Center of Functionally Integrative Neuroscience
& MIND*Lab*

ANNUAL REPORT 2013

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BRIAN'S TROMBONE (Brian's basun)
During construction and installation of equipment in the new Preclinical Imaging Facility (PIFa) in the basements under Aarhus University Hospital Building 10, a quench-pipe was installed. Brian Hansen has been a driving force in the planning of the new lab including calculations of the quench-pipe dimensions. It was only natural that this new addition to the AUH hospital building - at a place most CFIN / MI*NDLab* staff pass everyday on their way to work - was named after him.
Photo: Mikkel Blæsild Vuust

Introduction - 2013 in words

by Leif Østergaard

In 2013, Aarhus University and Aarhus University Hospital were fortunate to attract prominent international neuroscientists with impressive track-records within neuroimaging based research and translational neuroscience. David Brooks, who is among World's most highly-cited neuroscientists, joined the PET-Center from Imperial College London to lead research programs within neurotransmission and advanced neuroimaging studies of Alzheimer's Disease and Parkinson's Disease. He is joined by Nicola Pavese, also from Imperial College London, who will lead projects within the early characterization of Parkinson's Disease. Yury Shtyrov joined CFIN / MIND*Lab* in 2013 from Cambridge University to take up the position as head of the national MEG facility at Aarhus University Hospital. Yury Shtyrov is a leading international expert on the processing of language in the brain. He will extend his work in several areas, including the study of language processing in patients with neurological and psychiatric disorders. David, Nicola, and Yury bring unique knowledge and expertise that will strengthen several related research areas at Aarhus University and CFIN / MIND*Lab*, and – perhaps as importantly – they share their time and ideas generously with their new colleagues. They are now parts of several collaborations with researchers at CFIN / MIND*Lab* and throughout Aarhus University, and have started attracting competitive national grants to build strong research programs. In this report, we present these new distinguished members of the growing neuroscience community in the Danish Neuroscience Center building.

In the introduction to last year's CFIN / MIND*Lab* Annual Report, I wrote about negotiations within the Aarhus University Leadership to secure long-term funding for the experimental and administrative infrastructure that has proven essential to our development as a leading interdisciplinary research center within neuroscience and cognitive research over the past decade. The Danish National Research Foundation's initial investment in this ambition, and the running costs of our growing experimental infrastructure, were both secured until mid-2014 when Aarhus University attracted one of four national UNIK grants in 2008. Importantly, the 120 M DKK MIND*Lab* UNIK grant was intended for Aarhus University to strengthen and expand the fertile collaborations that had then grown among CFIN researchers and colleagues from across AU – with the obligation to embed MIND*Lab* into AUs activities and ordinary budget as of August 2014. The task of determining how this obligation will be fulfilled, however, has not yet been completed, and when writing these lines early August 2014, the future funding of several key CFIN/ MIND*Lab* researchers, and the majority of our academic, technical staff, remains uncertain. I am grateful for the support we have received from the Institute of Clinical Medicine this spring to provide long-term security for our administrative staff, and for alleviating the immediate personal consequences for those employees who stood to lose their income this summer. I regret the insecurity felt by our staff over the past year – and hope their unique skills, hard work, and loyal patience will be rewarded. Access to a unique range of neuroimaging methods at CFIN / MIND*Lab*, and the expertise of leading experts to guide their use to study the inner workings of the healthy and diseased brain, remains crucial to our mission to foster collaborations across disciplines at Aarhus University and among clinicians and scientist at Aarhus University Hospital.

The impact of CFIN / MIND*Lab* research continues to grow, both in terms of high-impact publications, and in terms of the interest it attracts from scientific peers and industry. In 2013, the Neuroinformatics Group took part in the development of innovative method to predict treatment responses in brain tumor patients – one of which were published in the prestigious Nature Medicine journal. The translational potential of the group's work was further underscored when Seed Capital invested in the formation of a spin-out company that will allow the group's segmentation methods to be developed into a software solution to improve the diagnostic evaluation of acute stroke patients. The Neurophysics Group developed innovative methods to study cortical microstructure in humans – and hence the cellular underpinnings of brain plasticity during brain development, learning, and disease. They now work with Siemens to make their methods available to scientists and clinicians world-wide. Our capillary dysfunction hypothesis was developed further, with CFIN / MIND*Lab* scientists and clinicians from Aarhus University hospital co-authoring 4 publications on this disease mechanism. This annual report presents methods to assess capillary dysfunction, and findings that support the concept in human disease.

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.

NEUROPHYSICS

by Sune Nørhøj Jespersen & Brian Hansen

The main advantages of magnetic resonance imaging (MRI), as compared to other imaging techniques, is its noninvasiveness and its versatility. However, being based on the magnetic properties of tissue, MRI's 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 of tissue. This involves a combination of mathematical modeling and subsequent validation using e.g. disease models and comparisons to traditional histology and stereology. Our longer-term goal is to translate these methods into clinically useful tools, which entails designing robust and rapid acquisition and estimation strategies.

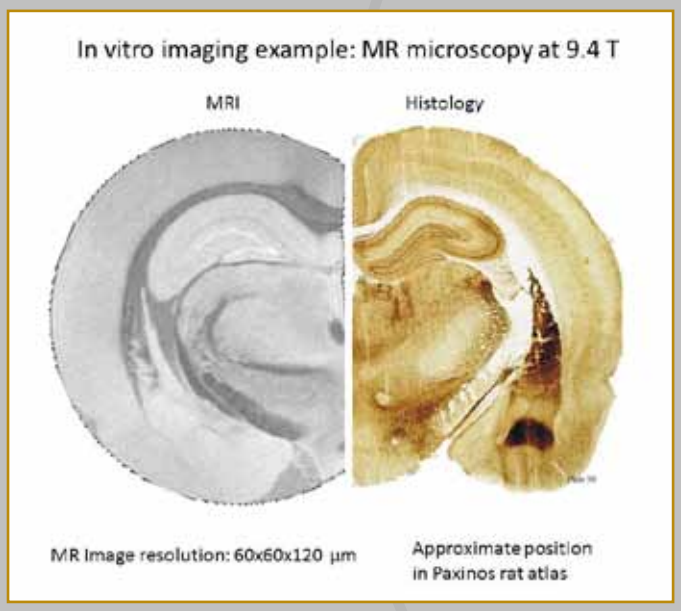

Figure 1
High resolution scan of fixed rat brain (left) with comparison to traditional histology at approximately the same position in the brain.

In 2013, progress was made on both fronts. In Hansen et al. [1], we presented a method to acquire mean kurtosis metrics in less than a minute with a few seconds of subsequent postprocessing. This is to be compared to existing state-of-the-art methods, which require on the order of 10 minutes scan time followed by hours of CPU intensive postprocessing. The method is already now being adopted as part of clinical research protocols at CFIN / MI*NDLab* and elsewhere, as a biomarker in e.g. cancer and mild traumatic brain injury. Siemens is currently working with us and our collaborator in Hamburg (Dr. Jürgen Finsterbusch) to provide a WIP (work in progress) package for the Siemens platform. This is to gauge interest of the research community in our invention, and will help Siemens decide whether to adopt it into their products. This work was also presented at ISMRM in Salt Lake City, where several group members participated. Recently, we submitted an abstract on an amended version of our protocol, which allows us to optimize acquisition parameters of the method. Further work in progress includes investigating the possibility of extracting other kurtosis tensor metrics from the fast acquisition protocol, such as kurtosis anisotropy and radial and axial kurtosis.

In another paper published in 2013 in NMR in Biomedicine [2], we demonstrated and evaluated a new metric of pore anisotropy in collaboration with the diffusion imaging group at Hvidovre Hospital. This method utilizes advanced diffusion pulse sequences, so-called double PFG diffusion imaging, to probe correlations in spin displacements over time. This has previously been shown to enable determination of anisotropic pore shapes in an isotropic sample. By proposing a special acquisition protocol, we demonstrated that it is possible to

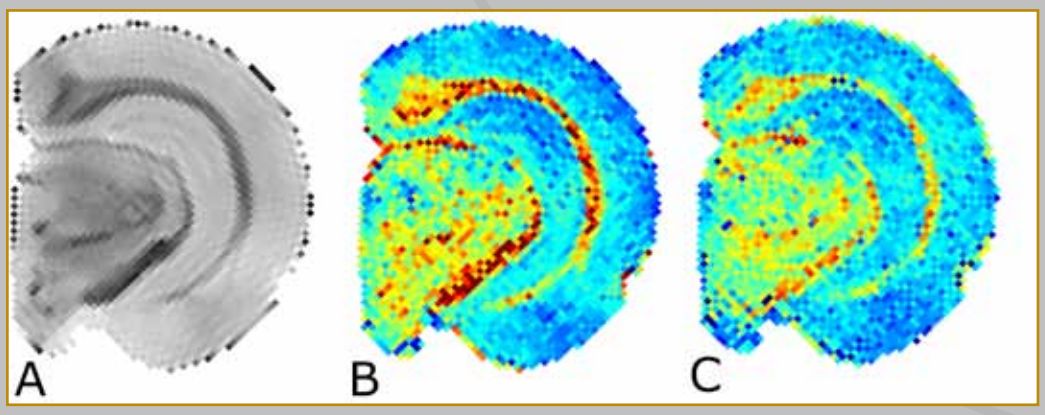

Figure 2
A) An example of a high resolution diffusion weighted image of fixed rat brain obtained on our new 9.4T Bruker system. This image belongs to a very large data set acquired for future modeling and optimization studies. B) Neurite density mapped in the same slice as shown in A. C) Mean kurtosis in the same image plane. Data sets such as the one illustrated here are crucial for development and refinement of neuroimaging methods.

characterize pore shape anisotropy even in the presence of macroscopic anisotropy. We also proposed a new metric which might appropriately be called microscopic fractional anisotropy, or μFA, as proposed by others subsequently [3]: this number has the same interpretation as FA for a single pore, but whereas traditional FA is affected by directional dispersion of the pores, μFA is not. These properties were demonstrated on images of fixated vervet monkey brain. We expect that these results might be of value for example as auxiliary input to fiber tracking algorithms, but also to have potential value as a biomarker for example in cancer. Besides at ISMRM, the work was also presented at a double PFG workshop in Kiruna, and a ISMRM workshop in Croatia, where Sune was an invited speaker.

The project "Cellular Underpinnings of Gray Matter Microstructure" supported by the Lundbeck Foundation also commenced in 2013. The main focus of this project is to use and validate our model of diffusion in gray matter [4, 5] using comparisons to quantitative histology in various animal models. Postdoc Ahmad Khan has a PhD in biochemistry from India began work on comparing 3D histology to diffusion weighted MRI. So far his work has resulted in an analysis method to automatically identify fiber directions in three dimensions based on confocal microscopy images for direct comparison to neurite morphology from our DWI models, and his first results will be presented at the 2014 annual meeting of the ISMRM. Ahmad Khan began his postdoctoral work with our close collaborator Chris Kroenke at Oregon Health and Science University, and is due to join CFIN July 2014. Closely related to Ahmad's work, Mikkel Bo Hansen published a paper in Frontiers in Integrative Neuroscience [6], using simulations in 3D digital renderings of real neurons to demonstrate that our model for the DWI signal can in fact correctly capture crucial aspects of the neurite orientation distribution.

Much of Brian Hansen's time in 2013 was devoted to the planning and installation of the new 9.4 T Bruker animal scanner (see page 56) acquired with support from the Institute of Clinical Medicine, the VELUX Foundation, and the Danish Research Counsil's Infrastructure program. Access to such a state-of-the-art MRI system is already of tremendous value to our work. Large data sets for modelling have already been acquired (and presented) and while much work remains before the system is fully operational we are pleased with the output of high-quality data so far. Images from the new system relating to neurophysics projects are shown in figures 1 and 2. Figure 3 shows preliminary results from a project in which

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
- Torben Ellegaard Lund
- Ryan Sangill
- Mikkel Bo Hansen
- Kennet Thorup
- Mads Hartmann Jensen
- Chris Kroenke
- Tim Dyrby
- Henrik Lundell
- Casper Kaae Sønderby

Conferences:

- Diffusion As a Probe of Neural Tissue Microstructure (ISMRM, Croatia, Podstrana).
- Annual Meeting ISMRM (Salt Lake City): Double PFG workshop, Kiruna, Sweden.

Invited lectures and Awards (Sune N. Jespersen):

- Diffusion as a probe of neural tissue microstructure. Diffusion workshop in Croatia.
- ISMRM: double PFG workshop, Kiruna, Sweden.
- Sune N. Jespersen was awarded a Distinguished Reviewer certificate from Magnetic Resonance in Medicine.

Committees:

- Sune N. Jespersen is secretary in the ISMRM diffusion study group Governing Committee.
- Sune N. Jespersen was on a PhD evaluation committee.
- Brian Hansen was head of a PhD evaluation 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.

Funding:

- Apart from funding from CFIN / MI*NDLab* the group has received funding from Lundbeck, NIH, and Kornings Foundation.

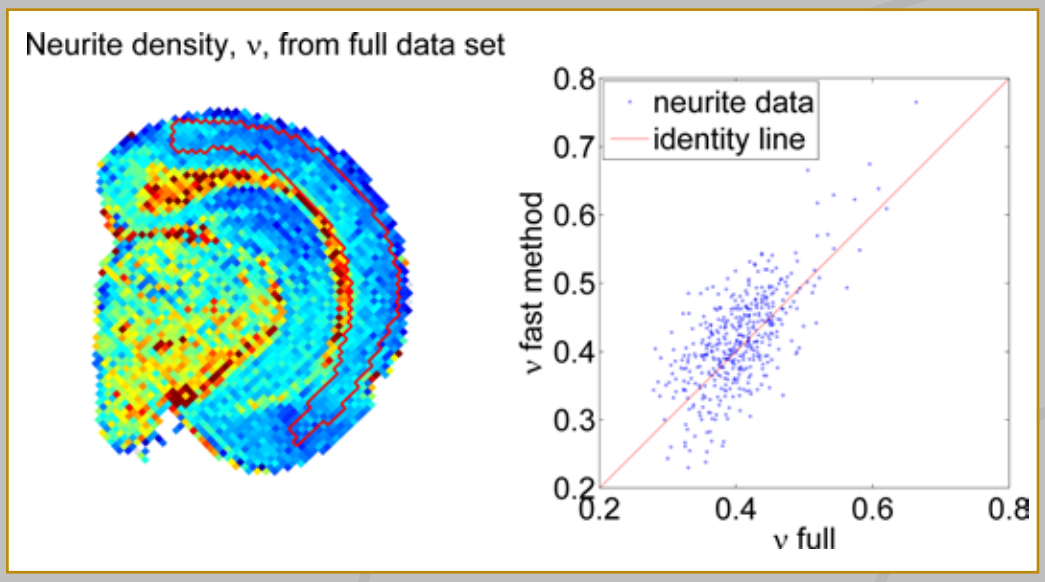

Figure 3
Preliminary results from a project on reducing scan time required to estimate neurite density. The graph shows neurite density in the region outlined in red in the map to the left as estimated from a large data set compared to the neurite density estimate in the same region from a clinically feasible scan scheme. The correlation is strong ($p<<0.01$) and we believe that this strategy will produce a method for estimation of neurite density in whole human brain based on approximately 12 minutes of scan time.

we aim to produce a fast method for estimation of neurite density in human brain. Neurites are the the microstructural basis for the plasticity of the brain and a method would be of great value for research and diagnostics e.g. in relation to stress and depression. We are grateful to Lippert's Foundation for a generous equipment grant allowing us to purchase a microscope and several other instruments that are important for these projects and many other ongoing projects in the lab. For further data examples and a status update on the pre-clinical research facility please see page 56.

Hugo Angley, who has a physics degree from France, started his PhD project on modeling the effects of capillary flow heterogeneity on the extraction of oxygen and nutrients. His work continues the modeling efforts initiated in [7], and is a project in collaboration with the functional hemodynamics group (Leif Østergaard) with close ties to many experimental activities at CFIN. Several Master's thesis students joined the group in 2013. Lise Trier Nielsen (physics) is working with physicists from iNANO to develop and test diffusion in phantoms of gray matter made by electro-spinning. Sarah

NEW FACE AT CFIN

Hugo Angleys, MSc (Physics), has studied engineering and physics in Paris, France.

During his master, he worked at Neurospin (south of Paris), on the evaluation of cortical folding during brain development, by applying a spectral analysis to anatomical MRI images acquired in preterm and term newborns. At ICM (Institut du Cerveau et de la Moelle Épinière, Paris), he focused on the analysis of cerebral functional coupling between two subjects, using and improving causality analysis such as Granger causality.

At CFIN, Hugo will work with Sune Nørhøj Jespersen and Leif Østergaard on a PhD project trying to extend the biophysical model developed by Jespersen and Østergaard, in which they focus on cerebral blood flow, and in particular on the relation between capillary transit time heterogeneity (CTH) and the tissue oxygen extraction fraction.

Hugo's PhD project entitled: Modeling oxygen and glucose extraction in brain and skeletal muscles is funded by The Velux Foundation. Read more about the project on the following pages.

Garney (physics) is using computer simulations to investigate the possible influence of dendritic spines (heavily involved in plasticity) on diffusion measurements. Johan Kruse Mortensen (physics), who is spending half of his thesis year with Chris at OHSU, is analyzing DWI data sets from human brain samples to compare a large number of mathematical models in order to determine the most appropriate description. Finally, Astrid Krabbe is implementing and evaluating a new mathematical method to detect causality in resting state fMRI data.

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FACTS

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

Modeling oxygen and glucose extraction in brain and skeletal muscles

by Hugo Angleys

Normal brain function depends critically on energy supply, and therefore on moment to moment regulation of oxygen delivery in the brain. The classical framework to understand brain oxygen regulation is neurovascular coupling: neural activation is accompanied by a local increase in cerebral blood flow, which then supplies the additional oxygen necessary to fuel increased energy demands. The fundamental relation between the brain's oxygen metabolism ($CMRO_2^{max}$) and blood flow (CBF) is encapsulated by the basic equation $CMRO_2^{max} = C_A.CBF.OEF^{max}$, where OEF^{max} is the oxygen extraction fraction, and C_A the arterial concentration of oxygen.

The relation between CBF and the availability oxygen in brain is traditionally based on the work by Christian Bohr, Seymour S. Kety, Christian Crone, and Eugene Renkin (Renkin, 1985). It leads to the classical idea that an increase in blood flow leads to better oxygenation. However, it assumes that all capillaries within a given tissue volume are identically perfused, but this is rarely so.

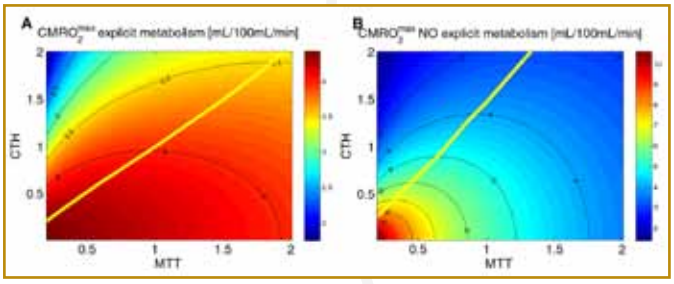

Figure 1
Preliminary results which illustrate the change on $CMRO_2^{max}$ maps induced by the incorporation of explicit oxygen metabolism. The transit time distribution is here assumed to be gamma variate.
(A) $CMRO_2^{max}$ map, assuming explicit oxygen metabolism governed by Michaelis Menten kinetics (B) shows $CMRO_2^{max}$ under the original model assumptions. In the two panels, for states on the left hand side of the yellow line, $CMRO_2^{max}$ decreases when flow is increased under constant CTH.

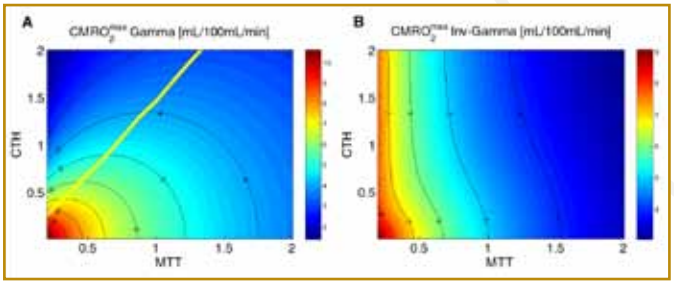

Figure 2
$CMRO_2^{max}$ maps computed under (Jespersen and Østergaard, 2012) assumptions and considering a gamma distribution (A), and an inverse gamma distribution (B).

Jespersen and Østergaard have recently extended the BKCR equations (Jespersen and Østergaard, 2012) to investigate the relations between CBF and oxygen uptake, when nonuniform capillary flow patterns are taken into account — so-called flow heterogeneity (CTH). This work suggests flow heterogeneity to be a vital ingredient for a proper understanding of oxygen delivery, and even points to conditions under which CBF increases are not accompanied by significant increases in oxygen extraction. This has fundamental consequences for our view of certain neurological diseases, for which the model has generated new hypotheses (Østergaard et al., 2013a, 2013b). Nevertheless, the extended BKCR equations were based on many simplifying assumptions which may be met only approximately in reality.

In this project, we aim to develop a physiologically more realistic model. Specifically, we account explicitly for oxygen metabolism in the tissue, which then (along with the oxygen supply) determines tissue oxygen concentration. This is in contrast to the original model, where tissue oxygen tension was treated as an independent parameter, considered to be uniform and constant. Additionally, we implement a number of different transit time distributions in order to ascertain that crucial model predictions are not related to peculiarities of the gamma distribution employed in (Jespersen and Østergaard, 2012). So far, it seems that the explicit incorporation of oxygen metabolism kinetics has a major effect on oxygen availability ($CMRO_2^{max}$), and predicts both an oxygen availability and tissue oxygen tension increase during functional activation in accordance with the literature. In addition, when considering physiological values and oxygen metabolism, the results seem to be largely insensitive to the choice of the transit time distribution considered.

Further work will consist in developing a model to describe glucose delivery and consumption, in order to study the relation between the blood flow pattern and glucose's clearance capacity. This involves including saturable glucose transport across the capillary membrane, as carried out by the GLUT4 and GLUT1 transporter proteins. This could enable us to better understand the underpinnings of aerobic glycolysis, which is an interesting and unresolved issue: during brain activation in normal brain, there is a build-up of lactate, even in states with high CBF (i.e. much oxygen available), where we would expect the glucose to be completely oxidized and to yield more ATP than when converted to lactate.

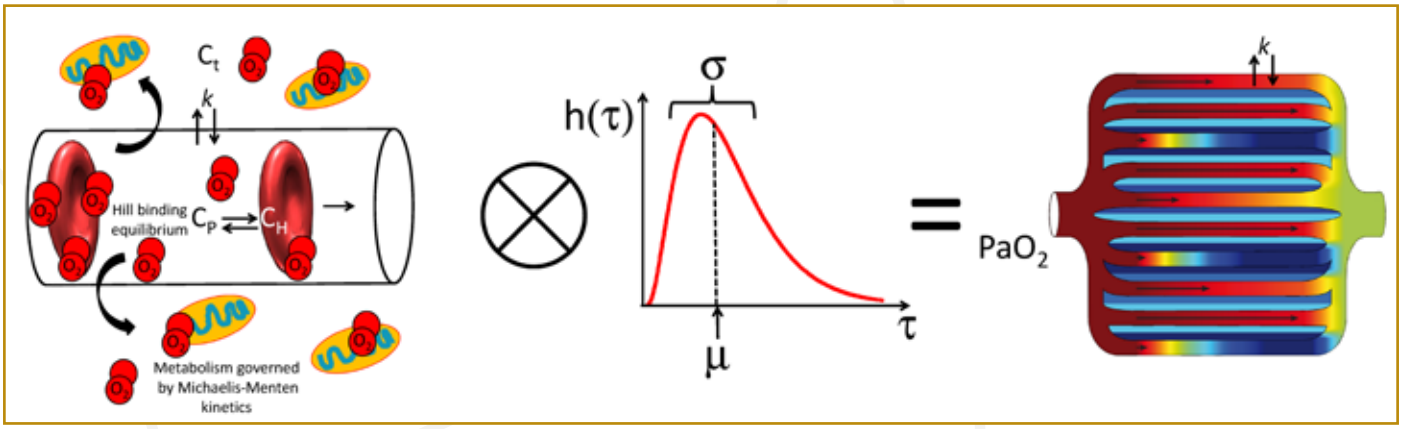

Figure 3
Model overview. On the left, the model for a single capillary is sketched. Oxygen is distributed across three compartments, oxygen bound to hemoglobin, oxygen in plasma, and oxygen in tissue. Oxygen in plasma is assumed to be in equilibrium with oxygen bound to hemoglobin, their concentration related by the Hill equation. Transfer of oxygen across the capillary membrane is modeled as a first order exchange process with rate constant k. Red blood cells have a capillary transit time τ. Tissue oxygen tension is determined by the balance between net oxygen extraction and the oxygen metabolism in the tissue and depends thus on τ. The capillary bed on the right is then obtained as a collection of capillaries modeled as described, but with different transit times τ taken from the transit time distribution $h(\tau)$, as shown in the middle. Oxygen tensions are not identical around different capillaries in the tissue compartment.

