Center of Functionally Integrative Neuroscience
& MIND*Lab*

ANNUAL REPORT 2012

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CFIN / MIND*Lab* researchers participated in the annual DHL Stafet in Mindeparken, 23 August 2012. Here, Yi Ching Lynn Ho, Jonas Lindeløv, Ryan Sangill, Jesper Frandsen, Mikkel Bo Hansen, and Dora Zeidler are waiting for their running collegues to cross the finishing line.
Photo: Henriette Blæsild Vuust

Introduction - 2012 in words

by Leif Østergaard

We are pleased to send you the 2012 CFIN / MIND*Lab* Annual Report. The slight change of name reflects the development of our Centre since CFIN was founded as one of the Danish National Research Foundation's Centres-of-Excellence in 2001: Thanks to generous donations from private and public grants and support from the Central Denmark Region and Aarhus University (AU), CFIN has been able to establish MIND*Lab*, our experimental infrastructure, with equipment and buildings now totaling over 100 M DKK. Researchers from across Aarhus University, and our national collaborators, can therefore conduct cutting-edge MRI, MEG, EEG, and TMS studies with the help and advice from CFIN / MIND*Lab* employees that are renowned experts within the development of methods, experiments, and advanced data analysis for these techniques.

The Danish National Research Foundation's initial investment, 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. This initiative – also dubbed MIND*Lab* – received 120 M DKK to strengthen and expand the fertile collaborations that had then grown among CFIN researchers and colleagues from across AU. With the help of the Central Denmark Region and Aarhus University, specialized buildings for neuroimaging equipment, and office space for 90 of our employees are now established at our Nørrebrogade hub. Here, skilled administrative and technical support personnel facilitates the practical and technical challenges of cross-faculty and cross-disciplinary interactions. We are currently negotiating a sustainable, long-term model to finance this unique resource for researchers at Aarhus University and Aarhus University Hospital, based on the value created by our employees in terms of external grants and teaching.

The format of the annual report has also changed slightly, reflecting the interdisciplinary cooperations within CFIN / MIND*Lab* and the activities in relation to our experimental infrastructure. Interdisciplinarity has evolved as a concept within research and research policy over the past two decades, causing concerns among some that the support for disciplinary research would suffer. CFIN / MIND*Lab* maintains that interdisciplinary research should be of the highest quality and relevance to either discipline involved. This approach requires highly skilled disciplinary researchers to spend time understanding the language, methods, and knowledge of other disciplines – while maintaining their own disciplinary 'roots'. Many CFIN / MIND*Lab* researchers therefore hold dual appointments, working and teaching part of their time at their 'home' Faculty and research center. Accordingly, this and future CFIN / MIND*Lab* Annual Reports will feature researchers and projects from collaborating research centers, while noting that the entire activity of these centers and groups will be featured in separate annual reports.

As a testament to the strong cross-faculty collaborations that have evolved from CFIN / MIND*Lab*, our co-director Andreas Roepstorff received 25 M DKK from the Aarhus University Research Foundation in 2012, to establish the Interacting Minds Centre at the Department of Culture and Society, Faculty of Arts. The Interacting Minds initiative was made possible by a Danish National Research Foundation Niels Bohr professorship that permitted Chris and Uta Frith to join CFIN in 2006, and has continued as a highly successful research theme in the MIND*Lab* UNIK project. With this recognition, Andreas Roepstorff becomes the director of one of Aarhus University's five new, interdisciplinary centers with unique opportunities to investigate new aspects of interdisciplinary research while maintaining close ties to CFIN/ MIND*Lab*.

Interdisciplinary research is a long-time investment. The interdisciplinary dialogue described above takes time, patience, and special skills: Curiosity, humility, and respect, are the key ingredients when building successful collaborations. Then, generosity and reciprocity in the exchange of time and resources are crucial in order to permit great ideas to grow. The support and generosity of the Danish National Research Foundation, the UNIK initiative, and our two host institutions, have been crucial for the scientific success we enjoyed so far. And yet, I have come to understand that we may have only just scratched the surface of major discoveries that lies ahead for this approach to research.

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

Many important steps towards consolidating the neurophysics group were taken in 2012. First, Sune Jespersen was granted tenure in a position split between CFIN / MIND*Lab* and the Institute of Physics and Astronomy. This is crucial because our research relies so heavily on physics and mathematics. Having formal ties to the Department of Physics, AU as well as teaching responsibilities there provides a good platform for recruiting skilled students from the natural sciences. Furthermore, in Autumn 2012 Brian Hansen entered a position as Associate Professor in advanced neuroimaging at CFIN/ MIND*Lab*. In this position he will be part of establishing combined PET-MR methods and high-field neuroimaging for pre-clinical research. More details on these techniques are provided below. In addition to these responsibilities Brian continues his involvement in research on MR microscopy and the modeling methods related to these techniques. In 2012, our primary results relate to the development of such methods for investigation of brain tissue microstructure using, primarily, diffusion weighted (DW) MRI. When comparing physical theory to real world measurements, a key concern is the elimination of contaminating effects in the experimental data. Therefore, most of our studies are carried out in relatively well-controlled systems such as fixed brain tissue samples, and with the use of high magnetic field MR systems where signal is abundant even at high resolutions. A host of other experimental techniques besides MRI are also employed in our research, most importantly tissue processing procedures for comparison of histology to the microstructural information that our models extract from the DW MRI data. Fortunately, a grant from the Lundbeck Foundation has permitted us to hire a new postdoc with extensive experience with such methods. With that, and the projected, new experimental equipment described below the group's activities are expanding.

Research

The combination of neuroimaging using diffusion MRI and biophysical and mathematical modeling has strong potential to unravel tissue microstructure noninvasively. One proven example of this is our model based method for estimation of volume fraction and organization of neurite material in brain tissue. The method, which relies on time-consuming diffusion weighted MRI protocols lasting up to 13 hours, was validated by comparison to histology and electron microscopy stereology in (2), and to confocal microscopy in (3). The neurites are small structures (dendrites and axons) that enable the nerve cells to communicate. Part of the brain's ability to adapt to change (its plasticity) is also due to properties of these structures. The neurite material undergoes change during brain maturation and aging, but change is also induced as a consequence of learning and in a host of pathologies e.g. dementias, alcoholism and severe stress. The effects of stress on brain microstructure was visualized using this method in (4) where neurite atrophy was shown in a rat model of mental stress. However, for this method to be applicable in humans the current time extensive protocol must be shortened. Therefore, we have considered a new diffusion kurtosis metric and developed a method that allow its estimation on a standard clinical MR scanner from images acquired in only 55 seconds. This kurtosis metric can be said to quantify the degree of nongaussian diffusion in tissue, which according to our model, is primarily caused by neurites. Preliminary data acquired in rat brain (see Figure 1) demonstrate a striking agreement between the original model neurite density (left), neurite density from histology (middle), and the new metric (right). With this protocol, it becomes practical to obtain estimates of neurite volume

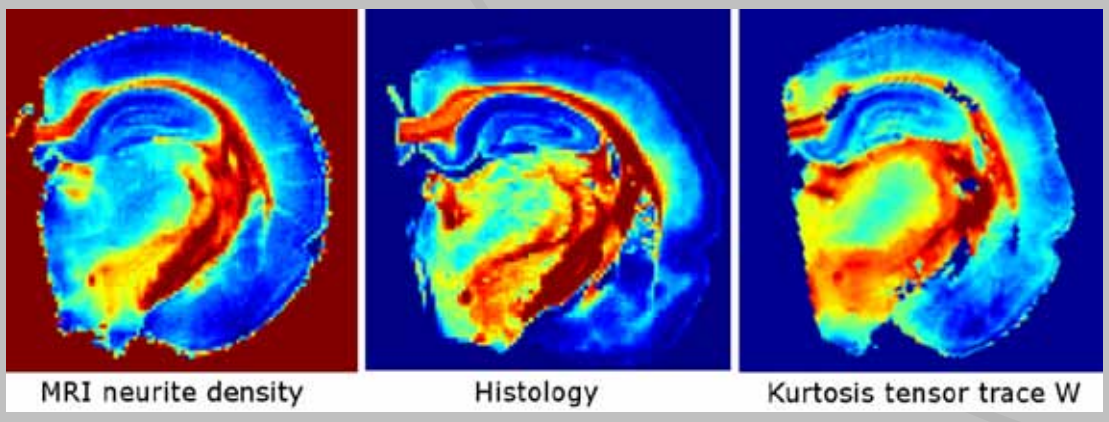

Figure 1
Preliminary data demonstrating the resemblance of the neurite density as estimated by our model-based method (left), histology (middle), and the significantly faster kurtosis method. This indicates that our method makes it possible to estimate neurite density in humans using a short series of diffusion weighted scans and a very fast post-processing method.

fraction in humans, and, specifically, to study early signs of Alzheimer's and disease progression in terms of functionally relevant tissue microstructure alterations. A patent has been filed on this new method and the publication is available ahead of print with Magnetic Resonance in Medicine online (5). In parallel, we are developing several other new and potentially helpful microstructural metrics. One such example concerns methods based on emerging diffusion correlation type sequences, termed multiple pulsed field diffusion sequences (6). In 2012, our group published a paper (7) on a new theoretical framework for microstructural analysis of double pulsed field diffusion sequences. We showed that, in contrast to widespread beliefs, new information in double pulsed field diffusion sequences is only obtained for high diffusion weighting, where one can examine cellular shape characteristics, despite several orders of magnitude lower image resolution. Cell shapes, and morphology of extracellular space, are likely to change during diseases such as cancer, and the method could be conceived to be helpful for characterizing e.g. tumor grades. We are continuing our research into these methods, and have formed a collaboration with the diffusion imaging group from Hvidovre led by by Tim Dyrby, with the aim of testing our ideas with experiments on fixated monkey brains.

