment rarely seek help elsewhere). However, a limitation in the data is that they did not include patients who were never in contact with a therapist (patients needed at least one session to be included).

Based on these findings the study recommends a rapid intake and assessment of patients. As a result of the study The Research Clinic on Gambling Disorders has taken measures to ensure early intervention.

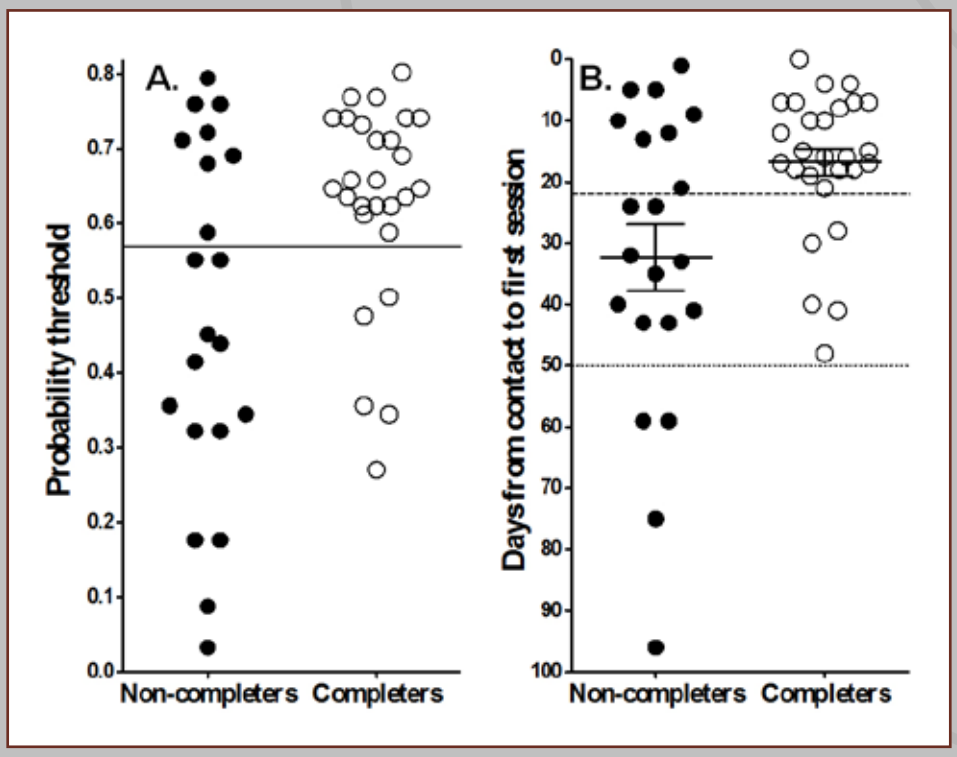

Figure 1
Probability threshold and days waiting for treatment
A. Classification accuracy of predicted treatment completion. The maximum classification accuracy of probability threshold between completers (white circles) and non-completers (black circles) is indicated by the horizontal solid line. The model predicts that patients above the line complete treatment, while patients below the line do not complete treatment. The model has an overall classification accuracy of 72.9%. The y-axis shows the models probability threshold.
B. Days waiting for treatment. Patients who are predicted to complete treatment wait fewer than 22 days for treatment (above dashed line). The y-axis shows the number of days waiting for treatment. Mean and Standard Error Mean (SEM) for the waiting time are shown for completers and non-completers.

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FACTS

The Research Clinic on Gambling Disorders (RCGD) is a self-financed clinic under Aarhus University Hospital, and a collaborating partner of CFIN. The RCGD is headed by Jakob Linnet, associate professor, ph.d., cand. psych. aut., who has more than 10 years experience in research and treatment of pathological gambling.
The RCGD is located at Trøjborgvej 72, building 30.

People:

Head of RCGD: Jakob Linnet
Psychologist (treatment): Stine Moldt Jensen
Psychologist (treatment): Thomas Marcussen
Psychologist (treatment): Elisabeth Biering-Madsen
Postdoc: Anders Sune Pedersen
Secretary: Gitte Bodil Jensen

www.forskningsklinikkenforludomani.au.dk

Collaborations 2014:

- Neuroinformatics, Center of Functionally Integrative Neuroscience, Aarhus University
- The Division on Addiction, Cambridge Health Alliance, a teaching affiliate of Harvard Medical School.
- McGill University International Centre for Youth Gambling Problemer and High-Risk Behaviors
- Robert Ladouceur, Laval University, Canada.
- Danish Games A/S and Mindwork Psychological Center.