It could be valuable to study the extent to which the redistribution of the flow and the subsequent variation of oxygen tension within a capillary network can induce changes in glucose metabolization pathways. We could determine whether such effects are the result of inherent, differential transport of glucose and oxygen across the blood-brain-barrier.

The third goal will be to adapt and apply the model to oxygen transport in skeletal muscle tissue, in order to address a long-standing controversy about the existence of capillary recruitment, and how redistribution of the blood flow and changes in blood properties can increase O_2 delivery sufficiently from rest to exercise. Adapting the BKCR model to study the oxygenation of skeletal muscles will enable us to simulate and quantify the impact of each hypothesized mechanisms on the oxygenation. It will be a way to assess the plausibility of each hypothesis and to better understand the mechanisms underlying the oxygenation and glucose uptake in muscles.

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FUNCTIONAL HEMODYNAMICS

by Leif Østergaard

Functional hemodynamics. Celebrating three Anniversaries.

The functional hemodynamics group continues to explore the effects of capillary transit time heterogeneity (CTH) – a phenomenon that may force us to reconsider how tissue can secure nutrients from its blood supply, and to re-evaluate central disease mechanisms.

The first signs that the distribution of blood flow across the capillary bed might be important for tissue function emerged almost precisely 15 years ago. Working with perfusion MRI data from acute stroke patients, an index that describes capillary flow heterogeneity turned out to predict with remarkable accuracy whether brain tissue had survived when the patient was reexamined a month later(1). David A. Chesler, a dear friend and colleague at the MGH-NMR (Martinos) Center at Massachusetts General Hospital, pointed out that this phenomenon might reflect a fundamental property of oxygen transport into tissue. With the support of the Danish National Research Foundation, we were able to confirm this phenomenon in two additional stroke studies, finalized and published 10 years ago, respectively(2, 3). Five years ago, Sune N. Jespersen completed the first biophysical model of the effects of CTH, while Kim Mouridsen developed a methods that permitted us to estimate this parameter based on perfusion MRI(4). After some time spent comprehending the model results, and even more spent convincing others that they were accurate, the manuscript describing the effects of CTH and its implications for our understanding of neurovascular coupling was published in 2012(5). In 2013, after an effort that has involved a dozen CFIN / MI*NDLab* researchers, Morten S. Jensen and Mark J. West from the Section of Neuroanatomy at Aarhus University, a dozen colleagues from the Departments of Neurology, Neurosurgery, Neuroradiology, Neuroanesthesiology, and Experimental Oncology at Aarhus University Hospital, and stroke experts from across Europe, we published four papers that critically examines the origin of major disease processes. The papers present a novel hypotheses regarding the origin Alzheimer's Disease(6), the origin of tissue damage in acute stroke(7), the lack of oxygen that prevent the efficient treatment of some cancers(8), and the brain injury that occur in the week following a subarachnoid hemorrhage(9). In late-afternoon meetings, scientists and clinicians have met in the CFIN / MI*NDLab* conference room to formulate and discuss these ideas, and to plan experiments and clinical studies to test them. The buzz over what may represent a paradigm shift in our understanding of central disease mechanisms has spread with our publications, all of which have been downloaded extensively, cited, and received much attention and discussion on expert websites over the past year.

Why 'celebrate' the 5th, 10th, and 15th anniversary, rather than mourn the slow progress? Some ideas take time, patience, and the knowledge, decades of failed/successful experiments, and approaches from many areas of research to finally mature. And some discoveries may never be made because some phenomena are inherently difficult to model, understand, let alone measure, with current knowledge. I remain convinced that, without the long-term support of the Danish National Research Foundation and then the Danish Government's UNIK initiative, this idea is one of many ideas within CFIN / MI*NDLab* that wouldn't have made it past shorter-term funding schemes. Nor would we have been able to develop the infrastructure, methods, and know-how that now allow us to soon study this phenomenon in animal models and humans, and initiate human studies of principles we hope will prove useful in terms of preventing or delaying the development of Alzheimer's Disease.

ARCADIA

VELUX FONDEN

Head of CFIN and MIND*Lab*, Professor Leif Østergaard received 9.850.000 DKK from The VELUX Foundation in 2013. The grant is going to be used to uncover causes of the cognitive decline that accompanies aging and dementia.

CFIN researchers have recently discovered an unexpected limitation in the brain's ability to obtain sufficient amounts of oxygen from the bloodstream - so called capillary dysfunction. With the grant from VELUX, researchers from different scientific disciplines will be able to develop advanced imaging techniques and data models that will enable the measurement of capillary dysfunction and its role in human brain function. The project will attempt to identify the molecular and cellular processes that causes the phenomenon and establish its extent in humans. Based on this knowledge, the researchers hope to better understand how cognitive decline and dementia in the elderly can be prevented and treated.

In 2013 we were fortunate and grateful to receive funding from the VELUX Foundation to acquire equipment and hire staff to study the capillary flow phenomena, and the accompanying early tissue damage, in animal models of aging and neurodegeneration. The generous funding will allow us to develop optical techniques with colleagues David Boas, Sava Sakadzic, and Jonghwan Lee from the MGH Martinos Center, Harvard Medical School. Meanwhile, we can acquire advanced imaging coils for neurite density imaging with our 9.4 T small-bore system, donated by the Danish Council for Research and Innovation's infrastructure program, the Department of Clinical Medicine, and the VELUX Foundation. Meanwhile, the European Union Joint Programming Initiative within Neurodegenerative Diseases awarded us funds to examine CTH changes in Parkinson's Disease and Alzheimer's Disease, in a collaboration that involves neuroimaging and genetics experts from Oslo, Stockholm, London, and Brno.

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- Mike Horsman and Thomas Nielsen, Department of Experimental Clinical Oncology, AUH.
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Guest visits abroad:

- Eugenio Gutiérrez Jiménez research visit at Optics Division of the Martinos Center for Biomedical Imaging at Massachusetts General Hospital (MGH) and Harvard Medical School.

Key publications:

- Blicher, Jakob; Stagg, Charlotte J; O'Shea, Jacinta; Ostergaard, Leif; Macintosh, Bradley J; Johansen-Berg, Heidi; Jezzard, Peter; Donahue, Manus J. Visualization of altered neurovascular coupling in chronic stroke patients using multimodal functional MRI. Journal of Cerebral Blood Flow and Metabolism, 08.2012.

- Jespersen, Sune Nørhøj; Østergaard, Leif. The roles of cerebral blood flow, capillary transit time heterogeneity, and oxygen tension in brain oxygenation and metabolism. Journal of Cerebral Blood Flow and Metabolism, Vol. 32, Nr. 2, 01.02.2012, s. 264-277.

- Dalby, Rikke Beese; Frandsen, Jesper; Mallar, Chakravarty; Ahdidan, Jamila; Sørensen, Leif; Rosenberg, Raben; Ostergaard, Leif; Videbech, Poul. Correlations between Stroop task performance and white matter lesion measures in late-onset major depression. / Psychiatry Research, Vol. 202, Nr. 2, 2012, s. 142-149.

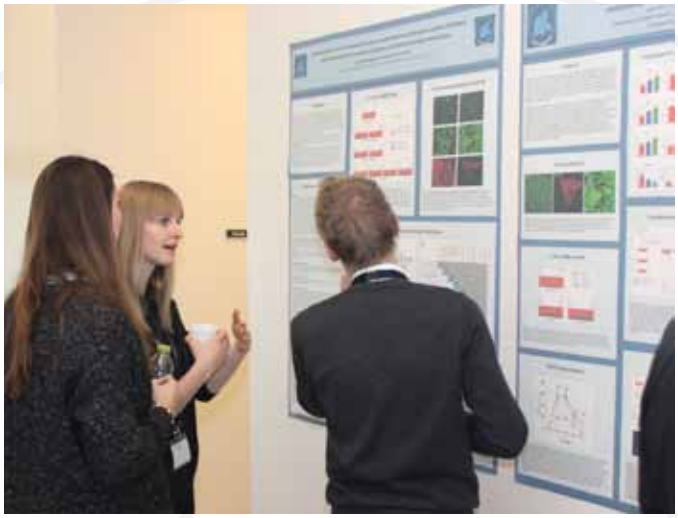
FUNCTIONAL HEMODYNAMICS

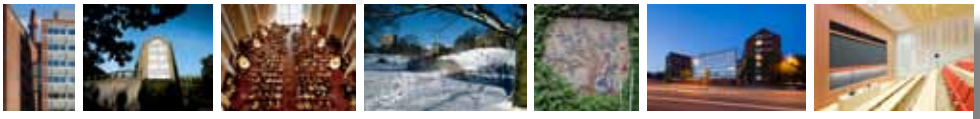
Aarhus CTTH Workshop 2013

Meeting Objectives

The Aarhus CTTH Workshop 2013 was the second international gathering of researchers working to explore and understand the relations between blood-brain-barrier function, vascular signaling, and neurovascular coupling in health and disease.

Leading international reseachers on neurovascular and neurodegenerative disorders took part in the meeting, alongside experts in the study of microvascular function and hemodynamics. The workshops aim to foster crossdisciplinary interactions and collaboration.





PROGRAM AT A GLANCE ...

THURSDAY 5 DECEMBER 2013, ARoS Art Museum

Talks by:

- Leif Østergaard (Aarhus): Welcome & Introduction. *Capillary Dysfunction: An important disease entity?*
- Berislav Zlokovic (UCS): Keynote Lecture: *The Blood Brain Barrier in Alzheimer's Disease*
- Ulrich Dirnagl (Charité): *Vascular cognitive impairment: Insights from a bilateral common carotid artery stenosis model*
- Conference Reception
- Workshop Dinner, ARoS Art Museum

FRIDAY 6 DECEMBER 2013, DNC Auditorium, Aarhus University Hospital

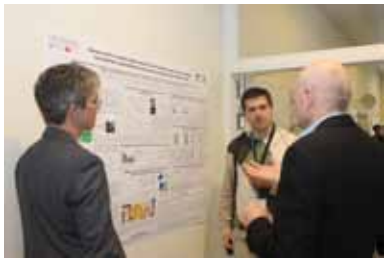
Talks by:

- Cor de Wit (Lübeck): *Connexins in the microcirculation: Molecules and mechanisms*
- Axel R. Pries (Charité): *Conducted responses in structural vascular adaptation and malperfusion*
- Wolfgang Kuebler (Toronto): *Conducted responses in hypoxia signalling and functional integration*
- David Attwell (UCL): *Capillary pericytes are critical regulators of cerebral blood flow in health and disease*
- Anusha Mishra (UCL): *Neurovascular Signalling at the Capillary Level*
- Renaud Jolivet (UCL): *Multimodal imaging in rats reveals impaired neurovascular coupling in sustained hypertension*
- Constantino Iadecola (Weill Cornell Medical College): Keynote Lecture: *Neurovascular Coupling in Hypertension and Alzheimer's Disease*
- Turgay Dalkara (Hacettepe University): *Cerebral ischemia: The roles of pericytes in incomplete microcirculatory reperfusion*
- Jean-Claude Baron (Paris): *Cerebral blood flow and oxygen metabolism in stroke: Lessons from PET*

SATURDAY 7 DECEMBER 2013, DNC Auditorium, Aarhus University Hospital

Talks by:

- David K. Menon (Cambridge): *Cerebral oxygen delivery and utilization in traumatic brain injury – insights from imaging*
- Ryszard M. Pluta (NIH): *Nitric Oxide Synthase(s) Function in Vasospasm after SAH*
- Nikolaus Plesnila (Munich): *NO in SAH*
- David Boas (Harvard): *Imaging cerebral microcirculation and oxygenation. OCT, 2PM, NIRS*
- Kim Mouridsen (Aarhus): *Determining CTH in humans*



Aarhus CTTH Workshop 2013
Photos: Kim Ryun Drasbek

NEW FACES AT CFIN

Maryam Anzabi, MD, PhD student, started January 2014, working on the project *The Influence of pericapillary nitric oxide levels and edema on capillary blood flow patterns in mice models of subarachnoid hemorrhage*, under the supervision of Professor Leif Østergaard.

Subarachnoid hemorrhage (SAH) is a devastating disease, associated with high rates of mortality and morbidity. Unfortunately the pathogenesis of SAH is poorly understood and effective treatment regimes are urgently needed.

Nitrite administration and cerebral edema management by hypertonic saline infusion have been shown to be neuroprotective in animal models and may increase cerebral tissue survival and improv SAH patient's outcome. We believe, these beneficial effects may be explained to capillary blood flow pattern changes. Testing this idea may provide new insights and lead to novel treatment targets and ultimately better outcome. In the current project, nitrite and hypertonic saline will be administered to mice models of SAH, and capillary blood flow pattern changes will be evaluated using two-photon microscopy. The project is funded by a stipend from Aarhus University.

Thorbjørn Søndergaard Engedal, MD, PhD student.
Started in the spring of 2013, working on the project *The role of capillary transit time heterogeneity in ischemic stroke*.

Since the discovery of the ischemic penumbra in the late 1970s, a large number of studies have studied the ischemic cascade that follows acute ischemia caused by an intracerebral blood clot. To date, although nearly 200 clinical studies on neuroprotective interventions have been performed, intravenous thrombolysis administered before 4.5 hours from stroke onset remains the only proven effective treatment. Perfusion imaging, and particularly capillary transit time heterogeneity, could serve to immediately and accurately evaluate the severity and extent of an ischemic stroke. This would allow for precise prognostication and patient selection for interventional trials. In addition, a better understanding of the role of microvascular flow disturbances could help guide future neuroprotective strategies.

Erhard Trillingsgaard Næss-Schmidt, Physiotherapist, PhD student, started his PhD project in 2013 studying structural and functional changes in the brain after mild traumatic brain injury (mTBI) with MRI.

The aim of the project is to study some of the more than 25.000 people exposed to mTBI each year in Denmark. Most people recover during the first 2 months after injury but up to 20 % have ongoing symptoms beyond 3 months. There is a need for more knowledge of the mechanisms causing these persisting symptoms. Sensitive MRI techniques are able to detect both structural and functional changes in the brain after mTBI and we hope to use MRI to find additional pathophysiological changes in the brain after injury.

The aim of the study is to use sensitive MRI techniques to detect changes in the brain after mTBI and examine whether they correlate with the symptoms and outcome after mTBI. Sensitive biomarkers are crucial for patient management, and in the evaluation of new therapies. The project will show whether sensitive MRI-techniques are sufficiently sensitive to detect changes in the brain after mTBI and whether specific MRI-markers can be linked to some of the persistent symptoms after mTBI.

The MRI study is a part study of a larger randomized controlled trial (RCT) study including a multidisciplinary clinical examination and treatment session and is a collaboration between The Region Hospital Hammel Neurocenter, Center of Functionally Integrative Neuroscience (CFIN) and The Research Clinic of Functional Disorders.

FUNCTIONAL HEMODYNAMICS

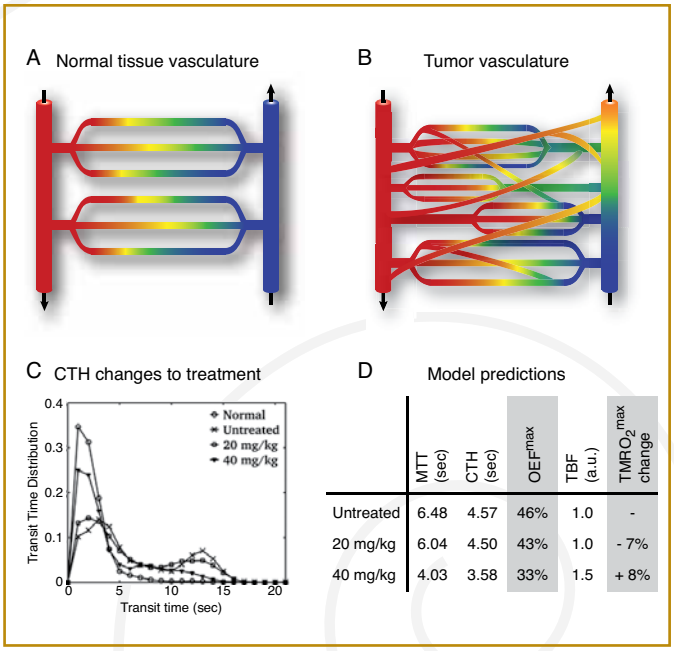
Why do tumors crave sugar - and run out of oxygen?

by Leif Østergaard

Tumors depend on large amounts of oxygen and glucose to grow. When cancer cells first develop, they 'steal' nutrients from their immediate environment. As these cells divide and the tumor grows beyond a few cubic millimeters, it must establish its own blood-supply in order to continue growing. By stimulating surrounding blood vessel to sprout and form new blood vessel, so-called angiogenesis, tumors can then grow in most tissue types, killing one in four of us. The tumors' need to create blood vessels in order to grow was originally thought to represent cancers Achilles' heel: By inhibiting their formation of blood vessels, it was hypothesized that one might efficiently combat cancer(1). Decades of research have now identified the mechanisms by which tumors stimulate surrounding tissue to build their blood-supply – and ways to inhibit this process(2). Disappointingly, such angiogenesis inhibitor drugs seem to have little effect on the growth of tumors when they are administered to cancer patients without any other treatment. Surprisingly, however, they seem to work very well when administered in combination with well-established, 'standard' chemotherapy and radiation therapies.

The mechanism thought to explain this puzzling finding is the exact opposite of the original rationale for developing angiogenesis inhibitors: Rather than depriving tumors of oxygen, anti-angiogenic drugs are thought to remove only part of the chaotic tumor microvasculature ('pruning') and allow blood – and thereby both oxygen and anti-cancer drugs - to distribute better across the tumor(3). When cancer cells lack oxygen, they become more aggressive, more resistant to chemo- and radiation therapy, and more likely to spread to other organs(4). So if angiogenesis inhibitor therapy improves tumor oxygenation, this phenomenon could explain the puzzling results from angiogenesis inhibitor trials. Now, herein lies the problem: Although proponents of this 'vascular normalization' hypothesis claim that anti-angiogenic therapy improves tumor oxygenation, making them more sensitive to therapies that kill tumor cells – this assumption is not entirely supported by experiments. In fact, just as many studies have shown that angiogenesis inhibitors reduce tumor oxygenation(5). Given the devastating effects of inducing tumor hypoxia (above), this paradox should be better understood in order to use angiogenesis inhibitors in the most efficient way.

We applied our model of tissue oxygenation to the tumor microvasculature – See figure 1. Using recordings of the distribution of transit times made by MRI in a brain tumor



	MTT (sec)	CTH (sec)	OEF^{max}	TBF (a.u.)	$TMRO_2^{max}$ change
Untreated	6.48	4.57	46%	1.0	-
20 mg/kg	6.04	4.50	43%	1.0	- 7%
40 mg/kg	4.03	3.58	33%	1.5	+ 8%

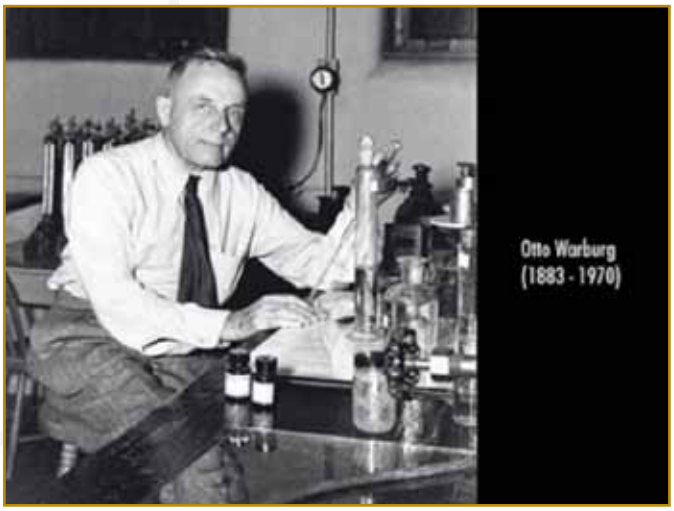
Figure 1
The figure illustrates how capillary flow velocities in normal tissue are regulated to provide efficient extraction of oxygen. Red indicates fully oxygenated blood while the transition over orange and yellow to blue indicates gradual deoxygenation. In tumors (panel B), tight control of capillary flow distributions is invariably lost owing to factors such as the lack of normal, contractile pericytes on capillaries, irregular luminal capillary diameters, capillary compression by tumor edema, increased blood cell adhesion to the endothelium, and loss of the conducted vasomotor responses that ensure appropriate blood distribution in normal microvessels. The oxygenation response to the removal of specific capillary paths by anti-angiogenic therapy in this example depends critically on the resulting redistribution of capillary flows and changes in TBF – estimated here by the capillary transit time heterogeneity CTH and mean transit time MTT parameters.

Panel C shows the effects of two different doses of an anti-angiogenic agent, SU11657, on the distribution of transit times as recorded by Quarles and Schmainda(6). Note how the highest dose almost normalizes the distribution of transit times compared to that of normal brain tissue. This homogenization would be expected to improve tumor oxygenation.

The first two columns of Panel D show MTT and CTH derived from the pre- and post-treatment transit time distributions in Panel C. Note that in this tumor type, treatment with SU11657 caused hemodynamic vascular normalization in the sense that CTH was reduced in a dose-dependent manner. Tumor oxygenation increased in the high-dose condition as a net effect of an increase in tumor blood flow(6) that outweighed the reduction in OEF^{max}, but decreased in the low dose experiment. The example underscores the importance of knowing the treatment-related changes in MTT and CTH in order to predict how the availability of oxygen in a given tumor is affected by various doses of anti-angiogenic therapy.

model(6), we found that theoretically, the removal of tumor vessels caused by one angiogenesis inhibitor dose lead to better oxygenation – while that caused by another dose lead to poorer oxygenation. This effect is not difficult to understand considering the randomness by which tumor microvessels are organized - and the difficulty in predicting how obliteration of some vessels affect the heterogeneity of blood flow through the remaining blood vessels. With time, we hope to develop imaging methods that allow us to monitor the changes in CTH in response to a 'test dose' of angiogenesis inhibitor across the tumor in each patient – so this therapy can be optimized to improve oxygenation – an thus optimize each patients response to radiation and chemotherapy.

The Elusive Warburg Effect



Otto Heinrich Warburg (1883-1970), who won the 1931 Nobel Prize in Physiology and Medicine *'for his discovery of the nature and mode of action of the respiratory enzyme'* discovered that cancer cells share a common peculiarity – a tendency to consume large amount of glucose without the use of oxygen – although this would render their metabolism much more efficient(7). This lead him to formulate the 'Warburg Hypothesis' of cancer:

Cancer, above all other diseases, has countless secondary causes. But, even for cancer, there is only one prime cause. Summarized in a few words, the prime cause of cancer is the replacement of the respiration of oxygen in normal body cells by a fermentation of sugar.

Today, the tendency for tumors to take up large amount of glucose is utilized in the diagnosis of cancer, by detecting the uptake of glucose analogs such as fluoro-deoxy-glucose (FDG) by positron emission tomography (PET). This provides high sensitivity to detect small tumors and tumor metastases, and to optimize cancer therapy. The Warburg effect is also being pursued as a means of developing novel therapies, with the hope that the tumors 'selective appetite' for glucose may render it vulnerable to disruptions of this metabolic pathway(8).

We modeled how CTH affects the extraction of glucose and oxygen in the chaotic microvasculature of tumors. Oxygen extraction is hindered to a larger extent than glucose extraction by the inherent inhomogeneity of capillary flow patterns – and it is therefore perhaps not surprising that tumor cells only survive if they are able to generate energy using very little oxygen: The most energy efficient way of metabolizing glucose - Oxidative phosphorylation (complete breakdown of glucose to ATP) - requires oxygen to be present in a ratio of approximately 5-6:1. If a relative lack of oxygen exists, ATP can be generated by conversion of the remaining glucose into lactate instead - glycolysis. So the extraction properties of oxygen and glucose in fact predict that the more abnormal their microvasculature, the more will tumors rely on the Warburg effect. And conversely, only the cells that possess the ability to utilize the Warburg effect will ever survive and grow to become tumors. The relation between tumor aggressiveness and their tendency to utilize glucose with little oxygen may therefore be better understood by considering their access to nutrients in an environment of chaotic tumor vessels(9).