Our group is also strongly involved in international collaborations. During 2012, Brian Hansen visited the Blackband Lab at the University of Florida twice to work on MR microscopy experiments with his close collaborator Dr Jeremy Flint. The CFIN / MIND*Lab* Retreat to Sandbjerg and the startup of a new series of experiments at CFIN provided opportunity for Dr Flint to visit AU in August 2012. Such live interaction is essential for the exchange of ideas and know-how between our groups and we are very fortunate that the NIH grant that funds our collaboration runs for some time still. In 2012 the UF-CFIN collaboration produced a first view into the diffusion properties of the interior of intact mammalian cells in place in spinal cord tissue (8). This direct observation of regional variation in water diffusion in neural tissue was the result of year-long effort to develop and improve MR microscopic techniques. In order to improve the utility of DW MRI as a tool in clinical radiology or in research there is a need to investigate biological tissues at the cellular level with DW MRI techniques. When combined with biophysical modeling, this is expected to aid in the development of new scan techniques for diagnostic use, and add to our understanding of basic biological mechanisms, of particular

FACTS

Group members, students and collaborators:

- Sune Jespersen
- Brian Hansen
- Peter Vestergaard-Poulsen
- Mads Sloth Vinding
- Mikkel Bo Hansen
- Peter Mondrup Rasmussen
- Birgitte Fuglsang Kjølby
- Søren Haack
- Louise Rydtoft
- Tue Skallgaard
- Jacob Hedager
- André Ødgaardstue
- Jeremy Flint
- Stephen Blackband
- Torben Lund
- Kim Mouridsen
- Ryan Sangill
- Leif Østergaard
- Chris Kroenke
- Tim Dyrby
- Henrik Lundell
- Casper Kaae Sønderby
- Niels Christian Nielsen

Conferences, research visits:

- Sune Jespersen: ISMRM 2012, Melbourne, Australia
- Brian Hansen: McKnight Brain Institute, University of Florida, January and October 2012, Bruker Biospin, Ettlingen, Germany, September 2012

Selected research projects:

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

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

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

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

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

importance is water diffusion in biological tissue, which is difficult to assess directly using other techniques.
In addition to visits from close collaborators, our group has also hosted visits from prominent international researchers. In July, Flavio Del'aqua from the Centre for Neuroimaging Sciences at King's College London gave a very inspiring talk on advanced tractography techniques for mapping brain connectivity and some of the pitfalls in this discipline. This meeting also had participants from the diffusion MRI research group at Hvidovre Hospital. Our research has also attracted some attention from the international research communities. As a result, Sune Jespersen is now part of the ISMRM diffusion study group committee and has given invited lectures at German and British universities in the last year. Sune also presented his results at the ISMRM conference in Melbourne, Australia.

Teaching

Our group contributes to teaching at AU through a series of three courses on MRI at the Faculty of Science and Technology, and a course on computational neuroscience hosted by the Institute of Physics and Astronomy. In addition we supervise several students from the bachelor's degree level and up. In 2012 our group provided supervision for three master's degree students: Tue Skallgaard graduated from the Biomedical Engineering program and Jacob Hedager and André Ødgaardstue graduated from the Institute of Physics and Astronomy. Our group also contributes to other teaching efforts by being censors on courses or thesis work at AU or other Danish universities.

Involvement in the new high field laboratory

A section of the hospital basement is currently being remodeled to house a preclinical imaging facility with various advanced imaging modalities for neurobiological research. This facility will greatly improve the range of experimental tools at our disposal and the Neurophysics group is particularly thrilled to be involved in the establishment of its PET-MR and high field MRI labs, made possible by an infrastructure grant from The Ministry of Science, Innovation and Higher Education to Professor Jørgen Frøkiær. Of particular interest to core research themes of the Neurophysics group is a 9.4T small animal system which is currently being negotiated with an estimated delivery time in Autumn 2013. This advanced imaging instrument will come equipped with strong gradient hardware ideally suited for research using diffusion weighted MRI e.g. structural imaging in genetically modified disease models or fixed tissue samples. The 9.4T system will make it possible to employ MRI techniques commonly used in clinical MRI in animal disease models. Thereby, our ability to interpret clinical images can be strengthened through the insight gained from animal models with a known disease stage and well characterized disease progression. Having this MR instrument available to us, and it being located in close proximity of the other experimental techniques present in the preclinical imaging facility (two-photon microscopy, micro-PET, electrophysiology among others), will be a major boost to our research group. We anticipate that the preclinical imaging facility will become a very fertile research environment where research groups have ample opportunity for interaction and collaboration. The 9.4T MRI system will also provide basis for collaboration with industry leaders on method development and hardware testing. In time, the prospect of sequential PET-MRI also holds great promise by enabling functional, structural and anatomical MRI to be combined with PET imaging acqusitions of cerebral metabolism and neurotransmission.

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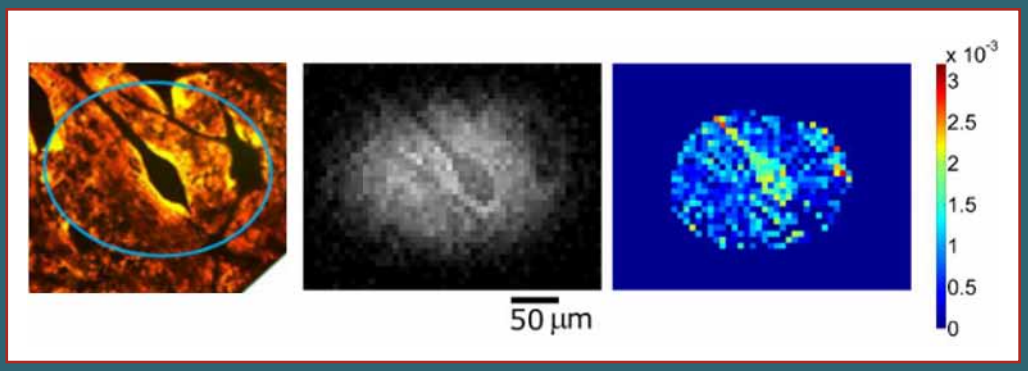
NEUROPHYSICS



The first direct observation of regional variation in water diffusion in neural tissue (intact cell bodies *in situ*) and with direct comparison to histology was presented in Flint et al. 2012.

Flint JJ, Hansen B, Portnoy S, Lee CH, King MA, Fey M, Vincent F, Stanisz GJ, Vestergaard-Poulsen P, Blackband SJ. Magnetic resonance microscopy of human and porcine neurons and cellular processes. Neuroimage 60: 1404-11, 2012.

MR microscopy is currently the only modality to offer mapping of water diffusivity in intact tissues. Such methods are of interest for improved interpretation of MR imaging and because diffusion is an essential mechanism for cellular function and viability. The colorbar represents water diffusivity in units of mm^2/s.

Cover of JCBFM, February 2012.

Part of Sune Nørhøj Jespersens work is spent modeling the biophysics of extraction of diffusible substances in the brain in close collaboration with the Functional Hemodynamics group.

Although Sune's extension of the classical flow diffusion equation may not make spectrum images, its significance made the cover of Journal of Cerebral Blood Flow & Metabolism (JCBFM) when the paper appeared in print in January 2012.

Jakob Udby Blicher and Sune Nørhøj Jespersen during the CTTH workshop in December 2012.
Photo: Kim Ryun Drasbek

NEUROPHYSICS

Localized imaging, spectroscopy and hyperpolarization

by Mads Sloth Vinding, Niels Christian Nielsen

Introduction

A broad interdisciplinary collaboration between CFIN, MIND*Lab*, inSPIN, and iNANO aims to develop means for early stage detection of the neurodegenerative disorders such as Alzheimer's Disease (AD). The formation of fibril β-amyloid plaques in, e.g., the hippocampi has been associated with early stages of AD.[1] The collaboration addresses suitable biomarkers that target these plaques. This may enable early stage detection, means for drug delivery, and *in vivo* monitoring of the disease process in the future. Our vision is to establish means of measuring the plaque load.

Magnetic resonance imaging (MRI) is potentially one of the candidates for early stage detection and progress monitoring, but it faces a number of challenges with respect to sensitivity and resolution. In any application of MRI, the images are always acquired with a trade off between acquisition time, spatial resolution and a signal-to-noise ratio that is inherently low. Research on the technical side of this collaboration regards advanced volume-selective radio frequency (RF) pulses that can be utilized for localized spectroscopy, or reduced field-of-view imaging, i.e., images with increased resolution. To improve sensitivity to the expected accumulation of amyloid plaques we also pursue hyperpolarization methods.