Ongoing Grants:

- Ministry of Health, the Research Clinic on Gambling Disorders (2014)
- Ministry of Health Danish Gambling Disorder Treatment Network (2014)
- Danish Research Councils, pathological gambling in online poker (2012-2015)

Publications:

1. Linnet, J. (2014). Neurobiological Underpinnings of Reward Anticipation and Outcome Evaluation in Gambling Disorder. Front Behav Neurosci, 8, 100.
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Highlights in 2014

CFIN / MIND*Lab* Retreat 2014

The 2014 CFIN / MIND*Lab* Retreat at Sandbjerg Manor was the last retreat within the MIND*Lab* funding period. So naturally the program focused on "MIND*Lab* highs - and visions for the road ahead", a title both MIND*Lab* director Leif Østergaard and co-director Andreas Roepstorff addressed in their talks. The retreat had two keynote lectures by Robert Turner from the Max Planck Institute in Leipzig, and David J. Brooks from the PET-Center in Aarhus.

One afternoon was allocated to a so-called 'poster-dating-workshop' where all retreat participants had prepared posters to present their current work and future plans for new projects and collaborations after the funding period.

The MIND*Lab* stream leaders presented highlights from across the MIND*Lab* project and looked at opportunities for future collaborations. Representatives from the MIND*Lab* infrastructure presented new methods and developments.

As always the retreat was also time to meet within CFIN groups and MIND*Lab* streams to plan ahead.

DHL Relay Race

Getting ready for DHL Relay Race
CFIN / MIND*Lab* participants in the Aarhus University tent where runners meet, prepare for the race and get food after the race. All teams receive a box of food and snacks, and there is lots of 'hygge' and social interaction during the DHL event.
Photo: Henriette Blæsild Vuust

As in previous years CFIN / MIND*Lab* participated in the DHL relay run & walk on a (slightly grey and partly wet) summer evening in late August 2014.

This event has become a cherished tradition, and in 2014 we participated with several running teams and one walking team.

The DHL Relay Race is a big event in Aarhus with lots of professional, semi-professional and amateur runners from companies and institutions. Aarhus University had 1.915 participants in the 2014 event - and CFIN / MIND*Lab* contributed to this number with around 30 people.

CFIN / MIND*Lab* Retreat 2014 at Sandbjerg Manor
Photo: Torben E. Lund








Site visit by Brain Prize Winner Professor Trevor Robbins in DNC

On 4 November 2014 the Danish Neuroscience Center hosted a visit from the Brain Prize Winner Professor Trevor Robbins, Head of the Department of Psychology, University of Cambridge. Professor Robbins gave a key note talk on his prize winning research, and a number of CFIN / MIND*Lab* researchers participated and gave short talks about their projects:

- PhD student **Freja Bertelsen**:
  "What can we learn from an Autistic rat?"
- Postdoc **Maria Witek**:
  "I feel good! The relationship between body-movement, pleasure and groove in music"
- Postdoc **Kristian Sandberg**:
  "Decoding conscious vision"
- Postdoc **Alina Leminen**:
  "Neurodynamics of language: From phonemes to grammar"
- Assistant Professor **Annie Landau**:
  "Preclinical animal model and tracer development"
- PhD student **Arndis Simonsen**:
  "Social cognition in Schizophrenia"

The Henry Prize

The communication of knowledge and ideas is key to CFIN / MIND*Lab's* mission: 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.

The Henry Prize is 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 2014 The Outreach Henry Prize was awarded to:
Peter Vuust and Lau Møller Andersen.

CFIN / MIND*Lab* staff

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Co-director: Professor Andreas Roepstorff, Interacting Minds Center (IMC), AU
Associate Professor Kim Mouridsen, CFIN
Professor Armin W. Geertz, Department of Culture and Society - Study of Religion, AU
Professor Dorthe Berntsen, Department of Psychology and Behavioural Sciences - Con Amore, AU
Professor Sten Vikner, Section for English, Department of Aesthetics & Communication, AU
Professor Troels Staehelin Jensen, Danish Pain Research Center, Aarhus University Hospital
Administrative Leader: Anne-Mette Pedersen, CFIN

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Susanne Smidt Christensen, Laboratory Technician

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Mai Drustrup, Secretary
Simon Jeppe Bjerg MIND*Lab* Scientific Coordinator

2014 Publications

Peer reviewed articles:

Andersen LM, Basile BM, Hampton RR. Dissociation of visual localization and visual detection in rhesus monkeys (Macaca mulatta). Animal Cognition, 2014, 17, 3: 681-687

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