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Neuroscience in China

by Kim Ryun Drasbek

CFIN / MI*NDLab* is deeply involved in the Master programme in Neuroscience and Neuroimaging being offered in Beijing, China, as part of the Sino-Danish Center for Education and Research (SDC). The SDC collaboration includes all Danish universities and from China all research institutes of the Chinese Academy of Sciences (CAS) as well as the University of the Chinese Academy of Sciences (UCAS). Both Chinese and Danish researchers contribute to the Master programme. The Master in Neuroscience and Neuroimaging was one of the first four educations in the SDC collaboration, admitting its first students in September 2012. This class of Danish and Chinese students is now working in different Chinese neuroscience laboratories as part of their Master projects. Currently, we teach a total of 39 1st and 2nd year students in Beijing.

The first annual SDC Neuroscience and Neuroimaging Spring Meeting took place in Beijing the 26th of February 2013. This meeting is part of several initiatives to bring Chinese and Danish Neuroscience and Neuroimaging research closer together. At the Spring Meeting all 2nd year Master students of the programme presented their projects and current progress for their fellow students, supervisors and Chinese and Danish neuroscientists in excellent talks. The meeting was a big success, showing the great progress of the students both scientifically and personally during their studies at the Master programme. All of the talks were of good quality and demonstrated their remarkably advances, in scientific understanding and in many cases very interesting data. In addition, these presentations contribute towards the Chinese Master degree, while their final exam this summer will grant the students Master degrees from both Aarhus University and UCAS. This Spring Meeting will take place every year in Beijing while a summer meeting is planned in Denmark, in relation to a summerschool.

Tingting Gu and Mette Vissing
Photo: Kim Ryun Drasbek

CFIN / MINDLab researchers involved in the SDC Neuroscience and Neuroimaging Master

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

Mette Vissing (2013 student)

I choose this Master degree because it is the only one of its kind offered through a Danish University, and because it offers me a unique combination within fields of neuroscience. Through the Danish-Chinese cooperation the best Danish and Chinese researchers within the different scientific disciplines teach us. Thus, Medical Doctors are teaching us about neurons and their function while Engineers gives lectures about the different imaging techniques.

The possibility of doing my degree in China gives me, not just a unique education, but also the possibility of interacting and learning from a country with great potential. Studying "Neuroscience and Neuroimaging" in China for two years not only gives me all these great scientific tools, it also develops me as a person, to see and understand the Chinese culture; not just on the street but also in the laboratory.

Tingting Gu (2013 student)

Having been a student in the "Neuroscience and Neuroimaging" programe for half a year, I think it's really a smart decision to join the SDC.

All the lecturers of the Neuroscience program are researchers and scientists. Thus, beyond the basic knowledge, I also learn about new trends and techniques in the field and real applications of what I learned, which is really interesting. Also their passion in their own research inspires me a lot.
Since we are a group of both Chinese and Danish students, life in SDC with two cultures can't be boring. We have sports day, quiz night, hiking during the weekend, making dumplings together in Winter Solstice Festival and also the grand Christmas party. All of this made the life in SDC interesting.

NEW BOOK

In collaboration with the Systime publishing company, researchers from CFIN have published a book for high school (gymnasie) students about brain research. The new book is in Danish and entitled: ***Hjernen - fra celle til samfund***

From the cover of the book:

The brain is the body's complex command center. It constitute 2 % of the body weight but uses 20 % of the body energy and contains up to 100 billion nerve cells connected in an enormously complex network. The brain enables man to walk on the surface of the moon, create masterpieces within philosophy, art, literature and music, and to produce advanced technical tools. Everybody has one, but what do we really know about this fabulous organ?

This book is written by brain scientists from Center of Functionally Integrative Neuroscience (CFIN) and MINDLab at Aarhus University. They have trained within disciplines such as physics, mathematics, language, psychology, theology, and music, but they now work close together with scientists from other disciplines to develop new brain research methods and new knowledge – not only about the brain but also about problems that are central to their original subject area.

The book provides insight into the many different scientific approaches to studying the brain. The authors have written about their individual subjects, and the book provides both basic facts about the brain and how we examine it, as well as a range of examples of actual brain research projects.

The authors hope that the book can form the basis for a wide range of interesting educational projects in high school, and that it will help inspire openness, curiosity and dialogue as students enter science in their later careers.

The book is edited by CFIN Communications Coordinator Henriette Blæsild Vuust.

To buy the book, please contact:
SYSTIME
Skt. Pauls Gade 25
DK-8000 Aarhus C.
www.systime.dk

Left:
Her Majesty the Queen Margrethe II broke ground for SDC's new building in Beijing on 26 April 2014. This building is funded by the Danish Industry Foundation and placed 60 km northeast of Beijing at the new UCAS Yanqihu Campus in Huairou District.

Right:
Visualization of the new UCAS campus at Yanqihu which is now almost completed. In the future, the SDC educations will be hosted here when the new SDC building is finished in 2015.

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 2013 the majority of our work focused on structural and perfusion MRI markers of AD. In 2013, the AIM group employed Rune Bæksager Nielsen as research assistant to work on MRI perfusion markers of AD.

EU funding

Imaging markers of AD was the subject of a proposal submitted to FP7 in the end of 2012. This collaborative project proposal was well received by the council, and invited to the second round of the call. Therefore 2013 started off with a major effort to compete for a European grant in what was the last call of FP7. CFIN/AIM acted as coordinator. After the very positive review of our expression-of-interest, we worked hard to write a competitive proposal within a short timeframe. Funding from EUopSTART provided ressources to work, and seven partners from UK, Spain, France and Denmark gathered in Paris in January to join forces, and work toward the quickly approaching deadline of February 6. The collaborative project PANDEMIA (Prediction, Detection and Monitoring of Alzheimer's disease) was born. The evaluation of our proposal was positive too, and the proposal passed the score threshold set by the research council. Unfortunately PANDEMIA was not prioritized among the projects for which the call had received funding. However, the ideas fostered through the collaborative effort live on and some have made it into other successful grant applications headed by our collaborators.

One of these successful grant applications are APGeM (Pre-clinical genotype-phenotype predictors of Alzheimer's disease and other dementia) funded by the EU Joint Programme - Neurodegenerative Disease Research. This proposal is coordinated by Tormod Fladby, University of Oslo and CFIN received €250.000 for measuring capillary flow and neurite density in AD, Parkinson's disease, and Lewy body dementia.

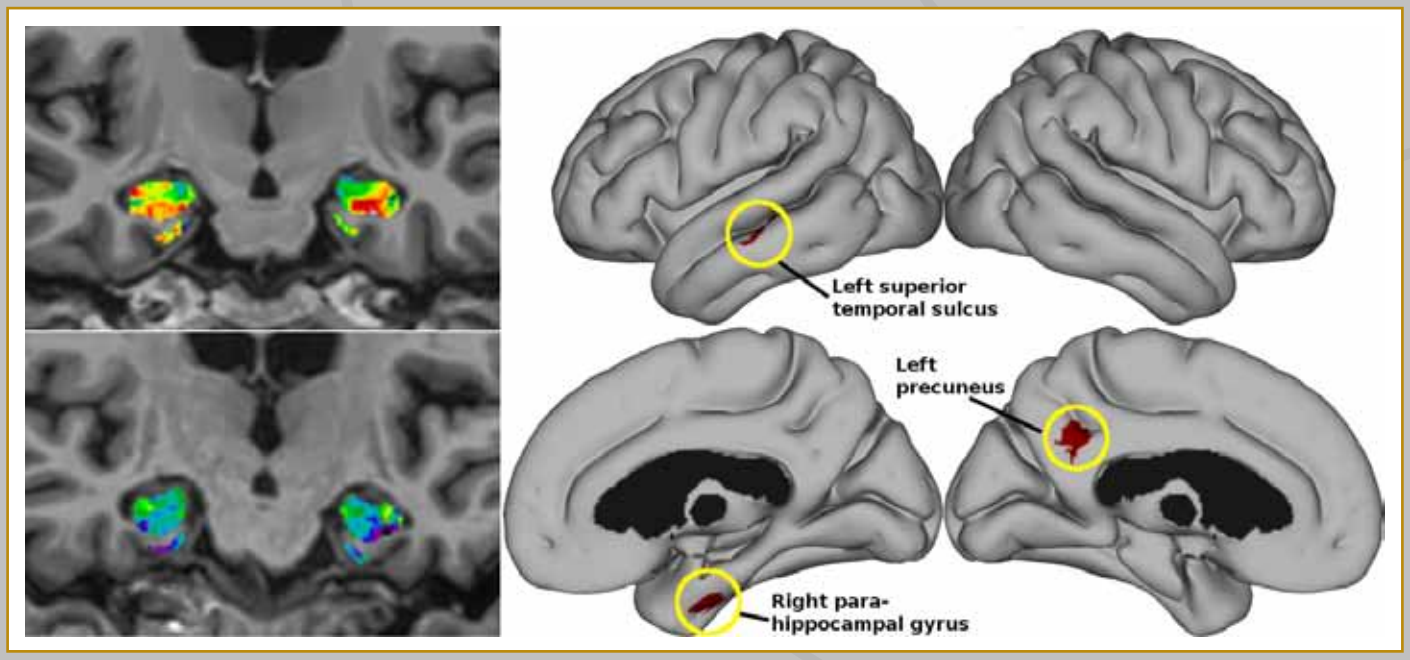

Figure 1
Five structural features optimize prediction of disease progression in AD. These are grading of left and right hippocampus (left figure) and cortical thickness measured in three specific regions (right figure) (Eskildsen et al., 2013).

Structural imaging biomarkers of AD

Collaboration with Professor Louis Collins at Montreal Neurological Institute led to the release of a new pipeline for analysis of longitudinal structural MRI (Aubert-Broche et al., 2013). Using this pipeline, we demonstrated how measurements of cortical thickness may improve prediction of disease progression in AD patients (Eskildsen et al., 2013). We extended on this work in collaboration with Dr. Pierrick Coupé from Bordeaux, and showed that automatically extracted features from a few key brain structures are sufficient to achieve relatively high prediction accuracy of disease progression (publication currently in press, Figure 1).

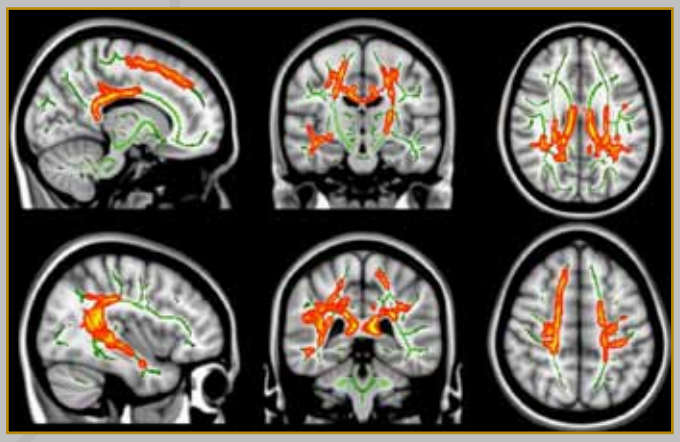

Figure 2
Hippocampal-cortical structural connectivity is reduced in AD patients compared to age-matched controls. Red and yellow areas have reduced connectivity in AD. The reduction is mainly found in the angular bundle, fornix, and superior longitudinal, inferior longitudinal, cingulate, uncinate and arcuate fascicles (Rowley et al., 2013).

In another collaboration with Professor Pedro Rosa-Neto from McGill Centre for Studies in Aging (Montreal), we used diffusion weighted imaging to demonstrate significantly reduced hippocampal-cortical structural connectivity in AD patients compared to cognitively normal age-matched controls (Figure 2).

Perfusion imaging biomarkers of AD

Although we can measure the impact of AD in the brain, the aetiology of the disease is not fully understood. This impedes the development of effective neuroprotective therapies and disease prevention strategies. In 2013 CFIN researchers

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

National & International collaborators:

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- 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.

Conferences:

- Simon Eskildsen: Alzheimer's Association International Conference 2013, Boston, USA

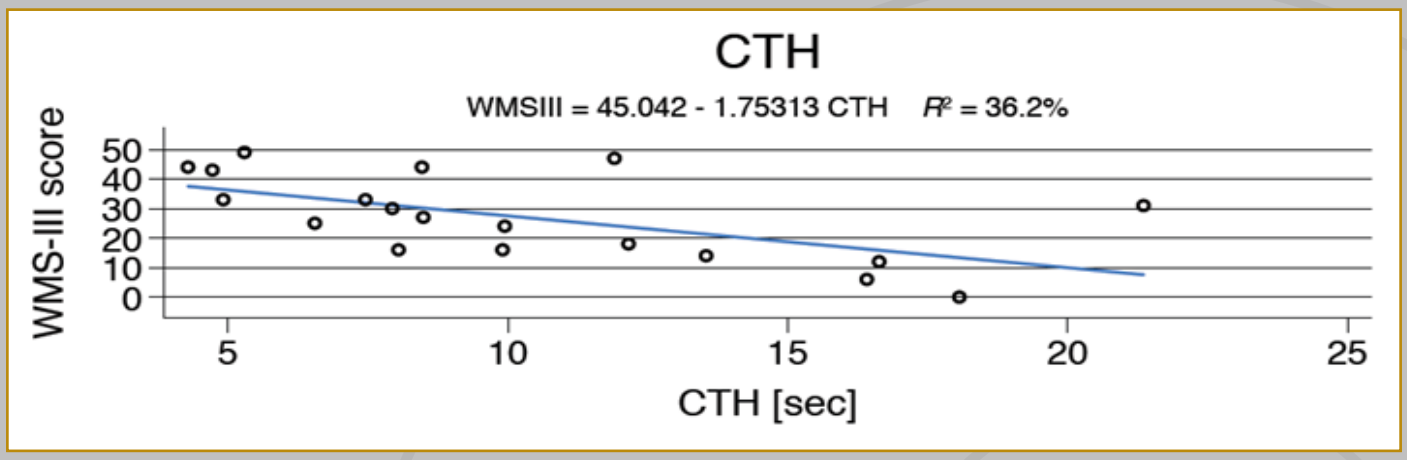

Figure 3
Cognitive test score as a function of whole brain capillary transit time heterogeneity (CTH) in 19 AD patients. CTH is measured using DSC-MRI (spin echo EPI). From Rune Nielsen's master's thesis 2013.

published a new hypothesis, proposing capillary dysfunction as an initiating factor of the pathophysiological process in AD (Østergaard et al., 2013). The fundamental assumption behind this hypothesis is a lifelong deterioration of the capillaries, caused by several cardiovascular diseases. This deterioration leads to impaired capability risk factors of homogenizing capillary flow, which facilitates oxygen extraction from the blood (Jespersen and Østergaard, 2012). The AIM group is involved in several projects aiming to test this important hypothesis. In 2013, Rune Nielsen finished his master's thesis entitled "Effects of liraglutide on regional cerebral perfusion and oxygen extraction as measured with DSC-MRI in patients with Alzheimer's disease - A pilot study" in which he showed correlations between whole brain capillary flow heterogeneity and cognitive decline in AD patients (Figure 3). In the fall we initiated a new project together with the PET-Center and Professor David Brooks looking at amnestic mild cognitive impaired subjects - a state typically preceding clinical AD. In this longitudinal study we focus on the relationship between capillary dysfunction, neuroinflammation, and the aggregation of the beta-amyloid protein in the brain parenchyma. In addition, we will apply several new MRI technologies to better detect and understand the first signs of neurodegeneration in these patients.

NEW FACE AT CFIN

Rune Bæksager Nielsen, Physiotherapist, MSc (Biomedical Engineering). After completing his Master in October 2013, Rune was employed as Research Assistant at CFIN. In a collaboration with CFIN and the Department of Biomedicine, Aarhus University, the master's thesis involved DSC-MRI measures of cerebral perfusion for evaluation of the type-II diabetes drug, liraglutide, in the treatment of patients with Alzheimer's disease (AD). Results from the thesis suggest that cerebral capillary flow patterns and oxygen capacity are correlates of cognitive performance. Inspired by this, Rune's work has been focused on linking measures of perfusion to neurodegeneration, amyloid plaque load, glucose consumption, and capillary dysfunction in AD.

Rune has applied for a PhD project, with the aim of investigating capillary flow patterns, neurite density, and atrophy in subjects with mild cognitive impairment. The goal is to establish whether capillary dysfunction is an early event in AD, and to create improved biomarker models for early diagnosis and prediction of AD.

Teaching in China

In 2013 the AIM group became involved in the SDC Neuroscience & Neuroimaging master's program in China. Simon Eskildsen went to Beijing to teach the first half of the course Statistical Analysis of Neuroimaging data. The course was well received by both the Danish and Chinese students. The AIM group will continue to be involved in the SAN course, which will be offered on an annual basis at the SDC campus in Beijing.

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FACTS

Selected research projects:

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 hearing signers.

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.

NEUROINFORMATICS

by Kim Mouridsen

Reliable estimation of hemodynamic markers including capillary transit time heterogeneity

The regional availability of oxygen in brain tissue is traditionally inferred from the magnitude of cerebral blood flow (CBF) and the concentration of oxygen in arterial blood. Measurements of CBF are therefore widely used in the localization of neuronal response to stimulation and in the evaluation of patients suspected of acute ischemic stroke or flow-limiting carotid stenosis. It was recently demonstrated that capillary transit time heterogeneity (CTH) limits the maximum oxygen extraction (OEF^{max}) that can be achieved for a given CBF. Here we present a statistical approach for determining CTH, mean transit time (MTT), OEF^{max}, and CBF using dynamic susceptibility contrast (DSC) MRI.

In the Neuroinformatics group we have developed a statistical technique based on expectation maximazation estimation in a Bayesian model for estimating traditional hemodynamic parameters as well as CTH and oxygen extraction capacity, based on bolus tracking imaging data such as PWI-MRI or contrast CT[1,2,8]. Figure 1 shows, in a digital phantom, that this technique estimates MTT with lower bias and variance than the traditional SVD and oSVD techniques even at low signal to noise ratio (SNR). Figure 2 shows that, analogously, CTH and OEF^{max} can be reliably estimated across a wide range of physiological conditions. Importantly, these estimates have also been demonstrated to be relatively insensitive to tracer delays between the site of AIF measurement and region of interest, which is a common concern in acute stroke imaging.

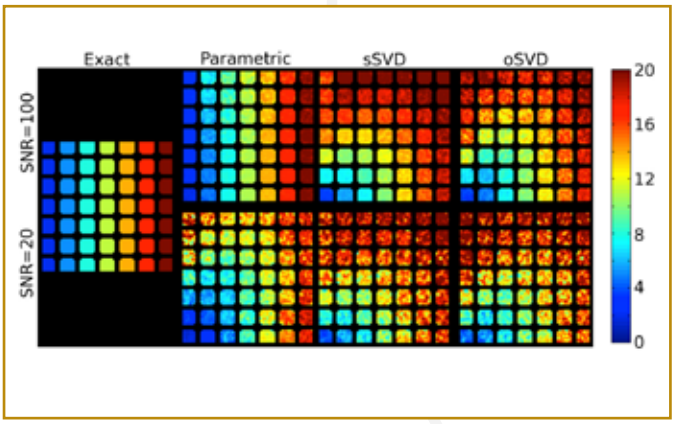

Figure 1

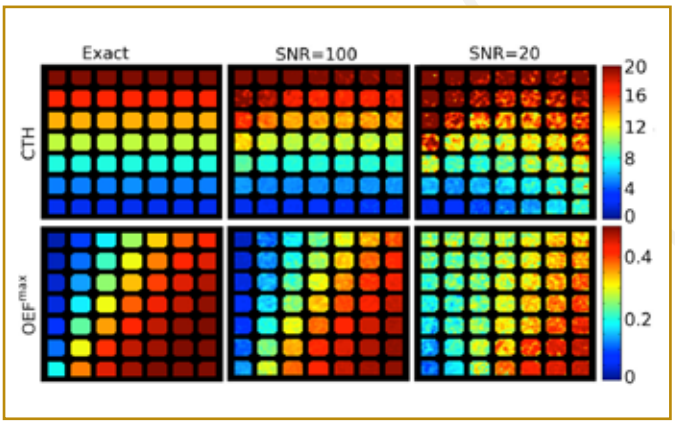

Figure 2

Figure 3 (next page) compares the new technology to traditional maps in seven acute stroke cases. In general, we note a better contrast between background, normo-perfused tissue, and areas of hypoperfusion with the proposed technique comparing it to SVD. Cases A, B and C exhibit scattered noise in SVD-based perfusion maps. In patient B we also note that the region of final infarct closely matches the area of low coefficient of variation (CoV=CTH/MTT), which signifies a region with a mismatch between average flow and the dispersion of microvascular transit times. In patient E the SVD methods display a large lesion, similar to case A. The clinical score for patient A was NIHSS=11 but for patient E only NIHSS=4, indicating less severe hypoperfusion in this case. Interestingly the new MTT map shows only a slight intensity elevation which is more consistent with the clinical finding than SVD, in these cases.

NEW FACE AT CFIN

Jens Kjærgaard Boldsen, PhD (Mathematics) was employed as a postdoc at CFIN July 2013. Jens did his PhD in abstract algebra, with focus on the development of an extensive computer system to calculate some abstract algebraic structures of which little is known. Besides his PhD in mathematics, Jens has a big interest in competitive cooperative algorithmic problem solving, and has, often with good outcome, participated in several different algorithm design competitions. At CFIN Jens will be developing and testing advanced algorithms and mathematical models to predict tissue infarction risk in acute stroke.

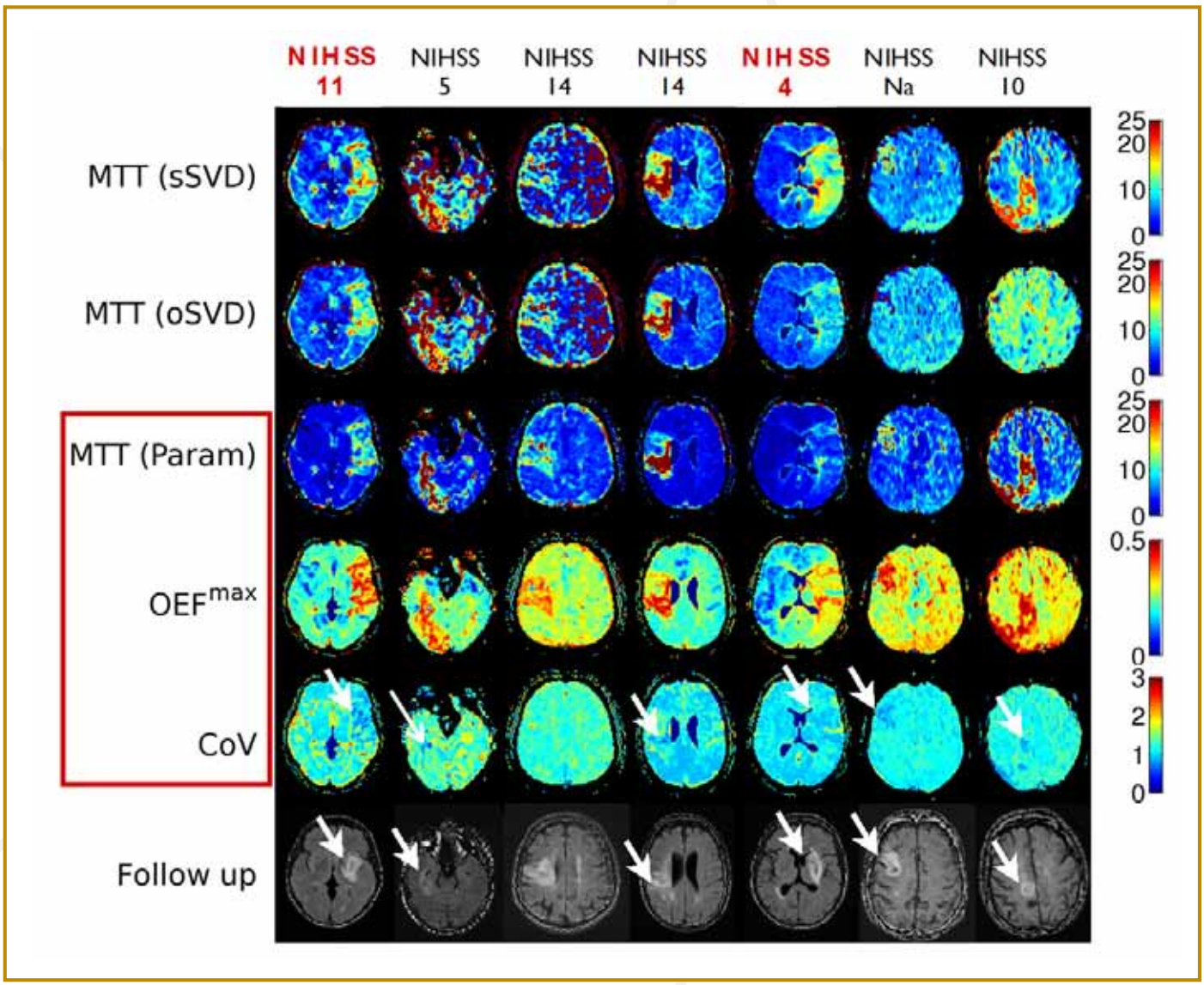

Figure 3

Critically patients F and G do not show any hypoperfusion on oSVD MTT, whereas lesions are clearly visible on parametric MTT, OEFmax and CTH. The lesion is visible on the sSVD MTT map for patient G, but less so in patient F. In both cases, the lesions observed in the parametric perfusion images are consistent with the 1-month follow-up FLAIR lesions.