Volume-selective RF pulses

RF pulses in MRI are normally used to select the image slice of interest. They are also used to prepare the magnetized body to further enhance specific contrasts, e.g., in angiography. Volume-selective pulses have the ability to let the signal be extracted from only a well-specified region, rather than a slice. Meanwhile, they are also capable of mitigating certain system and patient specific artifacts such as central brightening and image blurring as seen with high field systems. These extra abilities of volume-selection over ordinary selection require longer pulses and more advanced numerical optimization scripts, such as optimal control (OC). The patient tailored pulses must be available as fast as possible to be practical. Therefore, the primary objective of Mads Sloth Vinding's PhD study (defended in July 2012) was *Fast Optimal Control in MRI*.[2]

A 2D selective pulse can be calculated within few seconds (see Figure 1).[3] Current development goes towards true 3D selective pulses that supersede other volume-selective pulses in terms of optimization speed, fidelity, and pulse duration. A key tool in this research became available when the new two-channel Siemens Skyra system was installed as part of CFINs infrastructure. Volume-selective pulses have gained renewed, interest in the MRI community along with the introduction of multi-channel RF systems that enable pulse acceleration. Now, with this tool in-house and with collaborators situated abroad (PhD, Ivan Maximov at Institute of Neuroscience and Medicine, Forschungszentrum Jülich, and the group of Professor Dieter Suter at Technische Universität Dortmund, invited visit in December 2012) we are trying to develop advanced pulse techniques extending beyond "just" volume-selection.

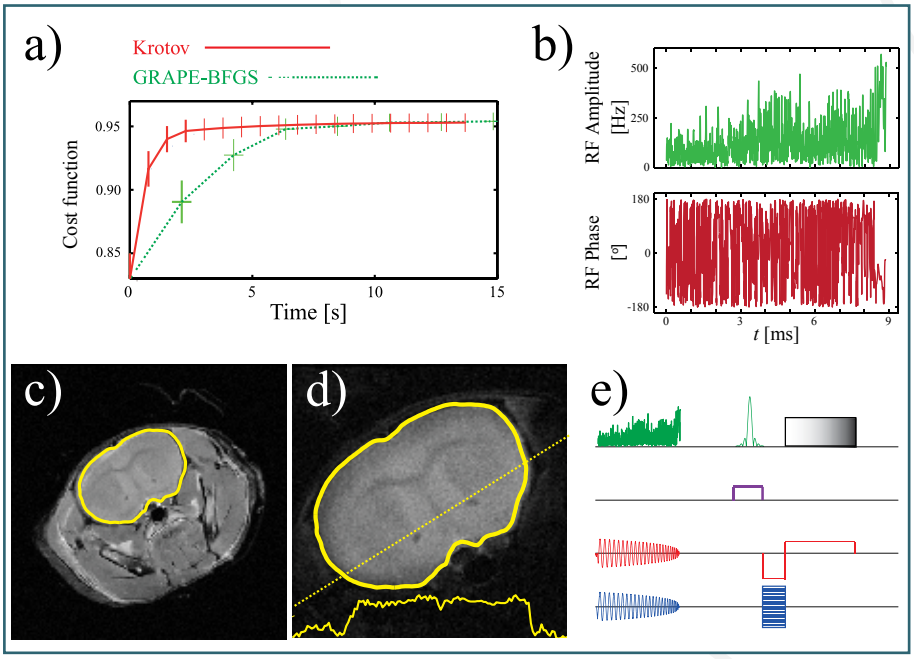


Figure 1
a) The convergence profiles (red) of the fast optimal control and another (green) slower, yet quite robust algorithm. b) A volume-selective pulse with its typical noisy appearance. c) Normal image of an *ex vivo* mouse head with the brain in the yellow loop as region of interest. d) A reduced field-of-view shot. e) Schematic of the MR pulse sequence.

Hyperpolarization

Currently, the most promising hyperpolarization approach suitable for *in vivo* studies is dissolved dynamic nuclear polarization (DNP), with potential signal gains above 10,000.[4] A clinical DNP hyperpolarizer is being established at the time of writing in Aarhus University Hospital, Skejby. However, in an ongoing collaboration with DRCMR at Hvidovre Hospital, who installed a preclinical DNP system, we managed to perform phantom experiments and obtained localized spectra and images of hyperpolarized pyruvate by volume-selective pulses (see Figure 2).[5] One downside with commonly known hyperpolarizable matters is the short polarization lifetime - typically a few minutes – hardly enough for intravenous travel, blood-brain-barrier crossing etc. A solution to this challenge could be the use of molecules possessing two spins that form triplet and singlet states. The magnetically "hidden" singlet state has a longer life time – many minutes – and pulse sequences for transferring polarization in and out of the singlet state have been established for advanced research systems.[6,7] On less powerful, clinical systems, we could show that OC-derived "in-and-out" pulses, will be a more effective alternative at the moment.[8] Our focus is now to better exploit the hyperpolarization over time, and biomarker research with long-singlet-lifetime molecules.

Figure 2
The cover of Journal of Magnetic Resonance from February 2013 with figures from Ref. 5 (the work was published online in ultimo 2012).

In September 2012, we made a visit to the Sir Peter Mansfield Magnetic Resonance Centre at the University of Nottingham and the group of Professor Walter Köckenberger. The purpose was to inspect a para-hydrogen hyperpolarization kit. Although challenging to exploit in MRI, the simple and rather inexpensive apparatus is an interesting alternative to the costly and advanced DNP setup. A crude replica of the Nottingham setup is currently being assembled in the iNANO basement (see Figure 3).

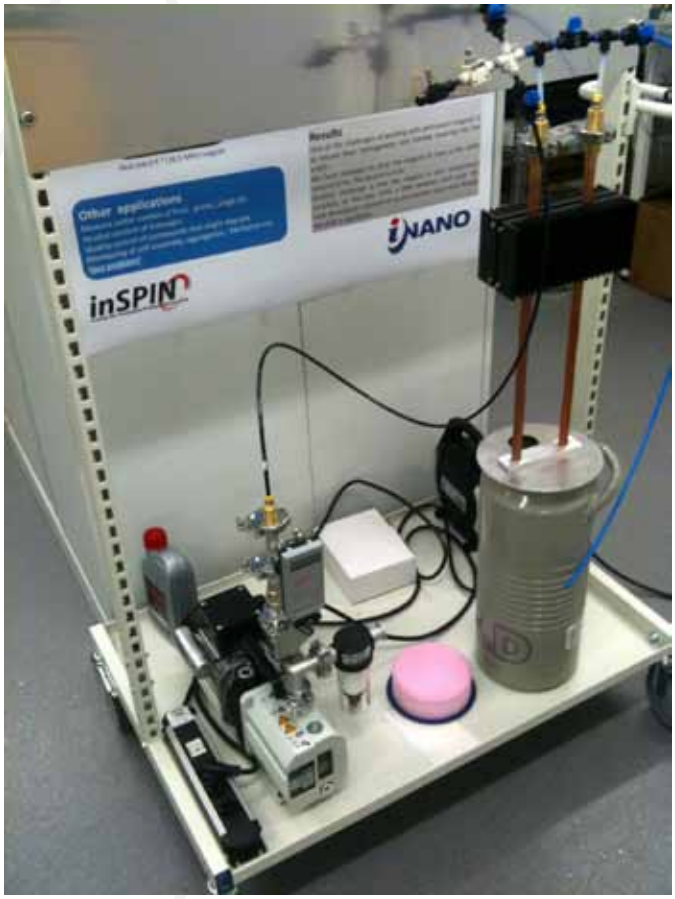


Figure 3
The para-hydrogen setup taking shape. It basically involves passing normal hydrogen gas through activated char-coal at liquid nitrogen temperature - and then to let the gas react with suitable target molecules just before detection.

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FUNCTIONAL HEMODYNAMICS

by Leif Østergaard

2012 in words

As reported in previous annual reports, our recent re-analysis of the transport of oxygen in tissue (Jespersen,S.N. 2012) predicts that capillary flow patterns have profound effects on the ability of tissue to extract sufficient oxygen to meet its metabolic demands. Means of assessing capillary flow distributions, either by direct microscopic observations in exposed tissue, or indirectly, by detecting and modeling the transport of intravascular molecules, are crucial to study this effect further. Over the past two years, the functional hemodynamics group has therefore invested considerable resources in the development of techniques to study capillary flow dynamics. Meanwhile, we have worked with collaborators at Aarhus University and Aarhus University Hospital to examine the implications of disturbed capillary flow patterns in our understanding of human diseases and their treatment. With financial help from the Institute of Clinical Medicine (Jens Christian Djurhuus and Kristjar Skajaa), the Faculty of Health (Allan Flyvbjerg), and the MIND*Lab* UNIK grant, we were able to purchase a state-of-the-art two-photon microscope for *in vivo* imaging in small animals. With help from the NeuroCenter leadership (Inger Schaumburg, Eva Sejersdal Knudsen, and Henrik Caspersen) who generously provided a renovated room close to the other preclinical imaging facilities in the basement of Building 10, its installation was finalized in the fall of 2012. The affiliated researchers, postdoc Nina Kerting Iversen, and Changsi Cai quickly and expertly took possession of the equipment and started generating impressive images of the microstructure of rodent brains. We are particularly grateful to Associate Professor Sebastian Frische from the Department of Biomedicine, who has agreed to take scientific leadership of the installation, and whose knowledge and hard work was indispensable in the tender process, and to Morten Skovgaard Jensen who generously makes his laboratory and knowledge available to Nina, Changsi, and PhD student Eugenio Gutiérrez Jiménez.

Our close collaborators, Professors Davis Boas and Sava Sakadzic from the Optics Division of the Martinos Center for Biomedical Imaging at Massachusetts General Hospital (MGH) and Harvard Medical School, have been an invaluable inspiration and support in our efforts. They pioneered optical imaging techniques to measure tissue oxygen tension by two-photon microscopy and specialized molecular probes, and more recently developed means of visualizing microvascular flow dynamics by optical coherence tomography (OCT). In 2012, they generously accepted Eugenio in their lab, where he worked alongside postdoc (and OCT expert) Jonghwan Lee, acquiring important skills and data for his future PhD studies.

To measure capillary flow dynamics non-invasively, CFIN / MIND*Lab* researchers has pursued various means of detecting the microvascular retention of intrasvasular contrast agents in the past years. Using models and algorithms developed by Kim Mouridsen, Sune Nørhøj Jespersen, and Mikkel Bo Hansen, such data can be analyzed to find the key hemodynamics parameters that predict to which extent the extraction of oxygen (and other diffusible substances) is limited. To that end, Anna Tietze, Martin Snejbjerg Jensen and Kartheeban Nagenthiraja successfully demonstrated that contrast enhanced ultrasound (CEUS) can be modified to assess these critical parameters. Working with Thomas Nielsen from the Department of Experimental Clinical Oncology, and Asger Granfeldt from the Department of Anesthesiology and Critical Care at Aarhus University Hospital, they produced the first, preclinical data to support that this new methodology may be used in future, clinical assessment of tissue oxygenation in cancer and in critical illness, respectively. In a parallel effort, Kim Mouridsen has worked with Mikkel Bo Hansen, Irene Klærke Mikkelsen, and Susanne Bekke to develop similar approaches for MRI and computed tomography (CT) for non-invasive assessment of oxygen availability in the brain.

It remains a crucial part of CFIN / MIND*Labs* mission to ensure that our research leads to better understandings of brain disorders – and that our results make tangible contributions to solve some of the challenges that physicians face every day in the adjoining NeuroCenter at Arhus University Hospital as they care for our patients. The exchange of knowledge that is necessary to make this happen must be facilitated in a number of ways. To this end, we have been fortunate that the CFIN and MIND*Lab* grants have provided funding for physicians who have been exemplar ambassadors for this exchange.

In 2012, Kristina Dupont finalized her PhD on remote perconditioning in acute ischemic stroke patients – a puzzling, neuroprotective effect that can seemingly be evoked by inducing intermittent ischemia in a limb by the inflation of a blood-pressure cuff. With the help of innovative image based analyses developed by Kim Mouridsen, and a herculean effort to analyze the 200+ patients Kristina examined by Lars Ribe and Irene Klærke Mikkelsen, she was able to demonstrate an effect which we will now go on to study in more detail in animal models. Meanwhile, our close collaborator, Professor

Grethe Andersen from the Stroke Unit will plan a larger clinical trial in order to examine this promising approach to salvaging precious neuronal function in acute stroke patients.

Rikke Beese Dalby, MD, PhD is another important example of a physician-scientists who, with the support of MIND*Lab*, manages to combine clinical training as a radiologist with scientific studies on the etiopathogenesis of a disorder that we understand all to poorly: Late-onset depression. Having published highly-cited papers in which she used innovative neuroimaging techniques to study the relation between small brain lesions and crucial, information-carrying fiber bundles, she went on to publish new results of her work in 2012, and now pursues new ideas on the origin of this devastating psychiatric disorder.

Anna Tietze, a neuroradiologist and part-time PhD student has become an invaluable link between research and clinical neuroradiology. She uses advanced neuroimaging techniques to study the effects of angiogenesis and anti-angiogenesis treatment on the prognosis of brain tumor patients. In parallel, she facilitates the implementation of innovative new neuroimaging techniques that might improve future diagnostics in our patients, working in a close collaboration with fellow doctor and postdoc Jacob Udby Blicher, and MR physicists Irene Klærke Mikkelsen, Birgitte Fuglsang Kjølby, Ryan Sangill, and David Alberg Peters. Jakob Udby Blicher, who shares time between a postdoc position at CFIN / MIND*Lab* and his training to become a neurologist is another key link to clinical neurology, neuro-rehabilitation, and neuroradiology. In 2012, he published the results of studies conducted with scientists at Oxford University, UK, and Vanderbilt University, USA on the neurovascular coupling in patients who suffered a stroke. His study questions the fundamental assumption that the blood oxygen level dependent (BOLD) contrast mechanism can detect neuronal function in this patient group – and thereby the functional reorganization of the brain during stroke rehabilitation. With Anna Tietze, he was able to present the first application of Chemical Exchange Saturation Transfer (CEST) MRI to demonstrate tissue acidosis in human stroke at a conference in Washington DC in September, 2012. Such examples of cutting-edge research and diagnostic innovation at the interface between patient management and basic research are made possible only by dedicated clinician researchers, and the close and trusting collaboration with our clinicians, not the least at the Department of Neuroradiology.

FACTS

Group members, students and collaborators:

- Eugenio Gutiérrez Jiménez
- Changsi Cai
- Ninna Kerting Iversen
- Jakob Udby Blicher
- Anna Tietze
- Yi Ching Lynn Ho
- Rasmus Aamand
- Kim Ryun Drasbek
- Simon Lykkemark
- Jesper Just
- Kristina Dupont Hougaard
- Søren Møller Madsen
- Paul von Weitzel-Mudersbach
- Rikke Beese Dalby
- Sune Nørhøj Jespersen
- Kim Mouridsen
- Irene Klærke Mikkelsen
- Jeanette Bødker Pedersen
- Birgitte Fuglsang Kjølby
- Kartheeban Nagenthiraja
- Mikkel Bo Hansen
- Susanne Bekke
- Lars Riisgaard Ribe
- Martin Snejbjerg Jensen
- Martin Gervais Dahlman
- Simon Fristed Eskildsen
- Arne Møller
- Leif Østergaard
- David J Brooks, Nicola Pavese, and Jørgen Frøkiær, PET Center Aarhus.
- Sebstian Frische, Mark West, and Morten Skovgaard Jensen, Department of Biomedicine, AU.
- Peter Kristensen, School of Engineering, AU
- Grethe Andersen and Hans Brændgaard, Department of Neurology, AUH.
- Else Tønnesen, Mads Rasmussen, Asger Granfeldt, and Niels Secher, Department of Anesthesiology, AUH.
- Mike Horsman and Thomas Nielsen, Department of Experimental Clinical Oncology, AUH.
- Hans Erik Bøtker and Steen Buus Kristiansen, Department of Cardiology, AUH.

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 2012

In 2012, we got additional support in these efforts from the Central Denmark Region, when they made it possible to update our 10 year old 3T MRI system to a new, 3.0 T Siemens Skyra scanner. We share this scanner with clinical neuroimaging, and the scanner thus serves as a platform for exchange of knowledge, and for the implementation of advanced neuroimaging techniques, with our clinical colleagues. We wish to thank the Central Denmark Region for their trust and help in maintaining state-of-the-art experimental equipment.

In December 2012, CFIN / MIND*Lab* held an international workshop - the Aarhus CTTH Workshop - to discuss the theory we recently advanced with regards to the metabolic significance of microcirculatory flow patterns.

We were proud that the World's elite within studies of the microcirculation and its coupling to brain function attended the workshop and made it a unique and immensely productive event. Professor David Attwell from the University College of London, David Boas from Martinos Center at MGH and Harvard Medical School, and Ulrich Dirnagl, Charité, Berlin, coordinated a three-day workshop featuring lively discussions on how to model cerebral microcirculation, how to quantify tissue oxygenation and capillary flow patterns, and the mechanisms that couple these to brain function.

The meeting featured a range of stellar presentations by leaders in a range of related fields, and several reports on still unpublished findings attracted special attention: Reports from the UCL and Boston groups suggest that changes in capillary diameters and in capillary flow patterns appear before the vasculature responds to neuronal activation – providing further experimental evidence to our growing suspicion that neurocapillary coupling mechanisms may be central in the control of oxygen extraction efficacy – in addition to the well known control of upstream control of arteriolar diameter and cerebral blood flow (Jespersen,S.N. 2012).

Program

- **Leif Østergaard & Sune Jespersen**: CFIN / MIND*Lab*, Aarhus University: *The Metabolic Role of Capillary Transit Time Heterogeneity*.