Paper in Nature Medicine

The Neuroinformatics group has a long and successful collaboration with the Martinos Center for Biomedical Imaging at Massachusetts General Hosiptal/Harvard Medical School. Development of advanced tumor imaging methods is a key focus of this scientific collaboration. Working with Kyrre Emblem from Oslo University Hospital we developed an MR analysis procedure which has the potential to identify tumor patients who will benefit from antiangiogenic treatment, which aims to reduce the tumor's ability to stimulate the growth of new blood vessels[3]. Roughly only half of patients respond to this treatment, and in glioblastomas, which represent a highly aggressive and fast-growing brain tumor type, it is critical to quickly establish potential response to antigagiogenic treatment early on, such that other treatment approaches can be immediately initiated if the tumor fails to respond.

The technique is dubbed Vessel Architectural Imaging and uses properties of perfusion weighted MRI scans to estimate the size and types of vessels at high spatial resolution. Simulations have demonstrated that these signals are also affected by the amount of oxygen extracted in the capillaries. This gives an interesting link to the oxygen extraction capacity imaging methods currently being developed at MIND*Lab*. The Neuroinformatics group received funding from Lundbeck in 2013 to further explore tumor vasculature and oxygenation in relation to treatment effects.

nature medicine

Combat Stroke. A MIND*Lab* spin-out company

It is a long-standing priority in the Neuroinformatic group to facilitate the use of advanced imaging techniques to provide important information about tissue status in acute stroke. When a major brain artery is blocked, a region of irreversibly damaged tissue, the so-called core lesion, develops within minutes. Importantly, a region around this area will also suffer insufficient blood flow and cease to function, but if the blood supply is restored within a short period of time, it will regain normal function. This is the so-called ischemic penumbra. Patients with substantial regions of potentially salvageable tissue are ideal candidates for thrombolysis.

MRI is ideally suited for image guided assessment of the extent of the ischemic penumbra because the core lesion can be identified with diffusion weighted imaging and areas of hypoperfusion can be imaged with perfusion weighted MRI. However, image interpretation is time consuming and depends on the experience of the physician, prolonging the time to treatment.

We have developed a set of techniques, that are able to automatically identify the core lesion and hypoperfused region in less than one minute[4]. We have shown that the results are in close agreement with lesions defined by expert consensus. Figure 4 shows results from 167 patients from 5 different countries, and demonstrates high accuracy in identification of core lesion as well as potentially salvageable tissue. Across two clincial trials with a total of 228 patients we have shown an overall accuracy of 93% in penumbra assessment compared to expert opinion[5].

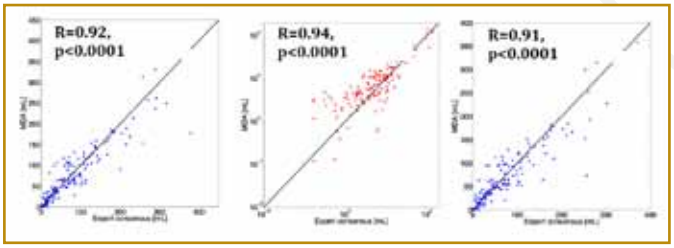

Figure 4

Kim Mouridsen and Mikkel Bo Hansen founded the spin-out company Combat Stroke in October 2013, and received over 3 million DKK in investment from SEED Capital and DTU Symbion based on the proprietary technology develped at CFIN / MI*NDLab*[6,7]. Combat Stroke will pursue partnerships with academic sites and industry for further development and dissemination of this technology.

Most recently the Combat Stroke technology has been selected for patient screening in a Danish multicenter clinical trial on Theophilline headed by Boris Modrau, Aalborg University Hospital.

Combat Stroke

SEED Capital

SEED Capital is the largest early stage venture fund in Denmark. Seed Capital invests in technology companies and medtech companies from Denmark and southern Sweden at the seed or even pre-seed stage. They invest in classic venture companies, meaning companies that as a minimum will provide an opportunity for a 10x return on investment. The company should have a highly innovative solution and a scalable business model for entering an attractive market with a number of identified paths to exit.

Advances in prediction of stroke

Stroke is a very serious disease, killing millions world-wide every year, and causing severe disabilities in even more. It is very important to offer patients fast treatment, but also that the treatment is based on as much information as possible. For stroke phycisians as well as medical stroke researchers, it is crucial to have as much knowledge on the evolution of tissue damage after a stroke in individual patients as possible.

Predictive algorithms are methods to predict whether brain tissue ends up being permanently damaged after acute stroke, based only on the acute MR scans. The basic idea is to use supervised learning techniques (such as logistic regression) to train models for prediction of stroke outcome. When using a predictive model in a patient, the result is usually a map that assigns a probability of infarct to each voxel. The resulting risk map represents the population based prediction of the stroke progression, which can then be used to select patients for different lines of treatment.

One way of improving such models is to divide patients into groups where each group is assigned its own model. This can be done in many different ways. To achieve the best division into groups we have used advanced iterative clustering algorithms to divide patients into groups based on how well models that are based on these groups predicts outcome in patients within and outside the group. This has resulted in division into groups that cannot be identified based on the patients' clinical data, and our results therefore suggests an added value of image-based stroke progression models in studying the complex processes of stroke evolution.

Another way of improving stroke progression models is to adjust and configure the neuroimaging variables used in the predictive models. That is: which MR scans and calculated images are most useful in prediction outcome? One new variable that has proved very useful for improving the models is the DWI-lesion distance. The DWI-lesion distance is the distance from a voxel to the closest voxel in the Diffusion Weighted Imaging (DWI) lesion, that is, the area in the brain already permanently infarcted at the acute state. Using this variable as a predictor we achieved an increase in AUC value (a measure of predictive performance) of about 10 percent. Figure 5 shows an example; the fourth image is the risk map obtained with traditional DWI and perfusion modalities whereas the fifth image shows the predicted outcome using also the DWI-lesion distance variable. Comparing these prediction maps to the final infarct (image 6) clearly shows that the DWI-lesion distance improves the prediction.

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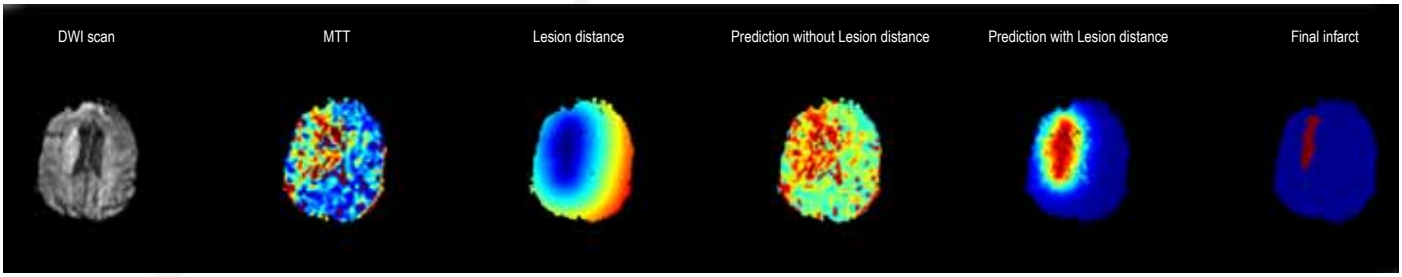

Figure 5

Perfusion MR in brain tumors

by Anna Tietze

Gliomas are common brain tumors, developing from the support cells of the central nervous system, the so-called glial cells. The most common glioma is a *glioblastoma multiforme*, an aggressive tumor that can affect all age groups, but is most frequently diagnosed in elderly people. Despite recent treatment advances, the prognosis for patients with *glioblastomas* is dismal with a median survival time of 14.6 months[1].

Hypoxia in tumors

Malignant tumors have a high demand for nutrients and oxygen to support their rapid growth and therefore develop numerous new vessels, a process termed *angiogenesis*. In spite of this vessel proliferation, most malignant tumors remain hypoxic, as the new vasculature is chaotic and unable to meet their metabolic needs. Tumor hypoxia is an important prognostic factor, as it lowers the therapeutic effectiveness of current radiation and chemotherapy strategies, and favours the survival of the most malignant cancer cells[2]. *Glioblastomas* are notorious for their excessive angiogenesis and hypoxia, leading to tissue death, so-called necrosis. This is illustrated in Figure 1, which shows a Magnetic Resonance (MR) image of a patient with a *glioblastoma*, where the bright parts represent viable tumor tissue (closed arrow) and the central dark areas necrosis (open arrow).

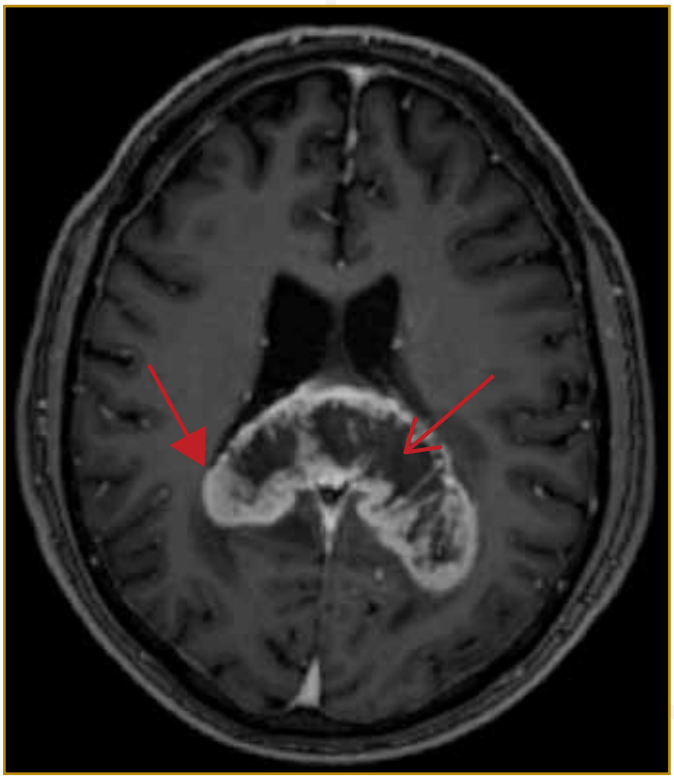

Figure 1
Sixty-year-old male with a *glioblastoma multiforme*, a highly aggressive brain tumor. The closed arrow indicates viable tumor tissue, while the open arrow shows necrotic tumor tissue.

Capillary Transit Time Heterogeneity (CTH) as a diagnostic and prognostic marker in gliomas

The recent physiological model of Capillary Transit Time Heterogeneity (CTH) which describes the effect of increased flow heterogeneity on the oxygen extraction in tissue, also helps us to understand the role of the microvasculature in hypoxic tumors[3,4]. Here, CTH is expected to be elevated due to abnormal capillary bed topology, arterio-venular shunts, and increased intracranial pressure, thereby limiting the availability of oxygen in tissue. The Neuroinformatics group therefore now developed a method that allows CTH to be determined by perfusion-weighted MR, and this new parameter can be acquired during routine clinical examinations[5].

We evaluated CTH in seventy-two glioma patients and found that maps of CTH helped to discriminate different glioma types. The diagnostic accuracy could be increased even more by combining CTH with maps of the traditional angiogenesis marker Cerebral Blood Volume (CBV). An example is given in Figure 2: (A) shows a T1-weighted post-contrast MR image of a patient with a *glioblastoma*, while (B) shows the corresponding CBV map. High CBV values (red, orange, and yellow colors) are seen in areas of ample angiogenesis. On (C) CTH maps, high values are noted in the surrounding tissue

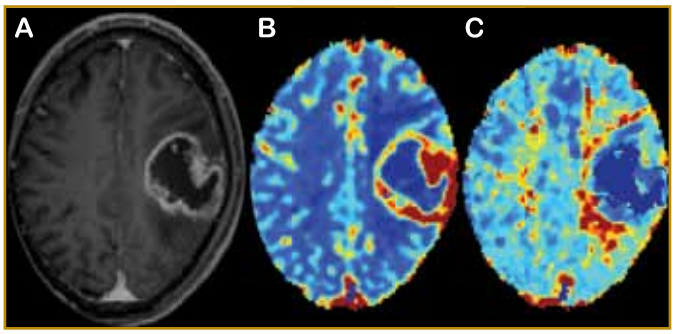

Figure 2
(A) T1-weighted post-contrast MR image of a seventy-one-year-old female with a *glioblastoma multiforme*. Corresponding (B) Cerebral Blood Volume (CBV) map shows high values in the enhancing tumor part with increased angiogenesis. (C) The map of Capillary Transit Time Heterogeneity (CTH) demonstrates high values in the surrounding brain tissue which may indicate early steps of tumor and growth angiogenesis.

possibly indicating early steps of angiogenesis that are not evident on (A) conventional images and (B) CBV maps.

The determination of the correct tumor type is clinically significant, as it is determining the choice of therapy. Surgery with removal of tumor tissue is not always feasible or practical, and reliable imaging biomarkers are therefore of great importance.

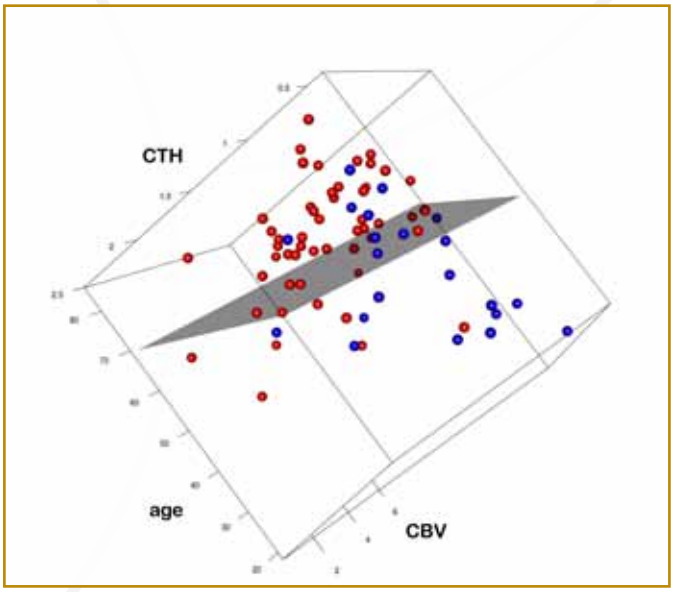

Figure 3
The combined value of patient's age, CTH, and CBV are used to prognosticate an adverse event after twelve months. The blue dots represent patients without and the red dots those with disease progression or death. The diagram helps to estimate the probability for the incidence of an adverse event: If a new data point lies far *above* the 50% probability plane, the occurrence is very likely, whereas lying *below* it is favorable.

We also found that CTH provided an excellent parameter when trying to predict the occurrence of an adverse event after twelve months, i.e. clinical deterioration, tumor growth on MR, or death. In Figure 3 average values of CTH and CBV, along with patient's age, are plotted for each of the seventy-two patients. Blue dots indicate patients who have lived for twelve months without any disease progression, whereas red dots represent patients who experienced deterioration or died from their tumor. The diagram helps us to estimate the probability of an adverse event for any new patient: If a new data point lies far *above* the grey 50% probability plane, the occurrence is very likely, whereas lying *below* it is more favorable.

Perspectives

As CTH estimates the hemodynamic properties of angiogenesis and, most importantly, the efficacy of oxygen extraction, it may be a valuable tool to monitor patients during treatment, particularly during anti-angiogenic therapy, which represent an emerging treatment approach. Moreover, prognostic biomarkers such as CTH may enable us to design more individualized treatment strategies in newly diagnosed patients in the future.

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CFIN interior, Aarhus University Hospital, Building 10G
Photo: Mikkel Blæsild Vuust

NEUROTRANSMISSION

PhD project: Impulse Control Disorders in Parkinson's Disease

by Mette Buhl Callesen, MSc Psychology, PhD

Dopaminergic medication administered to relieve motor symptoms in Parkinson's disease (PD) are now known to impact cognition and emotion in complex ways, including the impulse control disorders (ICDs) affecting up to 16 % of patients (Cools, 2006; Rowe et al., 2008; Cools et al., 2009; Poletti et al., 2010; Voon et al. 2007; Weintraub et al., 2010; Weintraub and Nirenberg, 2012). The aim of this PhD dissertation was to contribute to the understanding of ICDs in PD utilizing different methodologies.

ICDs define a category of behavioral disorders characterized by recurrent maladaptive and disinhibited behavior despite severe personal, relational and sometimes financial consequences. In Study 1 we systematically reviewed 98 empirical studies investigating ICDs in PD (Callesen et al., 2013a). Overall, the most commonly reported ICDs in PD were pathological gambling, hypersexuality, compulsive buying, and binge eating. In addition, the review implied that ICDs in PD are associated with certain risk factors, including a high dose of dopamine agonists, male gender, younger age, young age at PD onset, and longer disease duration, a personal or family history of ICDs or substance use disorders, smoking, symptoms of depression, and specific personality and genetic factors (Weintraub et al., 2012; Poletti et al., 2012; Voon et al., 2007; Joutsa et al., 2012).

Studies 2 and 3 were epidemiological surveys that evaluated 504 Danish patients with PD identified through the National Danish Patient Registry on symptoms of ICDs, depression, personality traits, and demographic and clinical variables including motor symptomatology (Callesen et al., 2014; Damholdt et al., 2014). Results revealed that 176 (35.9%) patients reported symptoms of ICDs at sometime during their disease (current symptoms in 73, 14.9%) - see Figure 1. Hereof, 114 (23.3%) reported multiple behavioral symptoms, and in agreement with earlier findings, patients with behavioral symptoms were significantly younger, were younger at PD onset, had longer disease duration, displayed more motor symptoms, and received higher doses of dopaminergic medication than patients without symptoms of ICDs. Furthermore, they reported significantly more depressive symptoms and scored significantly higher on the neuroticism personality trait and lower on both agreeableness and conscientiousness trait than patients without behavioral symptoms. ICDs in PD thus appear to share common personality features with depression in PD, including increased neuroticism and decreased conscientiousness. While these specific personality traits combined with low levels of extroversion predict depression in PD, only neuroticism act as a predictor for ICDs in PD. Instead, current smoking appeared to be the strongest predictor for ICDs in PD.

Study 4 was an experimental case study using [11C]raclopride PET imaging to assess dopaminergic neurotransmission during gambling in a single PD patient with concommitant pathological gambling, and four PD patients without pathological gambling (Callesen et al., 2013b). Despite almost similar gambling behaviour, we noted different dopaminergic responses to gambling stimuli when comparing the PD patient with pathological gambling to PD controls. While the patient with pathological gambling revealed a marked decrease in [11C]raclopride binding in the left ventral striatum upon gambling (see Figure 2), suggesting a gambling-evoked dopamine release, PD controls showed the opposite response, suggesting a gambling-induced decrease in dopamine occupancy.

In summary, our findings support the concept that ICDs which commonly occur among PD patients are treatment related. Furthermore our results suggest important clinical correlates of ICDs in PD that may allow early identification of patients at risk for developing such behavioral complications.

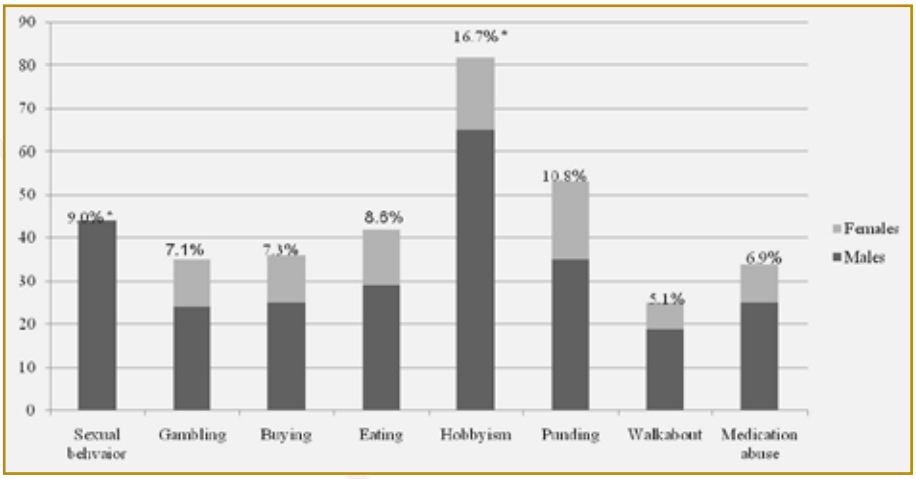

Figure 1
The overall frequencies of specific ICDs shown in %. Note: *significant difference at p<0.001 in gender distribution.

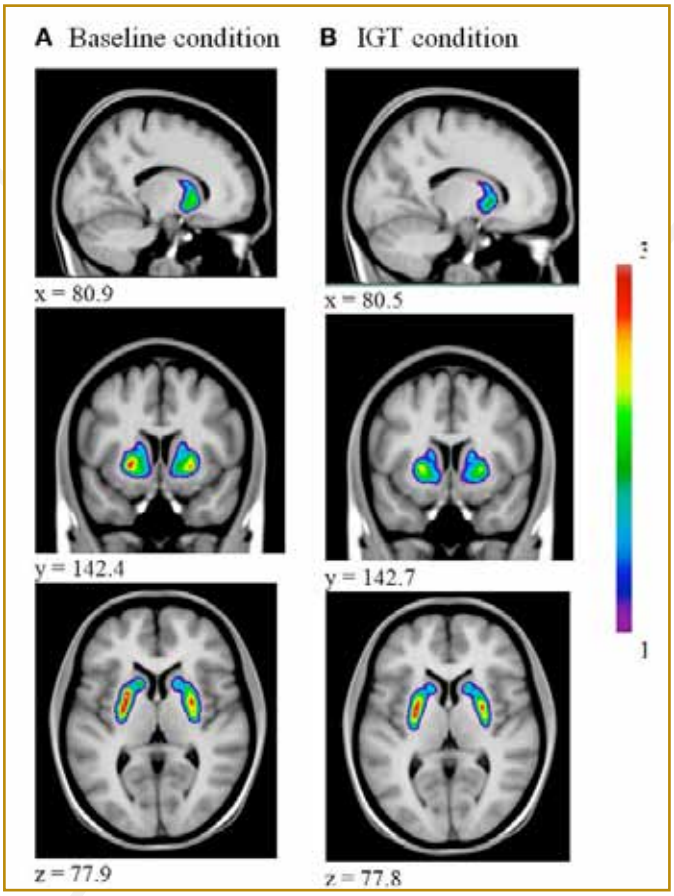

Figure 2
Decrease in striatal [11C]raclopride binding from baseline (A) to IGT performance (B).

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Mette Buhl Callesen discussing with opponent Professor Antoine Bechara, UCLA, during the PhD defense 25 November 2013.
Photo: Jørgen Scheel-Krüger

Mette Buhl Callesen (middle) with opponents Professor Valerie Voon, University of Cambridge and Professor Antoine Bechara, UCLA, after the PhD defense 25 November 2013.
Photo: Jørgen Scheel-Krüger

MIND*Lab*

David Brooks group

David J. Brooks MD DSc FRCP FMed Sci joins Aarhus University as Professor of Neurology, coming from the position as Hartnett Professor of Neurology in the Department of Medicine, Imperial College, London.

David Brooks is member of the KLIF Advisory Panel of the Austrian Science Foundation and has been a member of the Research Advisory Panels of the UK Parkinson's Disease Society, the German Dementia and Parkinson Networks, and INSERM. Member of the Biomedical Research Advisory Panel of Alzheimer in the UK. He was a member of the Scientific Advisory Board of the Michael J. Fox Foundation for Parkinson's Disease Research (2002-2006), UK Medical Research Council Neuroscience and Mental Health Board (2004-2007), UK Huntington's Disease Association, and was Chairman of the Scientific Issues Committee of the Movement Disorder Society (1998-2002) and a Director of the International Society of Cerebral Blood Flow and Metabolism (1993-1997). He was Chairman of the Council of Management of the UK Parkinson's Disease Society 1997-8.