Session I. Modelling capillary flow dynamics.
- **Axel Pries**, Professor, Department of Physiology, FU-Berlin: *Microvascular networks: Causes and consequences of heterogeneity.*
- **Bruno Weber & Patrick Jenny**, University of Zurich & Swiss Federal Institute of Technology (ETH) Zürich: *Modeling flows through Capillary Networks*

Session II. Imaging capillary flow dynamics.
- **David Kleinfeld**, PhD, Professor of Physics and Neurobiology, UC San Diego: *The cortical angiome: A 3-D interconnected vascular network with noncolumnar patterns of blood flow.*
- **Bojana Stefanovic**, PhD, Assistant Professor, University of Toronto, Sunnybrook Health Sciences Centre: *Microvascular network transit times and perfusion via two photon fluorescence microscopy and high frequence micro ultrasound.*

Session III. Imaging tissue oxygenation and neurovascular coupling.
- **Sava Sakadzic**, PhD, Instructor in Radiology at Harvard Medical School: *Imaging brain microcirculation, hemodynamics and oxygenation.*
- **David A. Boas**, PhD, Professor in Radiology at Harvard Medical School: *Spatiotemporal dynamics of the Neurovascular Coupling.*

Session IV. Neurovascular coupling.
- **Serge Charpak**, Neurophysiology & New Microscopies Laboratory: *Regional coupling of neuronal function, oxygenation and hemodynamics.*
- **Martin Lauritzen**, Professor, Department of Neuroscience and Pharmacology, University of Copenhagen: *Calcium activities in neurons and astrocytes as mechanism of neurovascular coupling*
- **Christof Leithner**, Dr, AG Leiter, Charité - Universitätsmedizin Berlin: *Vasodilation in the brain: Is it necessary ?!*

Session V. Pericyte Function.
- **Annika Armulik**, Postgraduate, University Hospital Zurich. Institute of Neuropathology: *Pericytes and the Blood-Brain-Barrier*
- **Francisco Fernández-Klett**, Department of Neurology, Charité, Humboldt-University, Berlin: *Pericytes, Capillary Diameter and Neurovascular Coupling*

Session VI. Control of pericyte Tone - *in vitro* and *in vivo*.
- **David Attwell**, PhD, Professor of Physiology at UCL Neuroscience, Physiology & Pharmacology: *Brain Pericytes*
- **Catherine Hall**, UCL Neuroscience, Physiology & Pharmacology: *Messengers controlling pericyte constriction and dilation*
- **Fergus O'Farrell**, UCL Neuroscience, Physiology & Pharmacology: *Cardiac Pericytes*
- **Leif Østergaard**, CFIN / MIND*Lab*, Aarhus University: *Concluding Remarks. Topics for 2013 meeting*

Aarhus CTTH Workshop

The workshop opening took place in the Aarhus University Main Hall. After the opening talk by Professor Leif Østergaard the workshop participants met for a reception in The Collection of Ancient Art at Aarhus University, and then went to the ARoS Art Museum to experience the Edward Munch Exhibition and a workshop faculty dinner in the ARoS restaurant.

Aarhus CTTH Workshop 2012 - opening in Aarhus University Main Hall, reception in The Collection of Ancient Art, visit to Edward Much exhibition at ARoS Art Museum.
Photos: Kim Ryun Drasbek

FACTS

Selected research projects:

Anna Tietze, Irene Klærke Mikkelsen, Leif Østergaard, Kim Mouridsen:
Perfusion in Brain Tumors.

Rasmus Aamand, Stine de Paoli, Simon Eskildsen, Arne Møller, David J Brooks, Morten Overgaard, Leif Østergaard:
Capillary Dysfunction in Alzheimer's Disease risk factors.

Nina Kerting Iversen: The pathophysiology of ischemic and reperfusion brain injury.

Changsi Cai: Neurocapillary Coupling.

Eugenio Gutierrez Jimenez, Mark West, Morten Skovgaard Jensen:
Alzheimer's Disease.

Thorbjørn Søndergaard Engedahl, Leif Østergaard, Irene Klærke Mikkelsen, Lars Ribe, Kristina Dupont, Grethe Andersen, Kim Mouridsen:
Capillary dysfunction in acute stroke patients.

Kim Ryun Drasbek, Peter Kristensen, Jesper Just, Simon Lykkemark:
Pericytes and capillary models.

Peter Mondrup Rasmussen, Kim Mouridsen, Leif ØstergaSune Nørhøj Jespersen:
BOLD signal dynamics.

Yi-Ching Lynn Ho, Jacob Udby Blicher:
Capillary Transit time heterogeneity and neurovascular coupling.

Asger Granfeldt, Anna Tietze, Niels Juul, Nina Kerting Iversen, Else Tønnesen, Mads Rasmussen, Niels Secher, Leif Østergaard, and many more:
The Microcirculation in Critical Care.

Mike Horsman, Kim Drasbek, Anna Tietze, Thomas Nielsen, Leif Østergaard:
Tumor microcirculation and hypoxia.

Hans Erik Bøtker, Steen Buus Kristiansen, Jørgen Frøkiær, Michael Hasenkam, Kisten Bouchelouche, Søren Møller Madsen, Leif Østergaard:
Capillary dysfunction in ischemic heart disease.

Søren Møller Madsen, Jørgen Rungby, Troels Krarup Hansen, Jens Sandahl Christiansen, Leif Østergaard:
Muscle microcirculation and insulin resistance.

FUNCTIONAL HEMODYNAMICS

Cerebral MRI in depression

by Rikke Beese Dalby

Depression is a common psychiatric disorder and one of the leading causes of loss of life quality and reduction in life years world-wide. The prevalence of depression in Denmark is estimated to be about 3%, corresponding to roughly 150,000 people[1]. The prevalence is twice as high in women than in men.

Cerebral white matter lesions

Increasing evidence suggests that cerebrovascular disease may be an important factor in the pathogenesis of a subtype of depression occurring late in life, termed "vascular depression"[2,3]. Vascular disease is thought to contribute to the impairments in late-life depression through cerebral white matter changes such as white matter lesions (WMLs). WMLs are identified as white matter signal hyperintensities on proton-density or T2-weighted magnetic resonance imaging (MRI) of the brain and are believed to reflect underlying cerebrovascular disease[4,5] (see Figure 1). The presence and severity of WMLs increase with age and have been shown to correlate with vascular risk factors, such as hypertension and smoking[6,7].

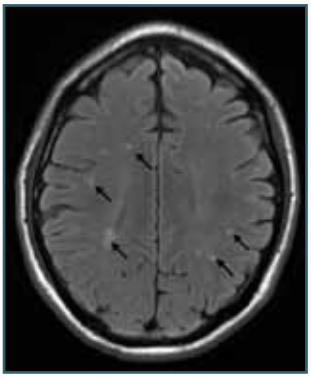

Figure 1
Illustration of WMLs.

Imaging studies using MRI have reported an increased frequency of these WMLs in late-life major depression[8]. WMLs are believed to affect the mood-regulating pathways, either by single, localized lesions or by an accumulation of lesions exceeding a certain threshold[2]. However, the relation between lesion characteristics, their interference with specific neuronal pathways, and the disease remains largely unknown.

Diffusion tensor imaging

Over the past decade, advances in MRI, such as diffusion tensor imaging (DTI), have enabled us to study the microstructural integrity of the brain tissue *in vivo* by reconstructing white matter trajectories - a technique known as tractography. In my PhD research project, we used DTI tractography to assess which pathways were affected by

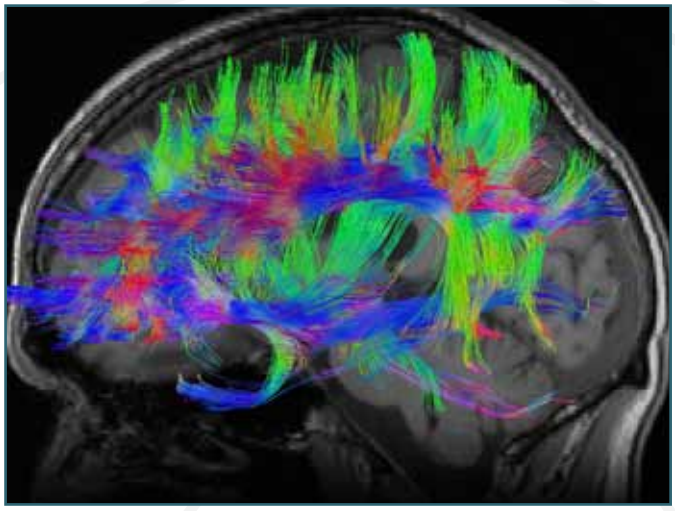

Figure 2
Example of tractography. The colors represent the direction of fiber trajectories. Courtesy of Jesper Frandsen.

WMLs. The aim of my studies were to describe the localization and impact of WMLs on cerebral white matter structure in patients with late-onset MD and non-depressed controls (see Figure 2).

Our results showed no difference in the number or volume of lesions between patients and controls[9]. However, among the subjects with WMLs, patients showed a significantly higher white matter lesion density in brain areas essential for cognitive and emotional functions. We also showed a significant correlation between depression severity and WMLs affecting pathways involved in mood and cognition[10]. By combining measures of diffusion and magnetization transfer, we showed that WMLs have a marked effect on measures of white matter integrity both within the lesion site itself and along the neuronal pathways they intersect[10].

The use of DTI tractography as a segmentation tool to map pathways that are intersected by WMLs enables the identification of specific white matter tracts potentially affected by WMLs. This allows for future, integrative approaches that combine cognitive and microstructural measures in order to address the functional impact of WMLs on tissue integrity in neuropsychiatric disease.

Neural growth factors

The prevalence of WMLs and the high comorbidity of depression and vascular disease, such as stroke or

ischemic heart disease[11], calls for reflections on a possible interaction between neural and vascular growth factors such as brain-derived neurotrophic factor (BDNF) and vascular endothelial growth factor (VEGF). The neural growth factors are important regulators of neural survival, development, function, and plasticity. An increasing body of literature suggests an important role for BDNF in the pathophysiology and treatment of mood disorders[12]. In a recent study, we examined the possible relationship between plasma BDNF and VEGF levels, WMLs, and white matter integrity in patients with late-onset depression and non-depressed controls, with respect to vascular risk factors[13]. We demonstrated a positive association between plasma BDNF level and prefrontal white matter lesion load, the latter measured as the number and volume of prefrontal WMLs, in both patients and controls. This association suggests an important role for BDNF in the repair mechanisms of neural damage due to WMLs, reflecting underlying small vessel disease that primarily affects prefrontal regions in both normal aging and late-onset depression. Future focus on neurotrophic factors, their interactions with vascular risk factors, and their impact on white matter integrity, may help us to a better understanding of the neural and vascular pathophysiologic mechanisms underlying WMLs, and eventually lead to new treatment and prevention strategies.

Cerebral perfusion

Perfusion parameters such as cerebral blood flow (CBF), cerebral blood volume (CBV), and mean capillary transit time are mutually dependent of cerebral autoregulation and perfusion pressure, and changes in these parameters reflect microvascular changes, such as regional hypoperfusion and reduction of capillary density. A recent physiological model combines the effects of CBF, CBV, capillary transit time heterogeneity (CTTH) on cerebral metabolic rate for oxygen ($CMR0_2$), and oxygen extraction fraction (OEF) in order to describe the regulation of oxygen supply by the cerebral bloodstream to meet changing metabolic needs in the brain[14]. CTTH may be a crucial part of the hemodynamic response to increased metabolic demand. However, conditions with disturbed capillary flow due to e.g. ischemia, may disturb CTTH and thereby the normal flow-metabolism coupling and oxygen metabolism in the brain.

Depression has been associated with changes in CBF and metabolism in a network of structures involving the frontal lobes, limbic system and basal ganglia. We are currently investigating the association between blood flow changes, changes in the hemodynamics of the cerebral microvasculature, and structural changes such as WMLs, in depression. Increased knowledge on perfusion changes in depression may help future application of perfusion MRI as a diagnostic tool and a tool for monitoring treatment in depression.

Perspectives

The use of vascular depression as possible future independent entity of major depression calls for more refined diagnostic approaches in future psychiatry[15], including increased focus on vascular risk factors and the use of advanced cerebral imaging techniques such as perfusion MRI and DTI.

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FUNCTIONAL HEMODYNAMICS

Capillary Dysfunction - a central disease entity in dementia and stroke?

by Leif Østergaard

The origin of most brain disorders remains poorly understood. Nevertheless, disorders such as dementia are typically classified as 'vascular' or 'degenerative' – based on the extent to which signs of restricted blood supply can be observed during examinations of our patients. Accordingly, dementia exists in 'vascular' and 'neurodegenerative', mostly Alzheimer's types. While the first is ascribed to tissue damage secondary to cardiovascular risk factors, the latter is traditionally thought to originate in the brain's various cell types: For poorly understood reasons, the brains normal clearance of protein waste products is reduced, leading to a build-up of toxic amyloid deposits in the brain, and ultimately to a severe loss of cognitive abilities. Disappointingly, several clinical trials designed to prove the benefits of removing amyloid from the brains of Alzheimer's Disease (AD) patients failed in 2012. Meanwhile, another fundamental question remains unanswered: Why do cardiovascular risk factors represent major risk factors for the development of AD if the disease in fact originates in brain cells?

The notion of 'vascular' and 'degenerative' diseases is closely linked to our understanding of the way in which organs receive oxygen and nutrients from the blood stream: Traditional physiology predicts that if the blood flow, measured as the volume of blood that passes through the microcirculation of each unit volume of tissue per minute, is normal, then so is the tissue's oxygen supply. As described in our 2011 Annual Report (Pages 20-22), we recently showed this fundamental assumption to be in error (Jespersen and Østergaard 2012). In fact, as we describe below, disturbances in capillary flow patterns may impair brain tissue's ability to extract oxygen from the blood. As a result, age- and risk factor related changes in capillary morphology can therefore, in theory, cause severe reductions in tissue oxygen availability at inconspicuous cerebral blood flow (CBF) levels. In 2012-13, CFIN/MIND*Lab* thoroughly analyzed this effect with Alzheimer's Disease experts Mark West and Morten Skovgaard Jensen from the Neuroanatomy Section, Department of Biomedicine, and Hans Brændgaard, head of the Dementia Clinic at Aarhus University Hospital (Østergaard et al. 2012). In a parallel effort, we analyzed how capillary flow disturbances might affect the pathophysiology of acute stroke (Østergaard et al. 2013). As we describe below, the origin of these conditions may be remarkably similar.

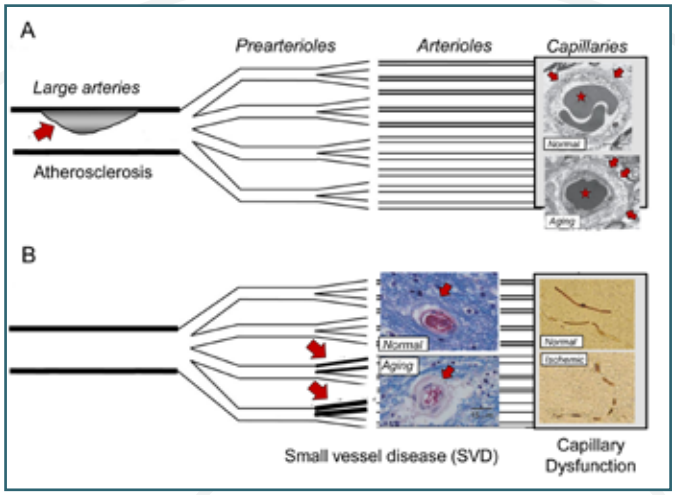

Figure 1
Vascular changes of aging in acute stroke and dementia.

Figure 1 shows some of the vascular changes that are typical of aging and of other conditions known to predispose to both acute stroke and dementia. At the arterial level, these include atherosclerosis - the formation of lipid-filled plaques in the walls of arteries. These hallmarks of cardiovascular disease tend to narrow the vascular lumen and restrict the flood flow to organs downstream. Meanwhile, they are a source of thrombus formation - releasing blood clots that cause blockage of smaller, downstream arteries and thereby extensive, hypoxic tissue damage. At the level of small arteries and arterioles, small vessel disease is now linked to a high risk developing stroke or dementia. The arteriolar walls contain smooth muscle cells that regulate vessel diameter, and thereby blood flow through the tissue downstream. In small vessel disease (SVD), the arteriolar walls become thickened and less responsive to signals that normally elicit increases in blood flow. Small vessel disease is a frequent finding in stroke patients and patients diagnosed with memory impairment and cognitive decline. The changes in capillary morphology that accompany aging, stroke, and dementia risk factors remains less studied. According to classical physiology, only capillary loss is associated with reductions in the supply of oxygen and nutrients via the blood stream, as long as upstream arteries and arterioles maintain sufficient blood flow. With the recent update of these physiological principles any disturbances in capillary flows caused by subtle changes in the walls of patent capillary morphology may, however, seriously affect the ability of tissue to extract sufficient oxygen for its metabolism. We refer to increases in CTTH that cannot be reversed during functional activation, *as capillary dysfunction*, and note that

this condition can be caused by either changes in capillary morphology or blood viscosity - a measure of the bloods 'thickness' or resistance to deformation as it flows through the narrow capillaries.

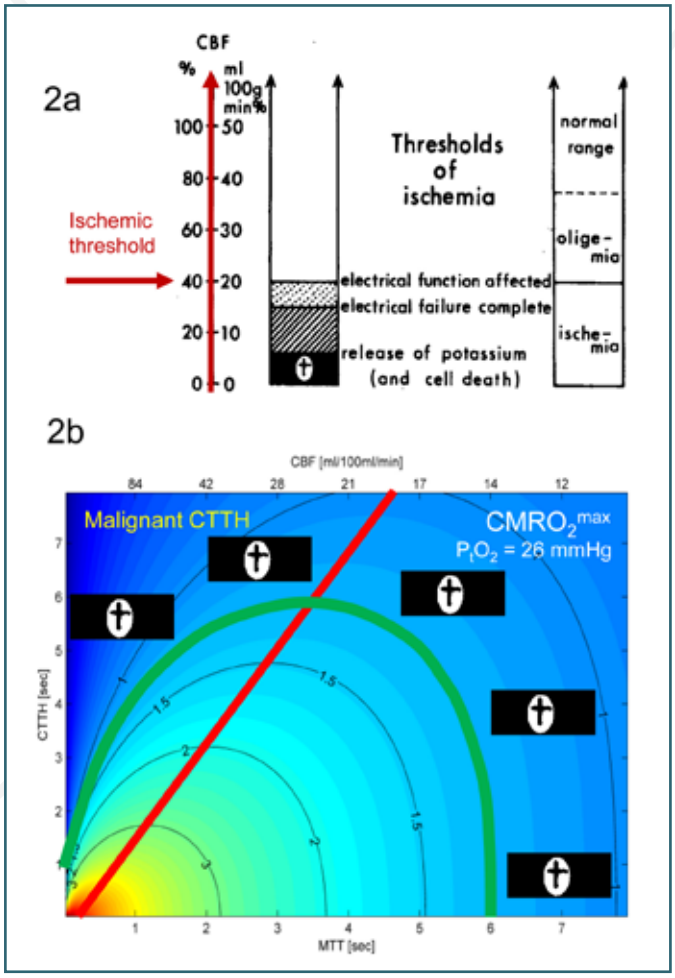

Figure 2
Oxygenation effect of capillary transit time heterogeneity.