David Brooks is Associate Editor of Brain and is on the Editorial Boards of the Journal of Parkinson's Disease, Parkinsonism and Related Disorders, Basal Ganglia, Journal of Neural Transmission, Synapse, Molecular Imaging and Biology, Journal of Neurotherapeutics, Clincal Neurology and Neurosurgery, and Current Trends in Neurology. He was on the Editorial Boards of the Journal of Neurology, Neurosurgery, and Psychiatry 1998-2004 and Movement Disorders 1994-1998.

In 2001, he was elected a Fellow of the Academy of Medical Science, UK. In 2002 he was invited to give the Stan Fahn Lecture at the International Congress of Movement Disorders, Miami, in 2003 the George Cotzias Lecture in Madrid, in 2004 the Charles E Wilson Lecture, the Psychobiology Institute, Jerusalem March 2004, in 2005 the Kuhl-Lassen lecture at the Society of Nuclear Medicine, Toronto, and in 2006 the Sprague lecture at UC Irvine, and in 2011 a Presidental Lecture at the World Congress of Parkinson's Disease, Shanghai.

David Brooks' research involves the use of positron emission tomography (PET) and magnetic resonance imaging (MRI) to diagnose and study the progression of Alzheimer's and Parkinson's disease and their validation of biomarkers therapeutic trials.

To date, he has published over 350 reports in peer reviewed journals, including Nature with an h index of 92. His research is supported by grants from the UK Medical Research Council, the Alzheimer's Research Trust, Parkinson's UK, the Michael J Fox Foundation, The Danish Medical Research Council, the Lundbeck Foundation, EU, and industry.

NEW FACE

Peter Parbo, MD, PhD student, started September 2013 working on the project *The relationship between beta-amyloid and inflammation in mild cognitive impairment – studied with PET* under the supervision of Professor David Brooks.

Early biomarkers of Alzheimer's disease (AD) may improve the diagnosis of early AD and prediction of disease progression. They are therefore important for the development of improved neuroprotective therapies and better targeted clinical trials for drug testing. Amnestic MCI patients are at risk of developing Alzheimer's disease. In this project we will investigate PET and MRI based imaging biomarkers in AD. The results will serve to validate the proposed biomarkers and shed light on the pathophysiological processes of AD.

The MRI based imaging is done in collaboration with Leif Østergaard, Simon Fristed Eskildsen et al.

The project is financed by The Danish Council for Independent Research and The Lundbeck Foundation.

NEW FACE

Ali Khalidan Vibholm, MD, PhD student, started March 2013 working on the project "*In vivo* detection of glutamate NMDA ion channel activation in paroxysmal neurological disorders with [18F]-GE179 PET" – under the supervision of Professor David Brooks.

Certain paroxysmal neurological disorders have abnormal activation of various ion channels.
One of these is the voltage-sensitive glutamate/NMDA ion channel, that also affects memory and learning ability. The channel is regulated by glutamate via a phencyclidine binding-site, which is only available when the channel is active.

GE Healthcare has developed the GE-179 tracer which can be used as a marker of glutamate NMDA ion channel activation. This tracer binds to the phencyclidine site of the open, active channels.

We hypothesise that [18F]-GE179 will non-invasively detect the open channel in the living brain with PET.

1. We will develop both a rat-model and a porcine-model of focal epilepsy by kindling one hippocampus with electrical stimulation. We will visualize side-differences in activity in the rat model by applying GE179 and using MicroPET/MR. In the porcine model we will measure regional [18F]GE-179 volume of distribution (Vd) either during spontaneous unilateral active seizure activity or seizures induced by electrical stimulation with Deep Brain Stimulation (DBS).

2. Patients with paroxysmal motor disorders including Parkinson's disease, will undergo a PET scan. In Aarhus we have a large DBS clinic for treating PD. We intend to study the effects of DBS on glutamate ion channel activity both in the locally stimulated brain nuclei and in more distant associated subcortical and cortical networks with [18F]GE-179 PET. During the scan, we will measure the focal uptake of [18F]-GE179, provided that it is possible to scan the patient during attack. 10 PD patients will be scanned withdrawn from medication and will have PET with stimulators switched off and then scanned a second time with the stimulators switched on when they are clinically responsive.

3. We will also study and scan 20 patients with focal temporal or frontal lobe epilepsy which is inadequately controlled on optimal anticonvulsant therapy, having repeated focal spiking on surface or depth EEG recordings. If patients can trigger episodes of absence or depersonalisation in the scanner by hyperventilation they will be scanned twice – once during seizure activity and again inter-ictally.

4. The functional effects of high frequency electrical stimulation of the brain by subthalamic and thalamic ion channel activation might also be considered in both the porcine model and in Parkinson's patients, having have had electrodes implanted therapeutic.

Thus, we hope to learn more about the role glutamate ion channels play, and we will be able to validate 18F-GE179 as a biomarker for the function of the ion channel.

The project is financed by The Lundbeck Foundation.

LUNDBECK FOUNDATION

A VBM study of the brain in patients with Klinefelter syndrome

by Anne Skakkebæk

Background

Klinefelter syndrome (KS)(47, XXY) affects 1 out of 660 men, making it the most common sex-chromosome aneuploidy in male[1]. KS is associated with verbal learning disabilities[2] and impairments of memory[3] and executive functions[4]. KS patients are vulnerable in terms of developing psychiatric diseases such as depression, anxiety, schizophrenia, attention deficit hyperactivity disorder, and autism spectrum diseases[5]. In the attempts to understand the neurobiology underlying the cognitive impairments and the increased risk of psychiatric disorders seen in KS, there has been a growing interest in brain imaging in KS. Structural brain imaging in patients with KS has demonstrated significant volumetric differences in multiple regional brain regions, but findings have been inconsistent[6-12].

An essential question in the KS scientific literature has been whether an association exists between the neuropsychological disabilities and the volumetric brain changes seen in KS. Furthermore, as KS is associated with hypergonadotropic hypogonadism, many of the KS patients start testosterone therapy around puberty or later in life when the syndrome is diagnosed, often with a substantial delay and a resulting long period of time exposed to hypogonadism. Sex hormones, and especially testosterone, may have both an 'organizational effect' and an´activational effect´ on neural tissue. This has raised the question whether testosterone therapy in KS patients could have a modulating effect on brain volumes.

VBM study (voxel based morphometry)

We studied brain volumes in a large sample of 65 KS patients and 65 age- and educational-matched in order to characterise global and regional brain volumes in patients with KS and to investigate the correlation between global and regional brain volumes and the neuropsychological phenotype seen in KS patients[13]. Magnetic resonance imaging (MRI) of the brain was conducted on a 3T General Electric Medical Systems (Milwaukee, WI, USA) MRI system and state-of-the-art VBM methods were used for data pre-processing.

Participants were administered a 3-hour standardised battery of neuropsychological test to assess the following cognitive domains: processing speed, working memory, visual construction and performance, visual memory and learning, verbal abilities, verbal memory and learning, executive functions, and response inhibition.

Results

With respect to global brain volumes, KS patients were found to have significantly smaller total brain volume (TBV), total grey matter volume (GMV) and total white matter volume (WMV) than controls, whereas no difference in CSF volume was found. No differences in TBV, GMV, WMV or CSF were found when compared to testosterone-treated KS (T-KS) and untreated KS (U-KS) patients. With respect to regional brain volumes, KS patients were found to have decreased GMV bilaterally in the insula, putamen, caudate, hippocampus, amygdala, temporal pole and frontal inferior orbita compared with to controls (see Figure 1). In addition, the right cerebellum and parahippocampal gyrus were smaller in KS patients (see Figure 1). KS patients had significantly larger volumes of voxels corresponding to the postcentral gyrus, parietal lobe and precuneus bilaterally compared to with controls (see Figure 1). No difference in regional GMV was observed when comparing untreated and treated KS patients. Multivariate classification analysis discriminated KS patients from controls with 96.9 % ($p<0.001$) accuracy (see Figure 2).

Multivariate regression analyses revealed no significant association between GMV differences and cognitive and psychological factors within the KS patients and controls, or the groups combined.

Conclusion and future aspects

Although the gene dosage effect of having an extra X-chromosome may lead to large-scale alterations in brain morphometry and extended cognitive disabilities, no simple correspondence links these measures. The lack of correlation between brain volume and neuropsychological test scores demonstrated within our large sample of KS patients indicates that the explanation of the neuropsychological deficits in KS may be related to the brain micro-architecture, rather than the mesoscopic anatomical brain level investigated by VBM. Our data indicate that the neuroanatomical etiology of the neuropsychological phenotype of KS is much more complicated than just simply differences in volumetric measurements. This complexity is mirrored in well-known gender difference in GMV. To understand the neuroanatomical etiologies of the neuropsychological phenotype seen in KS further studies are needed to investigate the brain in KS

patients by functional scans and to investigate the interaction between behavior, brain function and the possible relation to X-linked genes and changes in gene expression.

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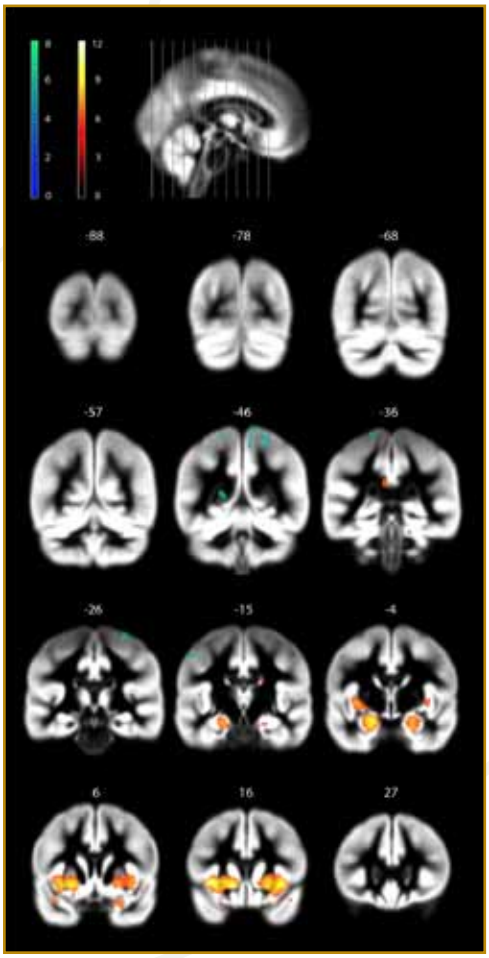

Figure 1

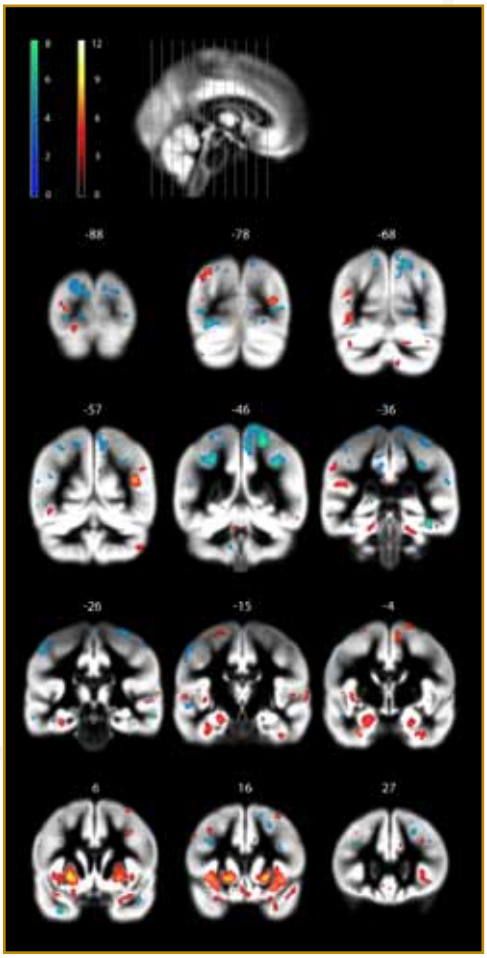

Figure 2

Figure 1
Coronal slice representation of grey matter differences between KS patients and controls. T-map displaying significant grey matter cluster differences between the KS patients and controls (p=0.05, FWE corrected) is overlaid brain template. Significant grey matter clusters were KS<controls is displayed in orange-red colors. Significant grey matter cluster were KS>controls is shown in green-blue colors (t (df), df=128)

Figure 2
Whole-brain representation of classification analysis (reproducible brain map (p<0.05FDR)). Increasing the signal locally in cold areas will make a particular brain scan more likely to be classified as a KS patient. Increasing the signal locally in warm areas will make a brain scan more likely to be classified as a control.

CFIN / MIND*Lab*

Magnetoencephalography at CFIN

by Yury Shtyrov

One of the newest and most rapidly developing brain imaging facilities at CFIN is the MEG (magnetoencephalography) laboratory. This complements the already available PET (positron emission tomography), fMRI (functional magnetic resonance imaging), EEG (electroencephalography) and TMS (transcranial magnetic stimulation) units at CFIN, which makes it one of the best equipped cognitive neuroimaging centres worldwide. Only the MEG technique (and the related EEG) can monitor brain activity with a high temporal resolution: the device installed at CFIN can trace neural activation with sub-millisecond precision. MEG does this by recording instantaneously miniscule magnetic fields generated by electric currents in neurons, the brain's main working cells. This technology is based on being able to pick up tiny magnetic fields using so-called SQUIDs (super-conductive quantum interference devices), sophisticated miniature superconductive sensors distributed around a person's head in a helmet-shaped device. In contrast with the older and more established EEG, this method does not require attaching large numbers of electrodes to the person's head, as the magnetic fields permeate through tissues and air and do not need a solid conductor between the head and the measuring device. This makes MEG recordings much more convenient and pleasant for experimental participants, as well as more time-efficient and hassle-free for researchers. Properties of neuromagnetic fields which allow them to spread from the brain without much interaction with other tissues of our body also allow for more direct estimates of activity sources in the brain. This enables us to see not only the timing but also the spatial location of neuronal activation in the brain with higher precision. So, MEG recordings can show in real time the complex interplay of various brain areas as they are processing the information coming to our central nervous system. The potential application of this technique ranges from investigating how the various complex functions (such as attention, memory, language or emotions) are organised and carried out by our brains, to exploring how this functionality may break apart in various brain deficits, leading to new insights into treating disorders of the brain.

Even though this device is the first of its kind in Denmark and Scandinavia, it is already actively used by very diverse research projects. These range from studies of patients with neurological conditions to investigations of speech and music perception, and are run in a cross-disciplinary effort by scientists from different AU departments as well as collaborators in Denmark, Scandinavia, and worldwide. To coordinate the MEG work, CFIN was in 2013 joined by Professor Yury Shtyrov, who has long-standing experience in MEG research. He and his colleagues have used MEG in a number of studies to delineate spatio-temporal patterns of brain activation in the process of language comprehension. They showed, for example, that the brain automatically recognises meaningful words almost instantly, within just tens of milliseconds, and that words of different types spark networks of activations in different brain parts reflecting the specific word's meaning.

The MEG device installed at CFIN is a masterpiece of state-of-the-art technology produced by Elekta Neuromag (Helsinki/Stockholm), an international leader in MEG technology. It incorporates 306 MEG sensors of different types making it capable of high resolution in all three dimensions; superficial, cortical surfaces are localised with highest precision. The technique is quiet and non-invasive: the recordings do not involve any currents or fields "injected" into the participant's body (we only record

Figure 1
MEG systems are designed to register brain activity in real time with maximum comfort for volunteers and efficiency for researchers.

Figure 2
Distribution of magnetic sensors around the subject's head ensures maximum coverage for registering neuromagnetic brain responses in a contact-free and comfortable fashion.

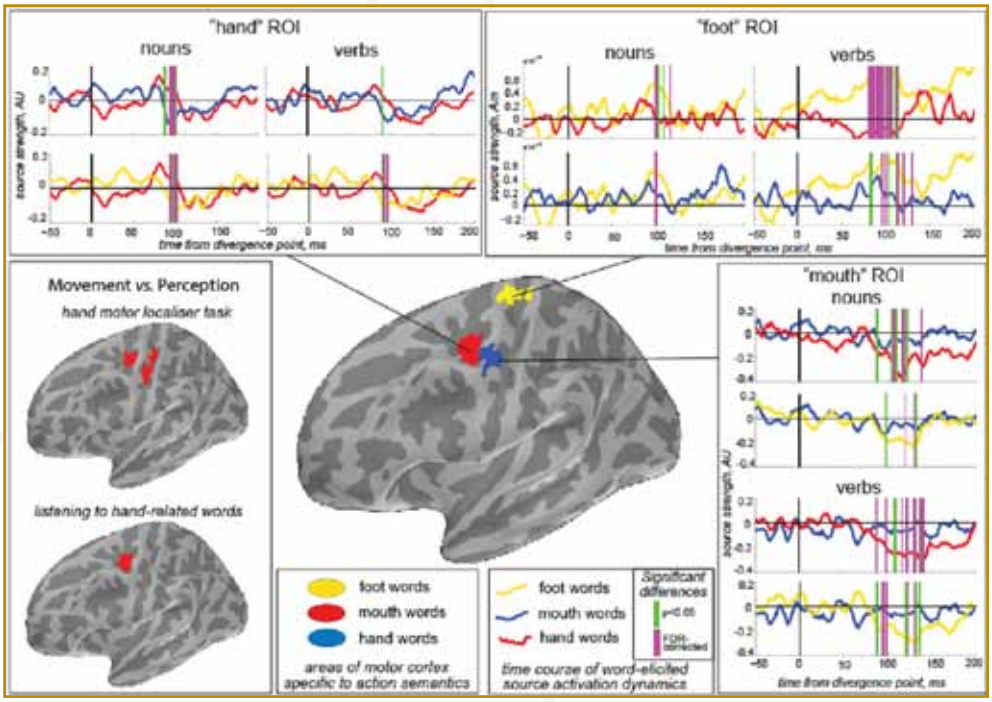

Figure 3
Using MEG, we have been able to document fine-grained spatio-temporal properties of brain networks involved in perception of words of different types. From Shtyrov et al: Automatic ultra-rapid activation and inhibition of cortical motor systems in spoken word comprehension. Proceedings of the National Academy of Sciences (PNAS), (2014)

what is generated by the brain itself), the operation is completely silent with participant seated in a comfortable chair in a spacious magnetically-shielded room. What's more, it is possible to combine MEG data with EEG and MRI recordings to optimise algorithms used in brain activity analysis. In combination, these methods can yield the accurate spatial-temporal image of brain activity currently possible. The new technology already generated a lot of excitement and new hopes in Aarhus neuroscience community. We are very much looking forward to see these expectations turn into new exciting discoveries in the years to come.

NEW FACE AT CFIN

In 2013, Aarhus University was joined by **Professor Yury Shtyrov**, who became the PI of the Magnetoencephalography Group at CFIN. With his basic training in Neurophysiology, PhD in Cognitive Neuroscience, and experience in fundamental, clinical and translational research, he has over 15 years of MEG experience in world-leading cognitive neuroscience centres. Prior to joining CFIN, he was working as a Senior Scientist and Head of MEG/EEG at the Medical Research Council in Cambridge and a Director of the Cognitive Brain Research Unit at Helsinki University.

His particular research focus is on the neurobiology of language function, where his special contribution has been in uncovering early and automatic stages of language processing and in detailing the time course of spoken language comprehension in the brain. This work has to a large extent contributed to a dramatic change in our understanding of how the brain analyses speech, which occurred in recent years. In this work, he shows how memory traces for linguistic elements in the brain can be probed using objective imaging tools, how they develop with learning, interact on different levels, as well as the interaction between the cognitive systems of language and attention. Most importantly, this work shows that these different processes occur rapidly and in parallel, something that was first met with disbelief but is now becoming generally accepted thanks to this and similar work. His most current work is focussed of applying this knowledge for better understanding of such neurocognitive conditions as dementia, aphasia, autism etc. He has dozens of international peer-reviewed publications including titles such as PNAS, Journal of Neuroscience, Nature Communications, Cerebral Cortex, Progress in Neurobiology, etc.

Hedonia: TrygFonden Research Group

2013

by Morten L. Kringelbach

The main research goal of Hedonia: TrygFonden Research Group is to understand pleasure in the human brain. 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.

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[1], sex[2,3] and social interactions[4,5], which are central to survival, but we are also interested in higher order pleasures such as music and art[6,7] which have strong links to *eudaimonia*: the meaningful and engaging life[8].

Infants are a focus of our research and especially how their sounds, looks and smells strongly influence the adult brain[4,9]. Understanding this special relationship is not only exciting but may also help to shape the way we can intervene when things go awry, e.g. in post-natal depression[10].

Another main focus is understanding and modelling how pleasure systems are fundamental in the dynamic allocation of brain resources[11]. 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[12]. We are also building computational models that allow us further probe and understand the human brain in health and disease[13].

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.

In 2013, my research group published 11 papers. One of these papers was published in PNAS as part of a collaboration with Professor Hans Lou[14]. Using MEG, we were able to show that there are altered paralimbic interactions in behavioural addiction (for more details see the following article by Kristine Rømer Thomsen). Kristine has handed in her doctoral thesis and has started a new project generously funded by Ludomani Fonden on further understanding the brain mechanisms underlying gambling addiction.

Some of our other papers continued to probe the brain mechanisms underlying the parental-infant relationship[15,16], in particular with reference to the role of the orbitofrontal cortex. We wrote a large review summarizing the findings from this exciting and important field[4]. All of us have parents and the parent-infant relationship is the most important template for our social interactions. Without this crucial early caregiving the human species would not survive. Much pleasure is to be found in this relationship but equally problems in this relationship (e.g. driven by post-natal depression) can have very serious ramifications in terms of our later overall mental health. Given this, it is perhaps surprising how little we know about how the brain changes with parenthood.

However, we will hopefully soon know more as the European Research Council (ERC) has awarded 2 million Euros for my new project "The plasticity of parental caregiving: characterizing the brain mechanisms underlying normal and disrupted development of parenting". This five-year project will commence 2014 and aims to study the longitudinal and cross-sectional effects of parenthood using behavioural, brain imaging and whole-brain computational methods.

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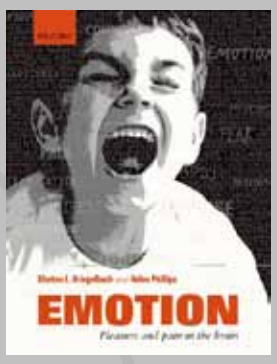

Over the last couple of years Helen Phillips and I have been writing a new textbook, *Emotion. Pleasure and pain in the brain* (published in 2014 by Oxford University Press), which aims provide an overview of the field of emotion research. It has been a real pleasure writing with Helen who has a doctorate in neuroscience but has devoted herself to science journalism and has written many articles for New Scientist over the years.

Emotions are often seen as an intrinsic part of what makes us human; they underpin how we feel about ourselves, and our interactions with others. New discoveries continue to reveal more about how emotion translates into brain activity - what is actually happening in our brains to make us 'feel' the way we do. They are also illuminating our understanding of dysfunctional emotions - the emotional basis of addiction, or the maladaptive emotional behaviors that characterize our difficult, and sometimes pathological, relationship with food.

The book presents the fundamental principles of the neural mechanisms underlying emotional processing, and reviews our current scientific understanding of pleasure and emotion. The book takes the reader from everyday conceptions of pleasure and emotion through to the latest insights into the nature and functions of emotions at the interface of psychology and neuroscience, before exploring topics such as the nature of subjective experience and future possibilities including emotions in silico.

Throughout, the book focuses on the principles of reward systems in the brain and its links with mainstream psychology, helping the reader to understand the function and nature of emotion and pleasure, and its relevance to the rest of psychology. In addition, it also offers a clear understanding of fundamental topics such as the social emotions, individual emotions and the role of emotion and pleasure in decision making.

The book also encourages the reader to achieve a better understanding of emotional disorders, which are central to clinical psychology and the treatment of a range of psychiatric disorders. We hope that the book will be interesting for any student wanting a clear, contemporary introduction to this complex yet fascinating subject.