Figure 2 illustrates how the oxygenation effect of capillary transit time heterogeneity forces us to rethink the origins of neurological symptoms and brain damage in patients with altered hemodynamics. Recalling that - according to traditional physiology - tissue oxygenation depends solely on CBF for fixed arterial oxygen levels and capillary density, an acute stroke is thought to reduce the availability of oxygen for critical cell functions according to specific CBF thresholds: At the CBF level 21mL/100mL/min, dubbed the *ischemic threshold*, oxygen levels have been shown to be insufficient for neuronal firing, causing neurological symptoms. While brain function can be restored in tissue suffering CBF levels below this threshold by restoring its perfusion, CBF levels below 8-12 mL/100mL/min result in irreversible tissue damage after only brief periods of time, as indicated by the 'tombstone-cross' in Jens Astrups classical figure reproduced in Figure 2a (Astrup et al. 1981). The oxygen availability that corresponds to CBF values below this threshold is thought to be insufficient for cells to maintain critical ion gradients across their membranes, causing the release of toxic ions. Figure 2b shows the corresponding 'threshold' when we take into consideration that in addition to CBF (the top x-axis in this plot), capillary transit time heterogeneity (CTTH – shown on the y-axis) also affects the amount of oxygen available for tissue metabolism, called $CMRO_2^{max}$. In this plot, the ∩-shaped iso-contours correspond to combinations CBF (or MTT, lower x-axis) and CTTH that permit a given consumption of oxygen (in mL/100mL/min) by the tissue. The iso-contour highlighted in green corresponds to the metabolic rate of normal, resting brain tissue as measured by position emission tomography (PET). Combinations of CBF and CTTH outside this contour therefore provide insufficient access to oxygen to support resting oxygen metabolism, as indicated by the crosses. Note that by this relation, low CBF is not a necessary condition for suffering irreversible cell damage: Rather, highly disturbed CTTH as a result of altered blood rheology alone can cause a critical lack of oxygen in the tissue. For example, blood is known to pass the capillary bed in a highly disordered manner during dehydration and after infections, as high white blood cell (WBC) counts and increased adhesion of blood cells to capillary endothelium cause blood to be shunted through the capillary bed. Surprisingly, this model property predicts that stroke symptoms – unlike earlier beliefs – can occur without the prior formation of a blood clot. It agrees well, however, with clinical observations: Dehydration and recent, bacterial infections are very common in acutely admitted stroke patients. Paradoxically, the model further predicts that the management of infections to reduce white blood cell count, and the re-hydration of patients as part of our general care, can restore tissue oxygenation in these patients until clot-dissolving agents can be administered.

We illustrated the way in which CTTH and CBF/MTT limits tissue oxygenation at the typical oxygen tension of normal brain tissue, 26 mmHg, in Figure 2. As CTTH increases and the extraction efficacy of oxygen from blood gradually declines, tissue oxygen utilization will remove oxygen from the tissue and reduce oxygen tension in the tissue. The lower

oxygen tension, in turn, increases the concentration difference between blood and tissue, and thereby the diffusion gradient that constitutes the driving force for the extraction of oxygen from blood. As a result, oxygen extraction becomes more efficient, and the normal tissue oxygen utilization can now be supported at even higher CTTH levels - only now at a lower tissue oxygen tension. Figure 3 illustrates the importance of lower oxygen tension as a means of compensating for increasing CTTH – and thereby, we hypothesize, for the accumulation of 'dents and bumps' in the capillary walls as we age and/or contract other risk factors. Here, the green iso-contours that correspond to the brain's resting oxygen utilization are stacked for all tissue oxygen tensions from zero up to 25 mmHg. Again, only combinations of CTTH, CBF (or MTT), and tissue oxygen tensions inside the resulting semi-transparent green surface can support normal brain function. Note how the iso-contours become wider towards lower tissue oxygen tension. As a result, tissue with increasing CTTH values can maintain their normal metabolism, only at a lower ambient oxygen tensions. Also note that if CTTH is set to increase, as indicated by the 'capillary dysfunction' arrow in Figure 3, then CTTH cannot increase beyond a value of roughly 2 sec at a tissue oxygen tension of 25 mmHg (The point labeled A on top of the cube in Figure 3). As CTTH increases and tissue oxygen tension is reduced, a new critical CTTH value is reaches as tissue oxygen tension reaches zero, and the opportunities for compensating for increasing CTTH thereby exhausted (The point labeled B in Figure 3). At this point, CTTH cannot increase further, and any changes in, say, blood viscosity due to infections or dehydration can now, in theory, elicit neurological symptoms. Note that the corresponding CBF value is 21 mL/100mL/min. While the green curve depends on the choice of our model parameters, the similarity to the ischemic threshold CBF value verified across a number of species is striking (Østergaard et al. 2013).

The analysis above, and Figure 3 in particular, has a number of implications for our understanding of diseases: First, ischemia (From Greek: isch - restriction; aimía - blood) and hypoxia (low tissue oxygen levels) are traditionally used interchangeably in the context of cerebrovascular disease. This is no longer accurate in that high CBF and high CTTH at normal CBF can clearly cause a critical lack of oxygen according to the extended physiological model presented here. This prediction may explain common clinical findings that have hitherto remained poorly understood: Stroke in patients that suffer from sickle cell disease is typically predated by

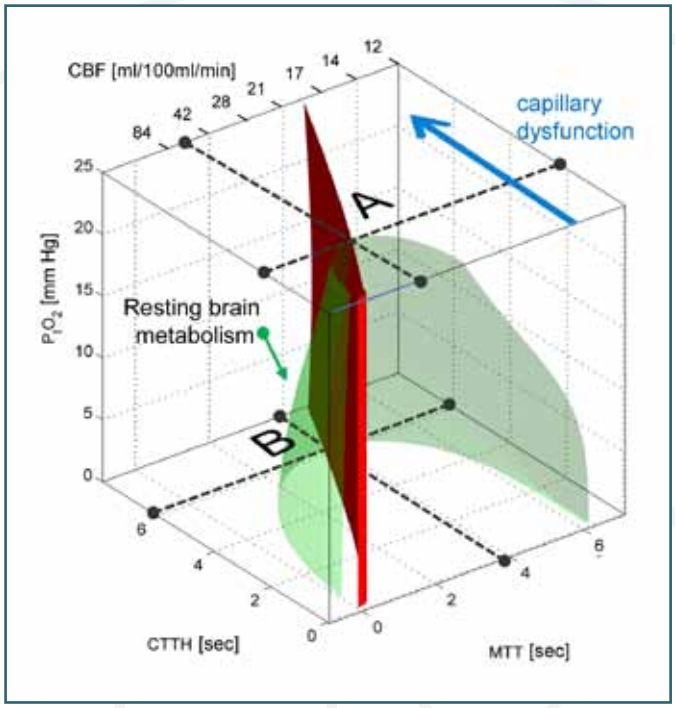

Figure 3
Lower oxygen tension as a means of compensating for increasing CTTH.

months of *increasing* CBF levels in response to anemia. Meanwhile, infections are frequent causes of neurological deterioration and of stroke, both in children and in the elderly. In terms of our understanding of the origin of Alzheimer's Disease (AD), the figure may also offer new understandings: Low tissue oxygen tension is known to increase the production and retention of amyloid, the toxic, defining feature of AD. Although AD share most of it risk factors with acute stroke, only few have related AD to disorders of the vascular system in that CBF values are generally far above the ischemic thresholds shown in Figure 2a. With the extended model of oxygen availability in Figure 3, it becomes clear that low tissue oxygen tension can exist at any level of CBF – and that capillary dysfunction may indeed be a common denominator for acute stroke and AD. In theory, the accumulation of amyloid in the brains of patients with Alzheimer's Disease may therefore represent a devastating byproduct of low tissue oxygen tension – which again, we argue, is the result of adaptations to capillary dysfunction that may have developed since early adulthood. We hope to initiate projects to examine this hypothesis and its therapeutic implications in the coming years.

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NEW FACE AT CFIN

Søren Møller Madsen, MSc in sports science from Aarhus University 2011. In collaboration with CFIN, the masters thesis involved *in vivo* measurement of capillary flow patterns during graded handgrip muscle work by means of contrast enhanced ultrasound (CEUS) in 10 healthy individuals.

Søren's research as a PhD student focuses on the metabolic importance of micro- and macro-vascular flow patterns in healthy and type 2 diabetes patients in response to high intensity interval training.

The aim is to elucidate the role of capillary transit time heterogeneity (CTTH) uptake of oxygen and glucose in the muscle, thus extending the original notion of capillary recruitment as proposed by August Krogh. During this work, further development of the CEUS technology will be performed. Additionally, the aim is to try to understand the role of endothelial dysfunction among type 2 diabetes patients.

NEW FACE AT CFIN

Rasmus Aamand, MSc, PhD (Biology). Employed as Assistant Professor in October 2012. Rasmus' main interest is the physiology of the cerebrovascular system, with a present focus on how it is affected by intake of nitrate and nitrite. The main workhorses are CFINs two 3T MRI systems called Trio and Skyra.