FACTS

Hedonia TrygFonden Research Group:

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Peter Whybrow

Selected ongoing research projects::

- Berridge K.C. & Kringelbach M.L. Neuroscience of affect: Brain mechanisms of pleasure and displeasure.
- Witek M.A.G., Clarke E., Wallentin M., Kringelbach M.L. & Vuust P. Syncopation, body-movement and pleasure in Groove Music. PLoS ONE, in press.
- Boccard SGJ, FitzGerald JJ, Pereira EAC, Moir L, Van Hartevelt T.J, Kringelbach M.L., Green AL, Aziz TZ Targeting the Affective Component of Chronic Pain: A Case Series of Deep Brain Stimulation of the Anterior Cingulate Cortex.
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- Van Hartevelt, T.J., Cabral J., Deco G., Møller A., Green A.L., Aziz T.Z. & Kringelbach M.L. Neural plasticity in human brain connectivity: the effects of long term deep brain stimulation of the subthalamic nucleus in Parkinson's Disease
- Cabral J., Kringelbach M.L. & Deco G. Understanding network dynamics underlying brain activity during rest.
- Nakagawa T.T., Luckhoo H., Woolrich M.W., Joensson M., Mohseni H., Kringelbach M.L., Jirsa V., Deco G. How delays matter in an oscillatory whole-brain spiking-neuron model for MEG rhythms at rest.
- Mohseni H.R., Kringelbach M.L., Woolrich M.W., Baker A., Aziz T.Z. & Probert-Smith P. Non-Gaussian probabilistic MEG source localisation based on kernel density estimation.
- Cabral J., Luckhoo H., Woolrich M.W., Joensson M., Mohseni H.R., Baker A., Kringelbach M.L., Deco G. Exploring mechanisms of spontaneous MEG functional connectivity: How delayed network interactions lead to structured amplitude envelopes of band-pass filtered oscillations.
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- Parsons C.E, Stark E.A., Young K.S., Stein A. & Kringelbach M.L. Understanding the human parental brain: a critical role of the orbitofrontal cortex.

TrygFonden

Hedonia: TrygFonden Research Group

Behavioral addiction

by Kristine Rømer Thomsen

Until recently, the diagnosis of addiction was limited to the use of substances. However, due to a growing body of evidence showing overlap in clinical symptoms and underlying neurobiology between drug addiction and pathological gambling, excessive gambling behavior has been classified as an addictive disorder in the newly released DSM-V[1].

Like drug addicts, pathological gamblers struggle with symptoms such as craving, withdrawal and tolerance, and often gamble to avoid negative feelings. On a neural level, increasing evidence supports shared impairments in the mesolimbic reward circuitry underlying phenomena such as gambling urges and cocaine cravings[2-4].

Another shared problem is impairments in decision-making processes, including self-control and self-awareness, and parallel changes in the functional anatomy of prefrontal-, anterior cingulate- and insular cortices[5,6]. Similar to drug addicts, pathological gamblers are unable to cut back or stop, and hence continue their abuse despite its detrimental consequences.

We recently provided new support for the crucial role of impaired self-control in behavioral addiction in an MEG study of pathological gamblers and healthy controls[7]. We hypothesized that pathological gamblers are characterized by impaired self-control, similar to drug addicts, and accompanying dysfunctions in a paralimbic network related to self-awareness and self-control, including the medial prefrontal part of the anterior cingulate cortex (ACC) and medial parietal part of the posterior cingulate cortex (PCC). During MEG scanning participants performed a stop-signal task[8] (a widely used measure of self-control) and rested for 5 minutes. By including gamblers with and without previous drug abuse we were able to account for possible toxic effects of drugs.

Results confirmed our hypotheses. Compared to controls, pathological gamblers had lower self-control, which was independent of previous drug abuse. This is in line with findings from studies of drug addiction[9], but to our kowledge this is the first evidence of deficient self-control in gamblers using a stop-signal task.

MEG data revealed abnormal gamma synchronization between ACC and PCC during rest in pathological gamblers (see Figure 1). In controls we found an expected decrease in gamma synchronization during task performance compared with rest. Importantly, pathological gamblers failed to show a similar decrease in gamma synchronization. The decrease in synchronization from rest to an active task in controls fits well with the literature supporting the default mode theory[10]. Studies have consistently shown that activity in main regions of the default mode network (which overlaps largely with the described paralimbic network) decreases during extrinsic cognitive tasks compared with rest[11]. The lack of de-synchronization from rest to task, combined with the significantly lower synchronization during rest, shows that this network is indeed impaired in pathological gamblers.

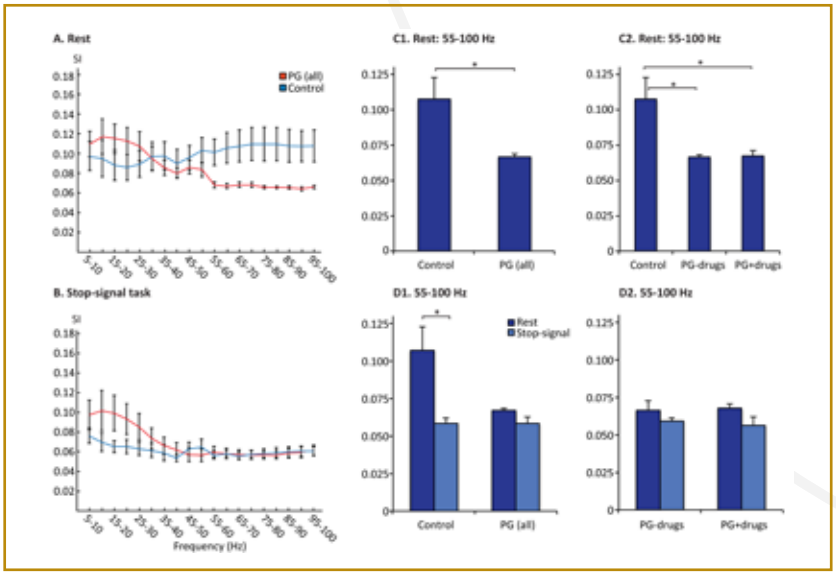

Figure 1
Abnormal gamma synchronization between ACC and PCC in pathological gamblers during rest.
(A,B) During rest pathological gamblers had lower synchronization than controls in the high gamma band, which was not the case during the stop-signal task. (C1,C2) Comparing levels of gamma synchronization during rest showed that pathological gamblers had lower levels compared with controls, which was independet of previous stimulant abuse. (D1,D2) Controls had lower gamma synchronization during task performance compared to rest, in line with previous findings[12,13]. Importantly, pathological gamblers failed to show a similar decrease in gamma synchronization from rest to task performance.

Another promising theory of drug addiction is the incentive sensitization theory[14], which has received support in animal and human studies[15]. So far the model has not been tested directly in behavioral addictions like pathological gambling. However, due to the described overlap in symptoms and underlying neurobiology between pathological gambling and drug addiction, the model holds promise in terms of improving our understanding of behavioral addictions like pathological gambling.

The model makes several testable predictions including: (a) gambling behavior is characterized by excessive levels of 'wanting' (i.e. craving) for the next gamble, which is independent of 'liking' (i.e. hedonic impact); (b) mesocorticolimbic systems react more powerfully to cues related to gambling, compared to cues related to other types of rewards, by eliciting greater neural and psychological responses of incentive salience attribution.

We are currently setting up a combined MEG and DTI study to test these predictions, using behavioral measures that tap into and segregate 'wanting' and 'liking' of gambling- and other cues. These studies can help inform us on whether incentive sensitization models (also) apply to behavioral addictions like pathological gambling.

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NEW GROUP MEMBER IN HEDONIA

Eloise Stark is a Research Assistant in Hedonia: TrygFonden Research Group, as part of the Scars of War Foundation based at The Queen's College in Oxford. She completed her undergraduate degree in Experimental Psychology at the University of Oxford in 2013.
Her current project involves working on a quantitative meta-analysis of functional neuroimaging studies of post-traumatic stress disorder (PTSD). This research aims to synthesise the large body of extant work in this field, in order to explore important functional changes in the brains of adults who have been exposed to trauma. This has the potential to guide the field towards refinement of neuroanatomical theories of PTSD, and direct future neuroimaging research in this area. In October 2014, Eloise will begin studying for a DPhil in Psychiatry with the Hedonia: TrygFonden Research Group, exploring experimental techniques for improving parent-infant interaction in the context of cleft lip and other craniofacial deformities.

MUSIC IN THE BRAIN

by Peter Vuust

The study of how music and musical training affects brain function and structure has recently established itself as an important and burgeoning topic within cognitive neuroscience. This success is partly due to music's remarkable ability to engage a wide range of brain areas and networks; some of these specialized for other purposes than music. Music perception and performance involves auditory processing, motor representations, and networks for emotion, visual perception, and mental imagery. Moreover, the study of how musicians' brains evolve through daily training is an effective way of gaining insight into the brain's remarkable potential for change during development and training.

The Music In the Brain group (MIB) is an interdisciplinary research group aiming at addressing the dual questions of how music is processed in the brain music and how this can inform our understanding of the principles of the brain processing. Situated uniquely between the musical excellence at Royal Academy of Music, Aarhus/Aalborg and the outstanding neuroscientific facilities at CFIN, MIB combines neuroscientific, musicological and psychological research in 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.

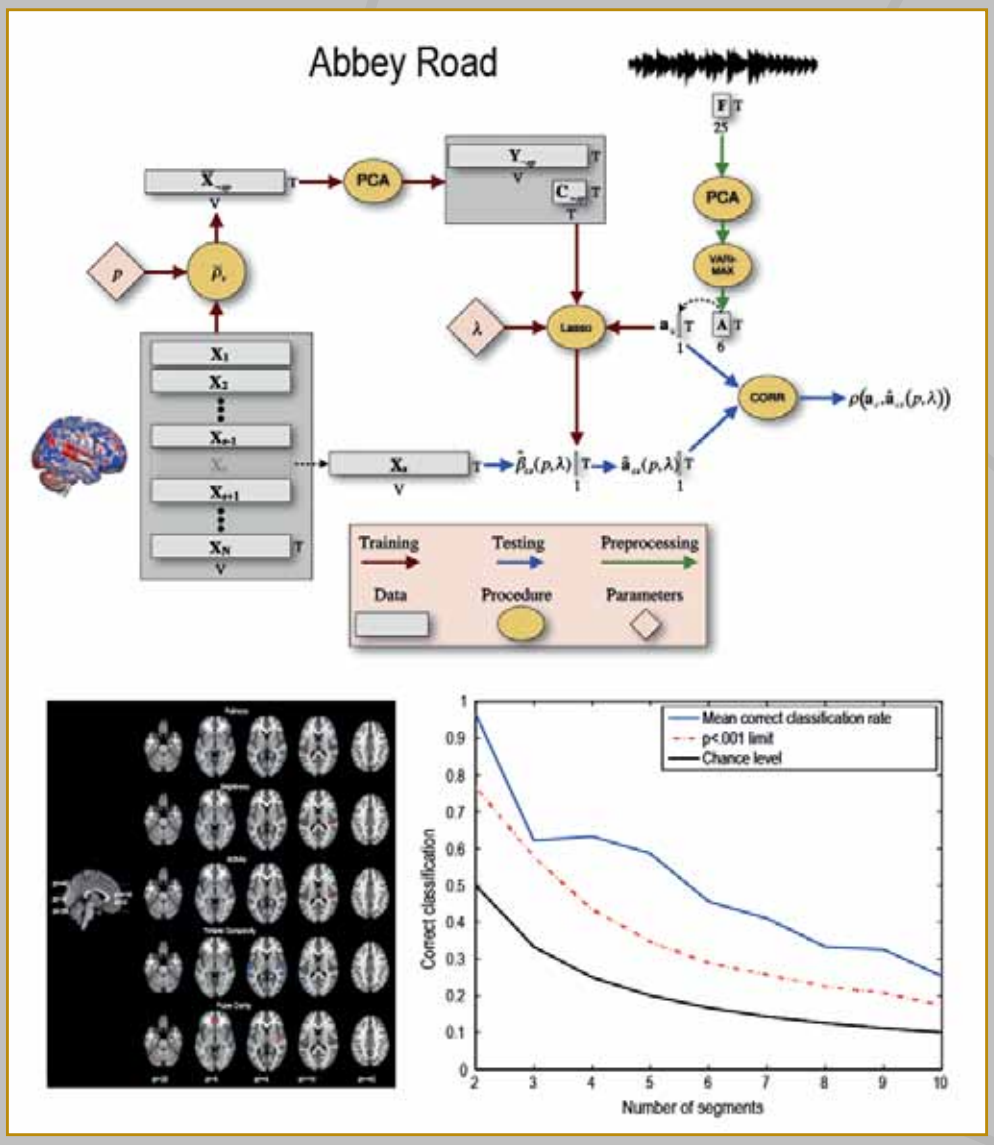

Figure 1
Continuous scanning and neural decoding. The main acoustic features (fullness, brightness, activity, timbral complexity, and pulse clarity) were extracted using the MIR Toolbox (D7) from the 16 minutes long medley from the B-side of "Abbey Road" by the Beatles[11]. The figure describes the process of correlating this with brain imaging data from participants listening to the songs (bottom left). Machine learning was used to train the algorithm on recognising the brain components related to these temporal acoustic features and subsequent testing showed that the mean correct classification rate was near 100% when dividing the song into two segments and was still above 50% with 6 segments (left panel on the bottom)[10].

In addition to studies of musical expertise[1,2] and on music and language[3] the study of musical rhythm has been a strong focus for the MIB group. In 2013 Maria Witek defended her PhD thesis on musical rhythm, done in collaboration between the MIB group and Eric Clarke and Morten Kringelbach at Oxford University. She used perceptual experiments, computational modelling, rating surveys, neuroimaging, and motion-capture recordings to study the relationship between body-movement, pleasure, and rhythm sequences ("groove") in music. She found that syncopation[4-6], which is one of the basic tools in creating interesting musical rhythms, relates in inverted U shaped ways to the subjects desire to move and feelings of pleasure, and used fMRI to investigate the neural activity in auditory motor and reward areas. This has instantly earned her an international reputation within the cognitive neuroscience of music, invitations to prominent conferences, and world-wide media attention. She is now doing her post doc with the music in the brain group.

The putative clinical applications of music are highly important to MIB[7,8]. In 2013, Line Gebauer defended her studies on emotional brain processing in participants with autism spectrum syndrome (ASD). Using functional magnetic resonance imaging, she investigated neural correlates of emotion recognition in music and language in high-functioning adults with ASD and neurotypical adults. Both groups engaged similar neural networks during processing of emotional music, and individuals with ASD rated emotional music comparable to the group of neurotypical individuals. However, in the ASD group, increased activity in response to happy, as compared to sad music was observed in dorsolateral prefrontal regions and in the rolandic operculum/insula, which may indicate a more cognitively demanding strategy for decoding happy music in individuals with ASD.

One of the highlights of 2013 was the publication of two papers in NeuroImage in collaboration with a Finnish research team led by professors Petri Toiviainen and Elvira Brattico[9,10]. These papers constitute a methodological breakthrough by demonstrating the potential of a novel fMRI method which allows continuous scanning while subjects listen to real music uninterruptedly and without distraction by any experimental task (see Figure 1). A comprehensive set of acoustic features is extracted from the stimuli and correlated with the fMRI time-series on a voxel-by-voxel basis, to determine where these features are processed. Unlike previous imaging studies that employed controlled settings with task requirements, it

FACTS

Group members, students and collaborators:

- Peter Vuust
- Bjørn Petersen
- Maria Witek
- Anders Dohn
- Line Gebauer
- Cecilie Møller
- Mads Hansen
- Niels Trusbak Haumann
- Kira Vibe Jespersen
- Niels Christian Hansen
- Mads Bjørn Christiansen
- Rebeka Bodak
- Risto Näätänen
- Petri Toiviainen
- Elvira Brattico
- Lauren Stewart
- Eus Van Sommeren
- Morten L. Kringelbach
- Marcus Pierce
- Krista Hyde
- Eduardo A. Garza Villarreal
- Ivana Konvalinka

Conferences, research visits:

- ICMPC in Thessaloniki, Greece
- Symposium on the Neurophysiology of Interval Timing, University of Monterey, Mexico
- ISMIR, Portugal
- Goldsmiths College, UK
- Helsinki University, Finland
- The Brain Prize Meeting, Sandbjerg, Denmark

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.

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

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

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

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

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

Vuust P, Kringelbach M. The pleasure of music.

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

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

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

Hansen NC, Pierce M, Vuust P. .Musical expectation mechanisms and statistical learning

is now possible to capture brain processing related to the full experience of music listening as it develops over time. Using this method in participants listening to a 16 minutes medley from the Beatles record "Abbey Road", Toiviainen et al[10] showed that it was possible to predict which part of the record a randomly selected participant was listening to by analyzing his brain data. This was done by comparing the participant's brain activity as measured by fMRI, to a model created by correlating the 14 other participants' fMRI with the acoustic properties of the medley. It clearly would have been easier to ask the participant which song he was listening to, but this experiment demonstrates how the novel method makes it possible to continuously follow the shifting focus of the brain activity, while we listen to music. These studies created a lot of media attention and were featured in among other places Wire Magazine.

The Abbey Road decoding paper was finalized while prof. Toiviainen was on a three months sabbatical with the MIB group in Aarhus. Other prominent researchers such as Professors Eckart Altenmüller, Katy Overy, Pascale Sandmann, Marcus Pearce, and Martin Norgaard paid visit to the MIB group in 2013, and attracted students from all faculties at AU to the high-quality MIB seminar program. In addition to other funding obtained by the MIB group in 2013, PhD student Niels Christian received the Ministry of Science, Technology and Innovations's "EliteForsk" travel scholarship for his project on statistical learning of music.

NEW FACE AT CFIN / MIB

Rebeka Bodak, PhD Mobility Fellow, Department of Clinical Medicine, Aarhus University.

Born a lover of music with a drive to contribute to people's health and well-being, and with an unshakable passion for learning, Rebeka completed a Bachelor of Arts (2001) followed by a Graduate Diploma in Music Therapy (2003) at The University of Queensland in Australia. This enthusiasm was taken forward into the working world in Australia (2004-2008) and the UK (2008-2013), where she was very fortunate to develop her clinical, teaching and research skills in neurorehabilitation, disorders of consciousness, and Huntington's disease. Having always been curious about the scientific underpinnings of music processing, Rebeka completed the MSc in Music, Mind and Brain (2012) at Goldsmiths, University of London, with the aim of becoming a better-informed clinician. During this time Rebeka explored whether playing musical sequences on a horizontally aligned instrument (chime bars) would bring about clinically significant improvement in chronic neglect during stroke recovery. She was so inspired by the MSc, that she felt propelled into pursuing a PhD.

Rebeka has been awarded a PhD Mobility Fellowship from Aarhus University which will be completed in collaboration with Goldsmiths, University of London. She will explore audio-motor coupling and its applications under the supervision of Peter Vuust at CFIN and Lauren Stewart at Goldsmiths (Music, Mind and Brain).

Behavioural and neuroimaging research on audio-motor coupling has key implications for the improvement of existing clinical interventions and the development of future treatment protocols aimed towards a diverse range of patient groups. A deeper understanding of audio-motor coupling also has the potential to inform music teaching and practising and contribute to the expanding scientific knowledge base on multimodal integration.

AARHUS UNIVERSITY

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UNIVERSITY OF LONDON

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FACTS

Public talks (Peter Vuust):

- *Hjernen og innovation.* Aalborg Kulturskole. 4 January 2013
- *I don´t mean a thing….?* Det Ny Senioruniversitet i Horsens, AOF Horsens/ Hedensted. 8 January 2013
- *Musik på recept!* Kulturregion Østjysk Vækstbånd. 17 January 2013
- *Musik og hjernen.* Scene 1, Møn. 27 January 2013
- *Musik og hjerne.* Lejre Musikskole. 29 January 2013
- *Hjernen og kreativitet.* Fotografisk Salon. 26 February 2013
- *Musik og hjerne.* Egå Gymnasium. 27 February 2013
- *Hjernens musikalske udvikling fra barn til voksen.* Midtfyns Gymnasium. 28 February 2013
- *Hvilken fysiologisk og funktionel viden om hjernen ligger til grund for de neuropsykologiske tests og udredninger neuro-pædagogerne arbejder ud fra i neuropædagogikken?* University College Lillebælt. 1 March 2013
- *Musik og hjerne.* Aabenraa Statsskole. 4 March 2013
- *Foredragskoncert: Musik og Hjerne.* Tågekammeret, Det Naturvidenskabelige Fakultet, Aarhus Universitet. 6 March 2013
- *Musik og hjernens musikalske udvikling.* "Akustikkens Dag". Dansk Akustisk Selskab. 7 March 2013
- *Musik og Hjerne.* Vestervig Kirkemusikskole. 9 March 2013
- *Musik og Hjernen.* Det Kongelige Danske Musikkonservatorium. 13 March 2013
- *Hjernen og innovation.* Statens Center for Kompetenceudvikling. 14 March 2013
- *Bliv klogere på hvad musikudførelse betyder for hjernen.* Lejre Musikskole. 23 April 2013
- *Stress og musikkens betydning.* Sølund, conference "Stress og psykisk sårbarhed". 23 April 2013
- *Musik på recept.* Aalborg Kommune. 30 April 2013
- *Music in the Brain.* XXVII Sandbjerg Symposium "Auditory and visual perception", Danish Society for Neuroscience. 6 May 2013
- *Hjernens musikalske udvikling fra barn til voksen.* Fusionstemadage ved Fuglekær Udviklingscenter. 7 May, 8 May, 13 May 2013
- *Musik om lederskab.* Inklusionsvejledere i vuggestuer, børnehaver og på ungdomsklubområde. 11 June 2013
- *Musikalsk ledelse og selvudvikling.* MacMann Berg konsulenter. 17 June 2013
- *Musik og Hjerne.* Silkeborg Højskole. 8 July 2013
- *Musikalsk Ledelse & Selvudvikling.* Ringsted musik og kulturskole. 13 August 2013
- *Musik og Hjerne.* Pædagoguddannelsen i Horsens. 15 August 2013
- *Musik og Hjerne.* Middelfart Musikskole. 21 August 2013
- *Plan your work - and work your plan.* Projekt Forkserspirer, Copenhagen University. 5 September 2013
- *Musik på Recept.* SoundFocus. 11 September 2013
- *Musik & Hjernen.* Vejgård Kirke. 19 September 2013
- *Musik & Hjerne.* Greve Gymnasium. 23 September 2013
- *Musik på Recept.* Middelfart MusikAftenskole. 24 September 2013
- *Den nyeste hjerneforskning og læring.* CPHBusiness Årskonference. 25 September 2013
- *Sanser og sundhed.* Sammenslutningen af Praktiserende Psykiatere. 26 October 2013
- *Foredragskoncert.* Ankestyrelsen. 31 October 2013
- *Hjerne, musik og bevægelse.* FOF Inspirationsforum. 1 November 2013
- *Musik og Hjerne.* Marselisborg Gymnasium. 4 November 2013
- *Musik og hjerne.* Frederiksberg Musikhøjkolens Aftenskole. 6 November 2013
- *Hvad gør (mangel på) musik ved vores børn?* Musikparlamentet, Debatmødet. 7 November 2013
- *It Don't Mean a Thing, . . . ?* Socialstyrelsen. 12 November 2013
- *Den kreative og lærende hjerne.* VIA, Silkeborg. 13 November 2013
- *Kreative veje til læring.* Nordfyns Kommune v. konferencen "Skole og Fritid". 13 November 2013
- *Musik og Hjernen.* Folkeuniversitetet. 26 November 2013
- *Formidling i forskning og musik.* The Music Center, Trustrup. 27 November 2013
- *Musik og Hjernen.* Folkeuniversitetet. 27 November 2013
- *Kvantitativ metode.* Det Jyske Musikkonservatorium. 4 December 2013
- *Det betyder musik og øvelse for os og vores hjerne.* Institut for Uddannelse og Pædagogik (DPU). 9 December 2013

MUSIC IN THE BRAIN

Neural processing of musical emotions in autism spectrum disorder

by Line Gebauer

Music elicits emotions, but not everybody experience emotions in the same way. Individuals with autism spectrum disorder (ASD) show difficulties with social and emotional cognition. Impairments in the recognition of emotions recognition are widely studied in ASD, and they have been associated with atypical brain activation during observation of emotional expressions in faces and speech. Whether these impairments and atypical brain responses generalize to other domains, such as emotional processing of music, is less clear. Using functional magnetic resonance imaging, we investigated neural correlates of the recognition of emotion in music in high-functioning adults with ASD and neurotypical (NT) adults.

Music and autism

Music is highly emotional; it communicates emotions and synchronizes emotions between people (Huron, 2006; Overy and Molnar-Szakacs, 2009). The social-emotional nature of music is often proposed as an argument for why music has sustained such prominence in human culture (Huron 2001). Processing of emotional music is found to engage similar brain regions as other emotional stimuli, including limbic and paralimbic brain areas, and regions related to reward processing (Koelsch, 2010; Zald and Zatorre, 2011) - see Figure 1. People experience and process emotional stimuli differently however. Individuals with ASD are often found to be impaired in recognizing, understanding and expressing emotions (Hobson, 2005). Despite somewhat conflicting findings, studies indicate that people with ASD have difficulties identifying emotions based on facial expressions (Baron-Cohen et al., 2000; Boucher and Lewis, 2006; Celani et al., 1999; Philip et al., 2010) see however (Jemel et al., 2006), on affective speech (Golan et al., 2007; Lindner and Rosen, 2006; Mazefsky and Oswald, 2007; Philip et al., 2010) see however (Jones et al., 2011), non-verbal vocal expressions (Heaton et al., 2012; Hobson, 1986), and based on body movements (Hadjikhani et al., 2009; Hubert et al., 2007; Philip et al., 2010). These difficulties in emotion recognition are associated with altered brain activations in people with ASD compared to neurotypical controls, i.e. with less activation in the fusiform gyrus and amygdala when viewing emotional faces (Ashwin et al., 2007; Corbett et al., 2009; Critchley et al., 2000; Schultz et al., 2000), and abnormal activation of superior temporal gyrus/sulcus and inferior frontal gyrus when listening to speech (Eigsti et al., 2012; Eyler et al., 2012; Gervais et al., 2004; Wang et al., 2006). It has previously been advocated that general social-emotional difficulties could render people with ASD less emotionally affected by music and less able to recognize emotions expressed in music (Huron, 2001; Levitin, 2006). Nonetheless, anecdotal reports dating back to Leo Kanner's first descriptions of autism (1943) seems to suggest quite the opposite, namely, that people with autism enjoy listening to music, become emotionally affected by music, and often are musically talented.

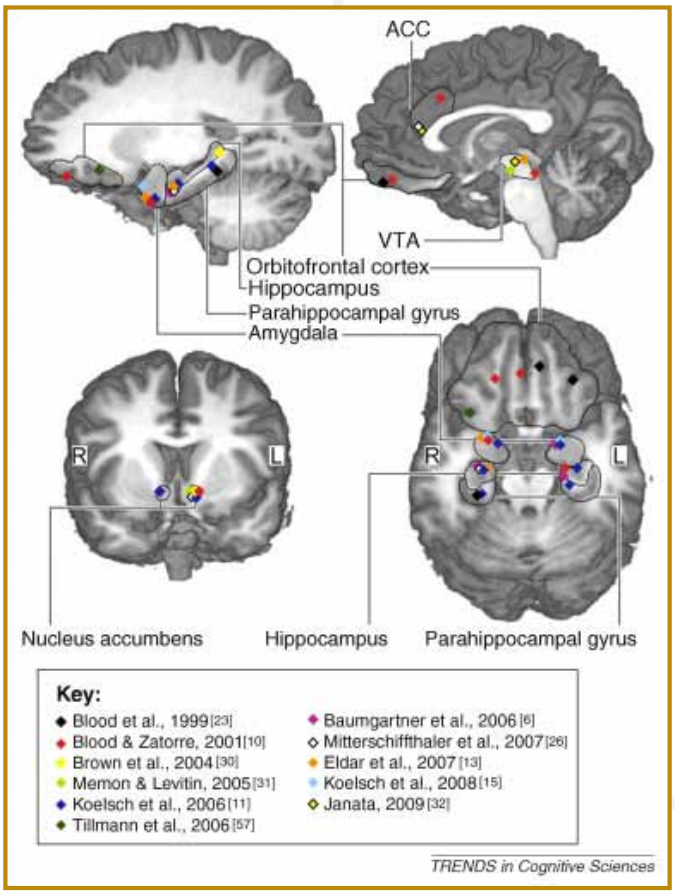

Figure 1
Reproduced from Koelsch, 2010 *Trends in Cognitive Sciences*
Review of brain regions implicated in processing of musical emotions.

Neural processing of emotional music in autism

Using fMRI, we investigated the neural activity in response to happy and sad music in a group of high-functioning adults with ASD (N = 19, 2 females) and a age-, gender- and IQ-matched NT control group (N = 20, 2 females). Our results demonstrate intact emotion recognition (Figure 2), and intact neural processing of emotional music in high-functioning adults with ASD compared to neurotypical adults. Across both ASD and

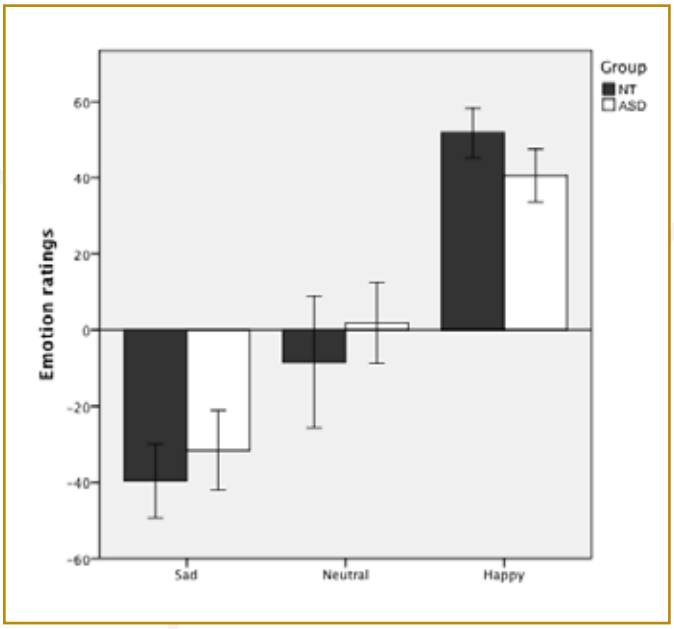

Figure 2
Mean emotion ratings (on a visual analog scale from -100 to 100) of sad, neutral and happy music excerpts. Error bars indicate 95% confidence intervals. No significant difference in emotion ratings for happy, sad or neutral music between the ASD and NT group.

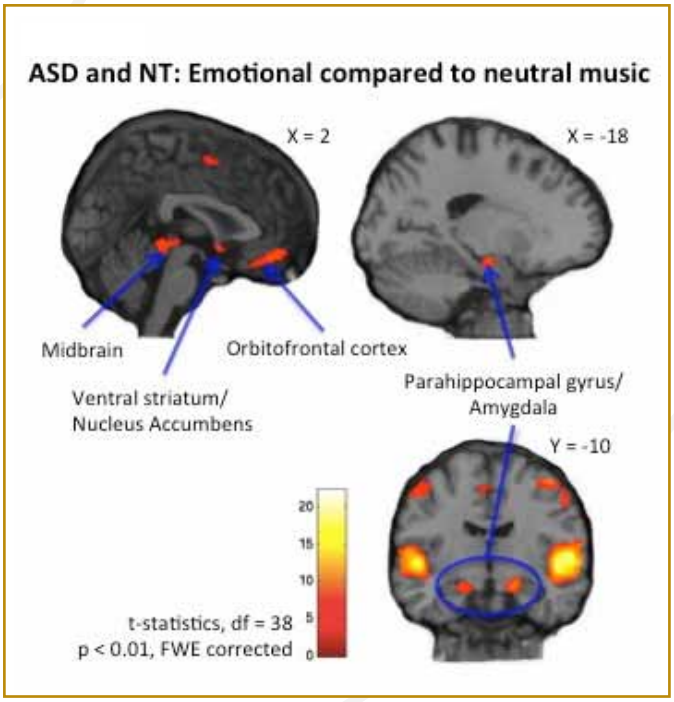

Figure 3

neurotypical individuals we found increased activation of limbic and paralimbic brain areas, including the parahippocampal gyrus and extending into amygdala, and of midbrain structures, including reward regions, medial orbitofrontal cortex, and ventral striatum (Figure 3). These regions are highly interconnected and have previously been identified as core regions for emotional processing of music (Koelsch 2010, see Figure 1), and other emotional stimuli (Adolphs 2002). Meanwhile, individuals with ASD displayed significantly greater activation in left dorsolateral prefrontal cortex (i.e. middle and superior frontal gyrus), and left rolandic operculum/insula, in response to happy contrasted with sad music, compared to NT individuals (Figure 4).

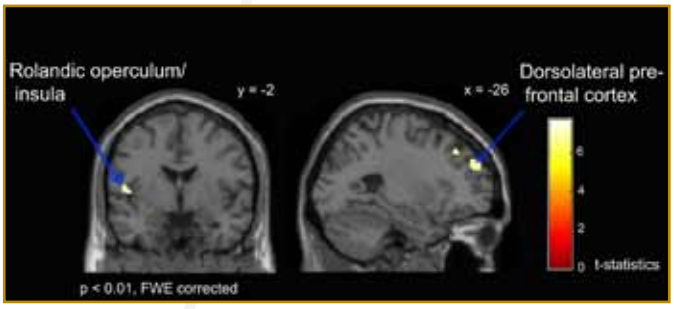

Figure 4
Increased activation in ASD in response to happy versus sad music

The difference in brain activation among the two groups when comparing responses to happy and sad music could be interpreted as an increased reliance on cognitive processing for emotion recognition of happy music in individuals with ASD. The dorsolateral prefrontal region is associated with higher cognitive functions, such as working memory and executive functions (du Boisgueheneuc et al., 2006). Meanwhile, the insula is critically involved in mediating cognitive and emotional processing, for instance in monitoring and regulating emotion (Gasquoine, 2014; Uddin and Menon, 2009), and the insula is previously found to be involved in emotional responses to music (Blood and Zatorre, 2001; Brown et al., 2004; Trost et al., 2012). Hence, the increased activation of the dorsolateral prefrontal cortex and insula found in this study is likely to be related to a more cognitively demanding emotion recognition strategy for happy music in the ASD group. This would be consistent with the findings of more analytical and cognitive strategies which have been suggested to govern face perception in individuals with ASD

(Jemel, Mottron, and Dawson 2006), and with findings of atypical verbal reporting of emotions (Bird et al., 2010; Heaton et al., 2012), including musical emotions in people with ASD (Allen et al., 2013).

In summary our study shows that individuals with ASD do not have deficits in emotion recognition from music in general, but in certain instances rely on different strategies for decoding emotions from music, which may result in subtle differences in brain processing.

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EliteForsk

At the annual EliteForsk event in Glyptoteket, the Minister for Higher Education and Science, Sofie Carsten Nielsen, presented 20 talented young PhD students with EliteForsk travel scholarships of DKK 300,000, to supplement their studies with stays at leading international universities within their respective fields. Among the recipients in February 2014 was CFIN researcher **Niels Christian Hansen** from the Music In the Brain Group (MIB).

Recipients of the EliteForsk Travel Scholarships 2014.
Niels Christian Hansen is seen in the back row on the right.
Photo: EliteForsk

Nina Kerting Iversen receives the Sapere Aude award.
Photo: EliteForsk

Also present at the EliteForsk event in Glyptoteket in Copenhagen was CFIN researcher **Nina Kerting Iversen** who was awarded one of The Danish Council for Independent Research's (DFF) Sapere Aude awards – as part of a talent development programme for the elite.

Read more at: www.eliteforsk.dk

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

In 2013 The Outreach Henry Prize was awarded to:
Arne Møller, Micah G. Allen and Henriette Blæsild Vuust.

MUSIC IN THE BRAIN

Syncopation, body-movement and pleasure in groove music

by Maria A. G. Witek

Moving to music is an essential human pleasure particularly related to musical groove. Structurally, music associated with groove is often characterised by rhythmic complexity in the form of syncopation, frequently observed in musical styles such as funk, hip-hop and electronic dance music. Structural complexity has been related to positive affect in music more broadly[1,2], but the function of syncopation in eliciting pleasure and body-movement in groove was, until recently, unknown.

Rhythmic entrainment, i.e. the process by which attention becomes coupled with another rhythmic stimulus[3], often overtly expressed through sensorimotor synchronisation[4], has been suggested to tap into affective mechanisms[5]. Yet, despite both pleasure[6,7] and sensorimotor synchronisation[8] being proposed as factors in music's evolutionary origin, few have studied the pleasure of sensorimotor synchronisation.

In a classic study, Berlyne[9] proposed that an inverted U-shaped curve reflects a general relationship between aesthetic appreciation and structural complexity in art. According to this relationship, increasing complexity correlates positively with liking, arousal and pleasure up to an optimal point, after which a further increase in complexity reverses the effect. The relationship between musical complexity and affect may also depend on the type of response associated with a genre. In groove, responses are largely rooted in sensorimotor synchronisation and dance[10,11]. Wanting to move is reported as the most consistently and robustly defined subjective experience in response to groove[12].

Syncopation is one of the most studied forms of rhythmic complexity in music[13-15]. It can be defined as a rhythmic event that violates listeners' metric expectations. Longuet-Higgins and Lee[13] proposed a computational index for calculating the strength of a syncopation, using a hierarchical model of metric salience. They define syncopation as a note on a metrically weak accent preceding a rest on a metrically strong accent, and their model computes the degree of syncopation based on the difference in metric weights between the note and the rest that constitute the syncopation.

Despite the ubiquity of syncopation in music associated with groove, its effects on affective and sensorimotor responses have remained largely unexplored. We investigated the relationship between syncopation and ratings of wanting to move and experienced pleasure, via an online survey[16], using a modified version of Longuet-Higgins and Lee's index of syncopation[13,17]. Participants heard funk drum-breaks with varying degrees of syncopation and rated the extent to which the drum-breaks made them want to move and how much pleasure they experienced. Participants were of both genders, from all over the world, e.g. Asia, Europe, North-America, Oceania and Africa, and aged between 17-63. A demographics questionnaire recorded years of musical training, enjoyment/frequency of dancing, and enjoyment/frequency of listening to groove music.

The results showed that medium degrees of syncopation elicited the highest ratings of desire to move and the most pleasure (see Figure 1). In other words, there was an inverted

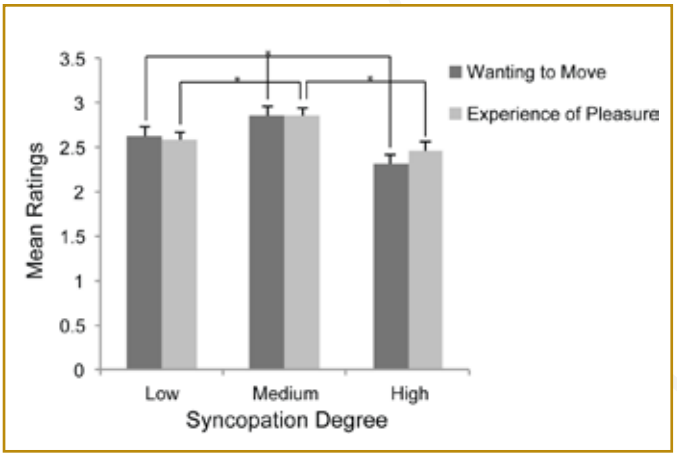

Figure 1
Effect of syncopation degree. Effect of 3-level parametric levels of syncopation degree – Low, Medium and High – on ratings of wanting to move and experience of pleasure. Error bars = standard error.
*Alpha adjusted $p < .005$.

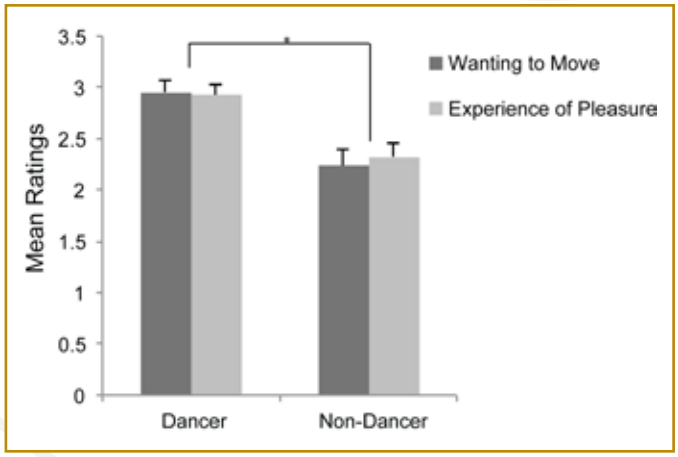

Figure 2
Effect of dancing experience. Effect of dancing experience on ratings of wanting to move and experience of pleasure.
Error bars = standard error. *$p < .01$.

U-shaped relationship between rhythmic complexity in groove, and both wanting to move and pleasure. Furthermore, it was found that those who frequently danced and liked dancing to music rated the drum-breaks as eliciting more desire to move and more pleasure than those who didn't (see Figure 2), but there was no effect of musical training or liking/frequency of listening to groove music.

Our study shows that not just liking and preference, but also motivation for overt action tendencies, such as sensorimotor synchronisation, is related to structural complexity in an inverted U-shaped way. In other words, Berlyne's theory of optimal perceptual stimulation in art[9] can be applied to models of affective engagements with music involving body-movement and dance.

Our results are of interest to researchers concerned with establishing the sparsely demonstrated link between entrainment and affect in music[5,10,18]. Although previous studies of groove have suggested that pleasure is involved, empirical evidence has been more consistent for sensorimotor synchronisation[10-12,19]. We show that, in groove, the rhythms that make people want to move also elicit feelings of pleasure and we add to the theory that emotions are grounded in the body[20] by showing that in groove, desire for body-movement is pleasurable. Furthermore, our findings indicate that affective responses to rhythmic entrainment are optimised when the music involves an intermediate degree of syncopation. In other words, entrainment feels good when there is some structural resistance against the regular pulse in the musical material[21]. This structural resistance could be the result of the violation of expectation that researchers often refer to when defining syncopation[13] and which is maximised at medium degrees of syncopation. With low degrees of syncopation, all or most metric expectations are confirmed, since there is little or no syncopation to violate them; and with high degrees of syncopation, there are only weak expectations to be violated, since the high degree of complexity disrupts metre perception and hence the generation of metric expectations. Medium degrees of syncopation, however, may provide just the right balance between sufficient rhythmic predictability for metre to be perceived and metrical expectations to occur, and sufficient complexity for those expectations to be violated and thus pleasure to be elicited[22].

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CNRU

by Morten Overgaard

Since 2007, CNRU has worked to build bridges between humanistic, psychological and neuroscientific perspectives on consciousness and related topics in cognitive neuroscience. In parallel, CNRU has worked to bridge experimental and theoretical "basic research" with clinical work, especially within neuropsychology, neurology and psychiatry. Whereas these ambitions necessitate the integration of knowledge from diverse and at times fragmented areas, CNRU is held together by the very ambition to integrate in and of itself, as well as by the goal to develop theoretical models of how mental phenomena relate to brain activity.

Interdisciplinary integrations

Visual consciousness

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

As one example from 2013, we have applied binocular rivalry in a MEG experiment to study conscious face perception. Multivariate analysis revealed that only early visual responses were able to predict the contents of consciousness (in the 120-320 msec range) within and between subjects. The work is the first to show that neural correlates of a particular conscious content is not only consistent over time, but also generalizes between individuals. At the same time, the experiment suggests that neural correlates of conscious vision overlap anatomically with areas normally associated with early visual processes rather than "higher order" or "metacognitive" processes.

In a rather different experiment, we set out to test what we named the "source misidentification hypothesis" - a hypothesis derived from research on unconscious vision and blindsight, according to which we may know about information around us without knowing how we have access to it (i.e. whether information is visual, auditory, tactile etc.). Using a multimodality paradigm and a statistical strategy designed to operationally test the hypothesis of non-equality, so that the usual rejection of the null-hypothesis admits equivalence, we were able to demonstrate that knowledge about perceptual modality, in fact, is a necessary precondition for knowledge about perceptual information.

Both experiments go beyond a mere "registration" of correlations between conscious content and particular neural or cognitive processes. They demonstrate particular features of conscious processing: that processes related to content can be distinguished from, and depend on, those related to knowledge of modality, and that the underlying

NEW FACE AT CFIN / CNRU

Mikkel Christoffer Vinding, MSc in Psychology, PhD student, started November 2012 under the supervision of Professor Morten Overgaard.

My project focuses on conscious intentions in motor-cognition. Focus is on phenomenological aspects of motor cognition and how various definitions of conscious intention are used, and can be used, in experimental cognitive neuroscience. This involves behavioural experiments and neurophysiological methods, primarily EEG/MEG. The second part of my work is to develop a conceptual framework for studying intention and free will scientifically, drawing upon literature from philosophy of mind, psychology and neuroscience. My aim is to make a common theoretical framework for linking science and philosophy of free will.

The project is part of the FKK project Phenomenal Consciousness and Cognitive Control lead by Morten Overgaard and conducted in collaboration with Mark Schram Christensen and Thor Grünbaum from University of Copenhagen.

neural processes are generalizable between subjects. We hope that this and similar future work will help us understand consciousness and its related functions better.

Intention and agency

Phenomenal consciousness enables us to enjoy the flavour and scent of good coffee and the thrill and excitement of off-piste skiing. But not only that, phenomenal consciousness also allows one to carefully deliberate about which house to buy, enables one to remove the splinter from underneath the nail or refrain from telling the spouse what one bought him or her as a birthday present. At least intuitively, being phenomenally conscious is in some fundamental way related to the ability to control one's mental processes and actions in particular ways.

It is a strong intuition both in science and common-sense that being conscious of something makes a cognitive difference for the subject. 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 be important to a subject's control of her own thinking and action at all.

Most of the "epiphenomenal" theories of subjective control and agency are at least to some degree based on the work of Benjamin Libet. In Libet's experimental work, participants performed self-paced actions and reported the time when they felt an "urge" to move, which was then compared to the readiness potential (RP) from motor regions in the brain and the actual movement. He repeatedly found that the RP preceded reported intention.

It is, however, far from obvious that all intentions, we have, can be measured like this. For instance, making decisions for the future is quite different from the kinds of "immediate" and fast-paced decisions made in Libet-style experiments. In 2013, we have found evidence that "distal intentions" (decisions for future movements) are behaviourally and electrophysiologically different from "proximal intentions" (for immediate actions). Thus, one cannot conclude from experiments studying proximal intentions only that

FACTS

Cognitive Neuroscience Research unit (CNRU)

http://www.cnru.dk/

Group members:

- Bochra Zareini
- Daniel Siboska
- Jonas Kristoffer Lindeløv
- Kristian Sandberg
- Lars Evald
- Lau Møller Andersen
- Mads Jensen
- Marc Schram Christensen
- Martin Dietz
- Mia Y. Dong
- Mikkel C. Vinding
- Morten Overgaard
- Rikke H. Overgaard
- Simon Hviid del Pin
- Thomas Alrik Sørensen

Collaborators (basic research)

- Patrick Haggard, University College London
- Geraint Rees, University College London
- Berit Brogaard, University of Missouri
- Axel Cleeremans, Universite Libre de Bruxelles
- Niko Busch, School of Mind and Brain, Berlin
- Jesper Mogensen, University of Copenhagen
- Søren Kyllingsbæk, University of Copenhagen
- Thor Grünbaum, University of Copenhagen

Collaborators (clinical research)

- Institute of Clinical Medicine (Neurology, Neurosurgery), Aarhus University
- 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

2010-2013: Danish Council for Independent Research/Humanities: Intentional Action, Attention to Objects, and Working Memory

consciousness is epiphenomenal. At the same time, we have found ways to study such distal intentions, even though they are not followed by an immediate movement, enabling us to learn more about how intentions work.

Clinical-basic research integrations

Assessment
As mentioned above, CNRU gives high priority to the use and application of basic research methods in clinical settings. As one example, methods to measure metacognition have long been discussed in cognitive neuroscience, and most researchers agree that "confidence ratings" (the subjective evaluation of one's own correctness in a task) involve metacognition. In schizophrenia research, it is widely believed, but never directly tested, that positive symptoms (hallucinations) express dysfunctional metacognitive functions rather than, say, dysfunctional perceptual functions.

In one experiment, we have tested the performance of schizophrenic patients with positive symptoms against healthy subjects in first-order perceptual tasks and higher-order metacognitive tasks based on the hypothesis that if such symptoms are in fact metacognitive in nature, patients should be expected to perform particularly bad at higher-order tasks.

In another experiment, we have investigated patients in coma, vegetative state and minimally conscious state looking at ERP data from different kinds of auditory stimulation. The three groups of patients are normally considered different in such a way that coma and VS patients are believed to be fully unconscious and have very few (if any) preserved cognitive functions. Minimally conscious patients are believed

NEW FACE AT CFIN / CNRU

Lau Møller Andersen, Bachelor in Philosophy and Linguistics, Aarhus University, Master of Science in Brain and Cognitive Science, Amsterdam University.

Being interested in the relations between mind and brain, I started studying philosophy, but I became increasingly frustrated by not being able to conduct experiments myself. Therefore, I went on to study at Amsterdam University, focusing on neuroimaging experiments using electro- and magnetoencephalography.

In the experiments that I am doing now, I try to unravel which neural correlates exist of visual experiences that differ in regards to the conscious content that subjects experience. For this purpose, I use MEG. A further goal is to investigate how the control that subjects have over tasks differs relative to the clearness by which they experience task-related stimuli.

The project is funded by a stipend from Aarhus University.

NEW FACE AT CFIN / CNRU

Mia Dong is a PhD student who started in January 2013. She has a background in Psychology and Cognitive Neuroscience from University College London and is now woking on the project *The measurement and neural correlates of human sense of agency*, supervised by Professor Morten Overgaard.

Her PhD project focuses on sense of agency, that is, the subjective experience that one is initiating, executing and controlling an intended action. The project intends to develop a standard measuring scale for sense of agency and to investigate the neural correlates of graded agency experience. Her project will expand the test battery important for examining the role of consciousness in sense of agency and the neural correlates of motor awareness. One potential future direction is that such brain networks could be used as biomarkers of consciousness of motor control in comatose and vegetative state patients.

The project is financed by The Danish Council for Independent Research.

to have comparably more intact cognitive functions and to be "more conscious". These "beliefs" are however motivated from observation of outer behaviour only although this in fact may be a rather poor guide to internal states. Our experiment's theoretical goal is to evaluate these matters, looking for preserved cognitive functions with new measures, and potentially to challenge the way in which the patients are categorized in the first place. Clinically, the experiment may provide us with predictors for positive outcome, where there currently are none

Rehabilitation
Although clinical neurology and psychiatry very much need new assessment techniques, there is possibly, even a greater need for new rehabilitation techniques. Currently, very few therapies are offered to patients with brain injury, and few, if any, can be said to actually rehabilitate cognitive functions.

In order to make progress in this area, we have focused on working memory rehabilitation, because almost all brain injured patients with cognitive deficits have disabling working memory deficits. Various ongoing projects investigate the effects of computerized cognitive training programs in healthy subjects and in patients with cognitive impairments. These experiments can be said to represent a "bottom-up approach" to rehabilitation where the repetition of the same task is believed to "train" underlying functions. In another, larger study, we have investigated the effect of hypnotic inductions on brain injury as a "top-down approach" to rehabilitation where we have attempted to target the functions themselves.

Results from these various rehabilitation strategies are expected to be published in 2014.

Future directions

Whereas the above-mentioned projects in themselves are important parts of our future plans, our work is moving towards a greater theoretical integration into "overarching models". Where each of the scientific "sub-fields" in cognitive neuroscience develop theoretical models to explain observations in individual experiments, our integrational perspective naturally leads us to attempt more large-scale theoretical models aimed at explaining several sub-fields as well as to understand both basic research and clinical findings.

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Example publications:

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2. Vinding, M.C., Pedersen, M.N. & Overgaard, M. (2013): Unravelling intention: Distal intentions increase the subjective sense of agency, Consciousness and Cognition 22(3), 810–815
3. Sandberg, K., Bibby, B. M., & Overgaard, M. (2013). Measuring and testing awareness of emotional face expressions. Consciousness and cognition, 22(3), 806–809
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CNRU
Cognitive Neuroscience Research Unit

MINDLab

Schizophrenia and the difficulties of social interaction

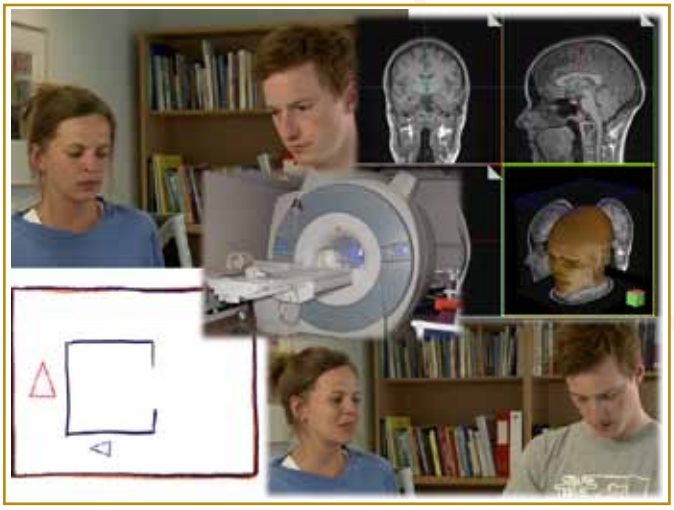
by Peder Holm Pedersen (AU Communication)
http://newsroom.au.dk/en/themes/tema-interacting-minds-centre/

There are big differences in terms of how successfully people with schizophrenia interact with other people socially. This is revealed by research performed by psychologist Vibeke Bliksted. Based on the latest research and interdisciplinary cooperation, she is currently developing courses of treatment aimed at training social cognition in patients who suffer from schizophrenia.

"Some patients with schizophrenia master social cognition – in other words, they are able to understand and interact with other people in a relatively unproblematic way. Others can't manage it at all – they have great difficulty in 'reading' other people."

This is how Bliksted explains the main conclusion of her PhD dissertation, which she defended in the spring of 2014. She's a specialised psychologist at the Department for Psychosis, Aarhus University Hospital in Risskov, which is part of AU's interdisciplinary Interacting Minds Centre.

In her PhD project, Bliksted collaborated with linguists from the centre as well as other specialists. She drew on their knowledge of semiotics and theories about how human beings constantly decode each other's tone of voice and facial expressions. Together, they set out to examine what happens in the brains of patients with schizophrenia when they are exposed to sarcasm. The focus of the study was on young patients who had recently been diagnosed with schizophrenia. A total of 59 subjects participated, 19 of whom were given so-called functional brain scans. The patients were shown short video clips of actors enacting everyday situations. Each scene was shown in both a straight version and a sarcastic version.



"The most severely affected patients couldn't spot the difference. They perceived all the videos as straight versions of what was going on, and brain scans revealed that this group of patients had lower levels of brain activity than healthy control subjects. Another group of patients were able to decode what the actors were doing successfully. However, brain scans of this group showed higher levels of brain activity than healthy control subjects, which might indicate that these patients have developed compensatory strategies in order to spot sarcasm," explains Bliksted.

"This knowledge is vital when deciding how to treat patients with schizophrenia", she says. *"It makes it possible to diagnose patients with greater precision – and not least to design treatment for each individual patient."*

Social cognition is the key

At the moment the systematic treatment of socio-cognitive difficulties is not available for patients with schizophrenia; but international research indicates that socio-cognitive difficulties have a huge impact on how well people with schizophrenia manage their everyday lives, explains Vibeke Bliksted.

"The research indicates that patients with good socio-cognitive skills manage their lives better. The patients I work with are young people aged 18 and up with most of their lives ahead of them; so of course it would be fantastic if we could give them more tools for use in interacting with other people, thereby increasing their chance of getting an education, getting a job and improving their lives in general."

Training the social cognition of patients also has an impact on how badly they are affected by psychotic symptoms, explains Bliksted.

"We know that when patients with schizophrenia are exposed to increased levels of stress and pressure, psychotic symptoms start to dominate their lives. And many of them find that situations requiring them to be with other people are a major source of stress. If we can teach them a few tricks about how to handle these situations better, we can probably help them with their psychotic symptoms as well."

Tone of voice and facial expression

Vibeke Bliksted currently applies for funding to support her work, which involves developing and studying ways of training socio-cognitive skills in patients with schizophrenia. Seed money from the Interacting Minds Centre has enabled her to start this work already, and she is starting collaborations with a Chinese psychiatrist who is also involved in research into newly diagnosed schizophrenia with a view to develop useful

methods of measuring the effect of socio-cognitive training via brain scans. In addition, she is developing a training programme in collaboration with Birgitte Fagerlund, a senior researcher at the research unit of the Psychiatric Centre in Glostrup, and colleagues from the Interacting Minds Centre with backgrounds in the fields of philosophy, semiotics, and linguistics.

These training courses help patients to interact better with other people, explains Bliksted.

"Understanding a social situation and what other people think is an extremely complex task. It's all about decoding and understanding everything – including other people's tone of voice and facial expressions as well as what they're actually saying. Lots of these particular patients find this extremely difficult."

This is why cross-disciplinary collaboration is so important for Bliksted when designing training courses and organising research designed to monitor patients and their progress.

"I'm a clinical psychologist, so I know a lot about the psychopathology of serious mental illness. But these courses are also about learning how normal people communicate and interact. Fortunately, some of my colleagues from the worlds of philosophy, language and cognitive semiotics know a lot about these areas. So I can draw on their expertise."

Role play and homework

One of the important aspects of the treatment involves practical exercises – almost like theatrical role play, explains Bliksted. The patients are asked to practise managing social situations and decoding other people in specific, recognisable contexts.

It might just involve a few simple ideas – for instance, that it's a good idea to look people in the eye when you're talking to them. But not for too long – it's rude to stare! The patients can practise this at home in a variety of specific situations.

Bliksted's plan is that the treatment should be accompanied closely by research.

"For instance, we'll be measuring whether the patients are better at being with other people at the end of the course. I also want to do some MEG scans to find out whether our training courses have an effect on brain activity – and if they do, I want to understand what's going on."

Doing mental overtime

When designing these specific and individual courses, the precise diagnosis of each patient plays an important role. And in this area Vibeke Bliksted can draw on her previous research, which showed that patients with schizophrenia could be divided into two groups depending on whether they mastered social cognition or not.

"The two groups need different types of socio-cognitive training," she explains.

"The group that could apparently decode social situations successfully turned out to have excessive brain activity. You could say that they were constantly doing mental overtime and analysing social interaction every minute of the day – which is known as hypermentalisation."

She explains that hypermentalising patients can be characterised by the fact that they reach erroneous decisions systematically.

"They're always jumping to hasty conclusions when interpreting their interaction with other people. They might be thinking: 'It looks as if he's waving his ballpoint pen around, but what he's really doing is giving someone a sign.' Or: 'You seem to be asking me a question, but what you really want to do is find out what I've been doing so you can call my boss and tell him to fire me.' This is why socio-cognitive training involves teaching people to recognise and try to put a stop to these patterns themselves."

World of Warcraft

The other group have insufficient brain activity in relation to social situations, which is known as hypomentalisation. They're characterised by what are called negative symptoms such as a lack of energy and initiative.

"A lot of patients with these symptoms don't think they've got a problem. They're quite happy playing World of Warcraft all night long even though they and their flat are falling apart because personal hygiene and cleaning are beyond them."

So socio-cognitive treatment for them will mostly involve more fundamental social factors. For instance, the ability to imagine that there's any point in spending time with other people every now and then.

"They need to practise some basic aspects of social behaviour and small talk so they don't end up being totally marginalised or even totally isolated."

PIFa

Preclinical Imaging Facility

by Brian Hansen and Steen Jakobsen

High field MRI and combined PET-MRI

Establishment of a high field MRI lab has been a long time ambition at CFIN. Thanks to the support of the Institute of Clinical Medicine, the VELUX Foundation, and the Danish Research Counsil's Infrastructure program, we were able to purchase a Bruker 9.4T small animal MRI system in 2013, and installation was begun in October 2013. The high field MRI system is intended as a research tool for the Neurophysics group (see page 4-9) and as a tool for general small animal research with a focus on neuroscience, combined PET-MRI, and as a resource for external users. The system is equipped for high resolution imaging of tissue samples, live animals (rodents), and spectroscopy and is already a valuable research tool at CFIN. Since both the Mediso PET-MRI system and the 9.4T are new additions it seems fitting to present preliminary data from a study where these systems are used to supplement each other. The aim of the study is to use an animal (mouse) model to compare fibrotic kidneys (TGFβ) to normal kidneys using 11C PET, high resolution MRI, microstructural MRI metrics, and histology. In this manner an understanding of the structure and function of the diseased kidneys is formed by comparison to normal kidneys. It is our hypothesis that this will shed light on both the disease itself and the appropriate diagnostic method for this disease. This is a prime example of the type of research PIFa is meant to facilitate by bringing together different imaging modalities and skill sets. Results from this particular study have been accepted for presentation at the 2014 PSMR conference in May 2014.

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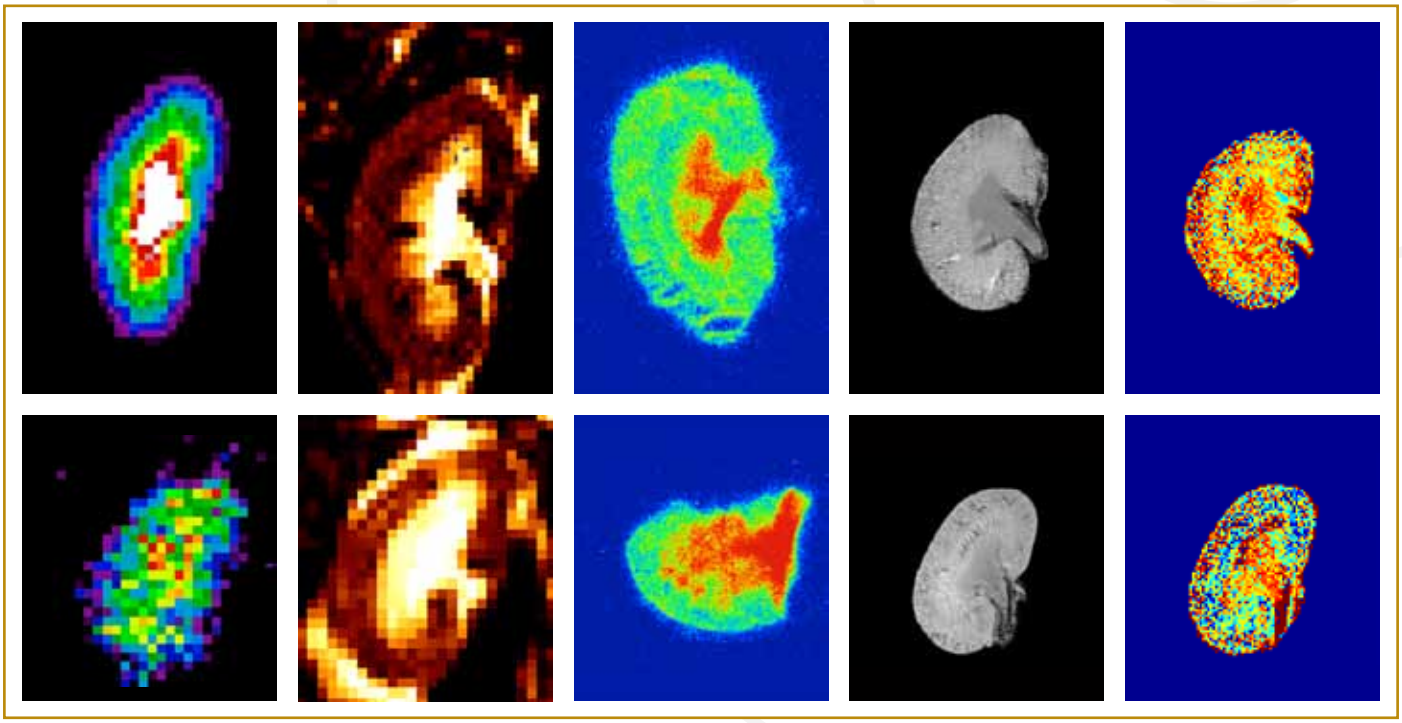

Figure 1
Data examples comparing normal mouse kidneys (top row) to fibrous mouse kidneys (bottom row) using (left to right): 11C PET (Metformin), 1T MRI *in vivo* (Mediso), autoradiography, *ex vivo* MRI (Bruker 9.4T), diffusion kurtosis imaging (microstructural marker). Interestingly, a difference between these two kidney groups is plainly visible in e.g. kurtosis images but not in the anatomical scans.

NEW FACE AT CFIN

Susanne Smith Christensen was employed as a Laboratory technician and Veterinarian nurse in June 2013.

She is experienced in animal models such as mice, rats, dogs and mini-pigs, an experience she achieved while working 5 years at LAB Research – a company that performs non-clinical studies within toxicology.

At CFIN Susanne will be co-responsible for the animal facility in relation to the preclinical imaging facility, particularily in the two-photon microscope laboratory, and the high field NMR lab.

Her main tasks are to order animals, supplies and equipment, and registrations of animals, chemicals, etc. in different types of databases.
She also coordinates experiments, and assist students in their experiments.

Susanne is also health and safety representative for the laboratory and the two-photon microscope facility.

Installation of Bruker 9.4T MRI system

Pictures from the delicate operation of bringing the new Bruker 9.4T MRI system into the basement of Aarhus University Hospital. October 2013.
Photos: Göran Schömer

MIND*Lab*

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 / MI*NDLab*. RCGD integrates research, treatment and prevention of pathological gambling in an interdisciplinary setting in close collaboration with CFIN / MI*NDLab*. Results from the Clinic are summarized below. The results underscore the importance of comprehensive diagnostic assessment in the treatment of gambling disorder.

Comorbidity

Comorbidity is common in gambling disorders. International studies show comorbidity rates of 30 % - 76% with depression and affective disorders, and 30% - 76% with alcohol and substance use disorder. Comorbidity data from the Research Clinic on Gambling Disorders are summarized in Figure 1. Figure 1A shows that affective disorders (depression, bipolar disorder, dysthymia, etc.) are the most common form of comorbidity (48% of all diagnoses), while substance use disorder is the second most common form of comorbidity (20% of all diagnoses), and anxiety disorders (phobias, OCD, PTSD etc.) follow in third place. “Other disorders” and ADHD represent 9% and 6% of all diagnoses, respectively.

Figure 1A shows the percentage distribution of diagnoses among patients with comorbidity. However, not all patients suffer from comorbidity, and some patients have multiple co-morbidities, such as substance use disorder, depression or social anxiety. Figure 1B shows the percentage of patients with comorbidity: A total of 41% of patients have one or more forms of current comorbidity, while 36% have one or more forms of past comorbidity. Overall, 77% of gambling disorder sufferers have one or more forms of current or past comorbidity. This corresponds to the international studies, and stresses the need for diagnostic assessment in the treatment of gambling disorder.

Figure 1
Comorbidity

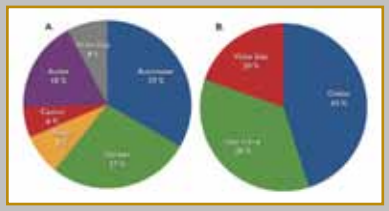

Figure 2
Types and forms of gambling

Types and forms of gambling

Among the treatment seeking patients 33% primarily play slot machines, while 27% primarily bet on sports. In comparison, poker accounts for 8% of patients seeking treatment (see Figure 2). A total of 45% patients primarily gambled online, while 35% gambled offline, and 20% gambled either offline or online, or did not answer the question.

Treatment effect

The Research Clinic on Gambling Disorders uses four main types of outcome measures to document treatment efficacy among patients: (1) South Oaks Gambling Screen (SOGS); (2) ratings of craving in percent (0 = “ no craving” and 100 = “maximum craving”); (3) ratings of gambling control in percent (0 = “ no control “ and 100 = “complete control”); and (4) ratings of time spent gambling in number of hours per week. Other outcome measures are used as well.

Preliminary data for 2013 are summarized in Figures 3 and 4 (not all patients have complete datasets). Figure 3 shows that patients completing treatment have significantly lower SOGS scores at the end of treatment, $t(15) = 4.65$, $p \leq 0.0005$. The average SOGS score at end of treatment is higher than expected ($M = 6.00$, $SD = 3.60$), because some patients filled out SOGS scores for the last 12 months (rather than 3 months). Therefore, both measures referred to the time before starting treatment. This error has now been corrected. Patients who completed treatment also spent significantly less time gambling at the end of treatment, $t(16) = 3.55$, $p \leq 0.005$. Figure 4 shows that patients who completed treatment, had significantly lower craving, $t(16) = 6.88$, $p \leq 0.00001$, and significantly greater control, $t(16) = 8.52$, $p \leq 0.00001$, at the end of treatment .

Figures 3 and 4 show that the treatment effect is stable over time, as the effect lasted for a 12 months follow-up period (FU1 - FU4), where FU1 - FU4 corresponds to 3, 6, 9 and 12 months follow-up. The effect is significant for all variables: SOGS $F(5, 4) = 13.40$, $p \leq 0.00005$; time spent gambling $F(5, 4) = 7.60$, $p \leq 0.001$; control $F(5, 4) = 14.47$, $p \leq 0.00005$; craving $F(5, 4) = 7.13$, $p \leq 0.00005$.

Although the data set is incomplete and based on few patients, the results are consistent with findings from major international studies, and they emphasize the effect and value of treatment and follow-up treatment. The majority of patients

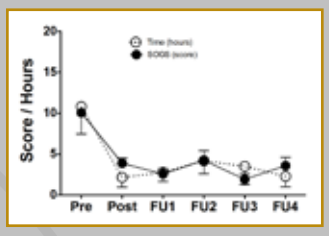

Figure 3
Treatment effect of SOGS and time spent gambling

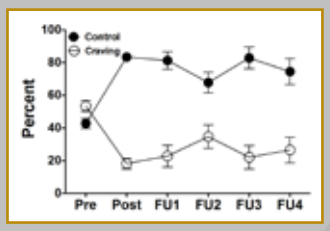

Figure 4
Treatment effect of craving and gambling control

who complete treatment no longer met criteria for gambling disorder at the end of treatment, and could maintain a healthy lifestyle subsequently.

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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
Postdoc: Anders Sune Pedersen
Secretary: Anne-Marie Andersen

www.forskningsklinikkenforludomani.au.dk

Collaborations 2013:

- 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 (2013)
- Ministry of Health Danish Gambling Disorder Treatment Network (2013)
- Danish Research Councils, pathological gambling in online poker (2012-2015)

Publications:

1. *Slot Machine Response Frequency Predicts Pathological Gambling*. Linnet J, Rømer Thomsen K, Møller A, Callesen M B. In: International Journal of Psychological Studies, Vol. 5, No. 1, 2013.
2. *Dopaminergic and clinical correlates of pathological gambling in Parkinson's disease: A case report*. Callesen M B, Hansen K V, Gjedde A, Linnet J, Møller A. In: Frontiers in Behavioral Neuroscience, Vol. 7, No. 95, 2013.
3. *The Iowa Gambling Task and the three fallacies of dopamine in gambling disorder*. Linnet J. In: Frontiers in Psychology, Vol. 4, 709, 2013.
4. *Graphs whose Complement and Square are Isomorphic (extended version)*. Pedersen A S, Milanic M, Verret G, Pellicer D. 2013.

Highlights in 2013

CFIN / MIND*Lab* Retreat 2013

The annual CFIN / MIND*Lab* Retreat at Sandbjerg Manor near Sønderborg was held on 19-21 August 2013.

The 2013 Mind*Lab* retreat focused on memory processes and on examining the context-sensitivity of remembering from biological and cultural angles in normal and clinical populations. The subject was approached broadly and the program zoomed in on various processes that come together each time we remember, and which can be initiated spontaneously as well as deliberately. These are processes related to neuro-connectivity, brain-patterns, resting state, mind wandering, episodic future thought, mental time travel, self, development, cross-cultural and historical factors.

The invited key note speakers included:

- Merlin Donald, Queen's University, Ontario, Canada
- Patricia J. Bauer, Emory University, Atlanta, USA
- David C. Rubin, Duke University, North Carolina, USA
- Karl Szpunar, Harvard University, Massachusetts, USA
- Jonathan Smallwood, Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany
- Qi Wang, Cornell University, New York, USA

Panel discussion with the invited key note speakers at the CFIN / MIND*Lab* Retreat 2013.
From left: Andreas Roepstorff, David Rubin, Jonathan Smallwood, Patricia Bauer, Qi Wang, and Karl Szpunar.
Photo: Alejandra Zaragoza Scherman

Participants in the CFIN / MIND*Lab* Retreat 2013
Photo: Alejandra Zaragoza Scherman

DHL Stafet & NeuroCup

The Aarhus DHL Stafet was held on 22 August 2013.

The DHL Stafet is a 5 x 5 km. relay race, and from CFIN 4 running teams, *The CFIN Running Brains*, and 1 walking team, *The CFIN Walking Brains* participated.

In the 2013 DHL Stafet CFIN even had a little help from some 'junior researchers', who helped fill the teams and defend CFIN colors.

Apart from being a fantastic social event the DHL Stafet is just one of many athletic activities at CFIN.

For the past 2 years CFIN has participated in ... and won ... the annual NeuroCup, where teams from the different neuro related departments at Aarhus University Hospital challenge each other in a soccer tournament.

In 2013 the NeuroCup took place on 31 May 2013, and for the second time running CFIN brought home the NeuroCup trophy.

The proud CFIN soccer team with the NeuroCup trophy. 31 May 2013.
Photo: Arne Møller

CFIN / MIND*Lab* Retreat participants gathered on the lawn at Sandbjerg Manor. 19-21 August 2013.
Photo: Alejandra Zaragoza Sherman

CFIN interior, Aarhus University Hospital, Building 10G
Photo: Mikkel Blæsild Vuust

CFIN interior, Aarhus University Hospital, Building 10G
Photo: Mikkel Blæsild Vuust

CFIN / MIND*Lab* staff

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CFIN Leadership

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http://interactingminds.au.dk/the-interacting-minds-centre/people/

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Mallar Chakravarty
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Per Borghammer
Yoshiyuki Nomura

2013 Publications

Peer reviewed articles:

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The DNC Building is a site of collaboration between industry and academia. In 2013 Combat Stroke opened office on the 4th floor of the building. Read more about Combat Stroke at page 24.
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