Contrary to what one might think the research of today indicates that nitrate and nitrite could be of great benefit to the cerebrovascular system. As a consequence our research aims at investigating whether dietary nitrate can help aid the response of the cerebrovascular system. In particular we are interested in knowing whether or not nitrate can be utilized as a preventive treatment option in sporadic Alzheimer's disease, where many of the main known risk factors relate to a deteriorating cerebrovascular system. This will be the main focus of Rasmus' research efforts the next couple of years.

Vertumnus. Giuseppe Arcimboldo, ca. 1590.

Illustration used in Rasmus Aamand's PhD thesis: *From Nitrate and Nitrite to NO - Coupling Blood and Brain.* The PhD thesis was defended Friday 9 November 2012.

FUNCTIONAL HEMODYNAMICS

In vitro Pericyte Lab

by Kim Ryun Drasbek

It has been proposed that pericytes regulate capillary diameter in the same way as arteriolar diameter by smooth muscle cells. We have proposed that pericytes may be involved in the normal regulation of capillary transit time heterogeneity (CTTH), taking part in an active neurocapillary coupling mechanism that secures sufficient oxygen extraction to meet the metabolic needs of the tissue (Jespersen and Østergaard 2012). The so-calledcapillary dysfunction hypothesis predicts that the development of neurodegenerative changes in the brain may be linked to reductions in the availability of oxygen owing to a gradual increase in CTTH. Pericyte dysfunction and pericyte loss may therefore be involved in the development of neurodegenerative diseases by contributing to the characteristic capillary wall changes seen in Alzheimer's Disease (AD), and AD risk factors (Østergaard et al. 2012). These include a thickened and irregular capillary basement membrane. This membrane is formed and maintained by pericytes and capillary endothelial cells in concert as they control basement membrane formation, capillary morphology and maintenance of the blood-brain barrier via close physical interactions and exchange of signaling molecules (Winkler et al. 2011).

To better understand the role of pericytes in neurodegenerative diseases, it is necessary to understand pericytes-endothelial cell interactions as well as pericyte contraction and relaxation in response to neurotransmitter stimulation (e.g. glutamate, GABA, serotonin, and dopamine), to vascular innervation (noradrenergic fibers from the locus coerulus and cholinergic fibers from the basal forebrain), and to a range of vasoactive substances (NO, angiotensin-II, endothelin, etc.). The study of pericytes and their function are made difficult by the fact that the known pericyte markers either only recognize a subset of pericytes or recognize other cell types in the brain. Therefore, the development of pericyte-specific molecular tools is crucial to the characterization of pericytes. Using advanced recombinant antibody technology, screening millions of different unique antibodies, PhD student Jesper Just has isolated a number of recombinant antibodies that show high specificity for pericytes while not binding to other cell types found in the brain (see Figure 1).

To study basement membrane formation, blood brain-barrier function, and pericyte-endothelial cell interactions in detail, PhD student Simon Lykkemark is in the process of developing 3D co-culture systems in structures resembling capillaries with pericytes enshealthing an endothelial lined tube with medium flow. These microstructures can in theory be engineered in any pattern, and enable the study of pericytes and endothelial cells in a system that mimics the *in vivo* setting but is fully controllable in regards to medium composition, flow rate, temperature and oxygen tension. We are greatful for our close collaboration with Peter Kristensen from the Department of Engineering, AU. The methods and experience made available by his laboratory is a unique asset to our joint research.

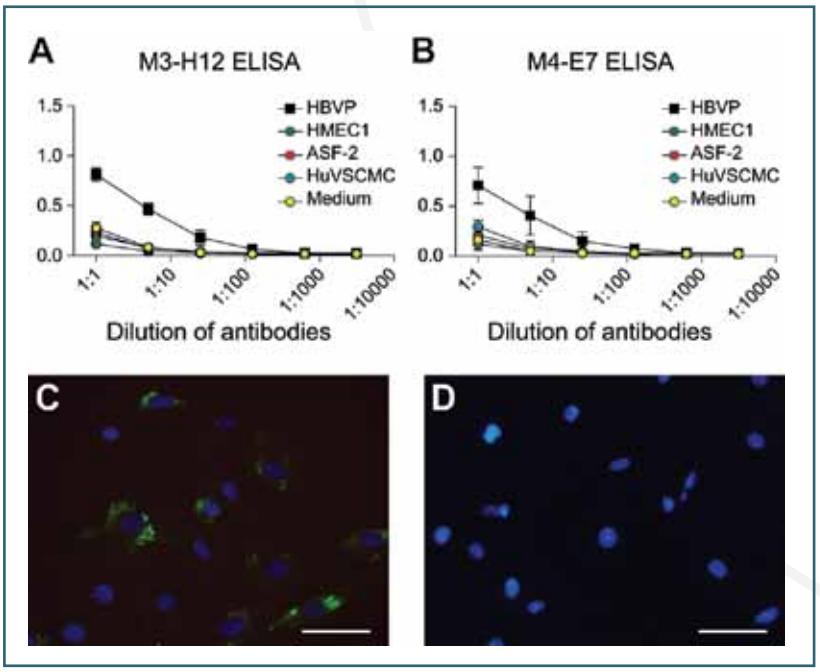

Figure 1
Pericyte specific recombinant antibodies were isolated from the recombinant Predator antibody library using cultured pericytes. The two selected Predator antibodies, M3-H12 (A) and M4-E7 (B), preferably binds to Human Brain Vascular Pericytes (HBVP) over endothelial cells (HMEC-1), fibroblasts (ASF-2), Human Vascular Smooth Muscle Cells (HuVSMC), and cell medium in ELISA. Only Human Brain Vascular Pericytes (HBVP) (C) were stained with the M3-H12 predator antibody (green), while endothelial cells (HMEC-1) (D) were not stained. The cell nuclei were stained with DAPI (blue) (scale bar, 20 µm.).

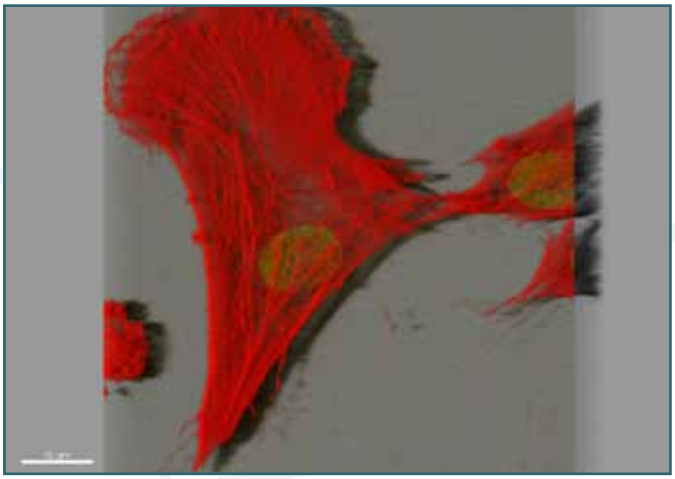

Figure 2
The image shows the cytoskeleton of cultured human brain vascular pericytes as visualized by 2-photon microscopy. F-actin, one of the cytoskeletal proteins of the pericyte, was stained with Alexa Fluor 568 phalloidin (red). By this approach we hope to detect subtle changes in pericyte morphology during contraction and in response to Aβ, glucose, and other substances believed to affect pericyte function and survival.

To investigate pericyte signaling and contraction by the 2-photon microscope we plan to utillize ion sensitive fluorescent dyes to study Ca^{2+} and Cl^{-} fluxes, and to visualize morphological changes in the pericyte cytoskeleton upon exposure to signaling molecules and different pharmaceuticals (see Figure 2). These techniques will be important in the study of pericyte control and their response to known as well as new pharmaceuticals. We believe it is crucial to develop therapeutic means of controlling pericyte function in order to reduce CTTH and thereby prevent the development of changes that lead to neurodegenerative diseases. Decades of research have led to the development of powerful antihypertensive drugs, which affect vascular smooth muscle cells and thereby vascular resistance and tissue blood flow. However, little is known about how these drugs affect downstream capillary flow patterns and thereby affect tissue oxygenation.

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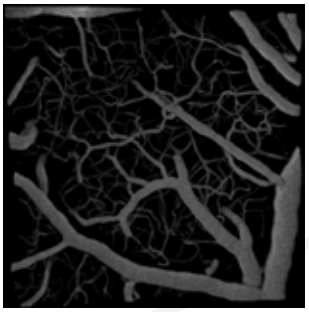
NEW FACE AT CFIN

Changsi Cai, PhD (Biomedical Engineering) was employed as a postdoc fellow in January 2012. She has six years of research experience in electrophysiology both *in vivo* and *in vitro*. During her Master and PhD, she was involved in the development of optic nerve prostheses in China. In the last two years of her PhD, she visited Harvard Medical School and joined in the Boston Retina Implant Project which is the collaboration of Harvard and MIT in the field of artificial retina.

At CFIN, Changsi will primarily be working on the roles and mechanisms of capillary transit time heterogeneity (CTTH) in animal models, based on two-photon imaging and electrophysiology. By using electrophysiology to measure the brain cell activities, and using two-photon imaging to estimate the flow heterogeneity, she will examine the roles of pericytes and astrocytes etc. in the regulation of flow in capillary networks.



Left:
3D reconstruction of capillary network.

Right:
The new Two-Photon Lab at CFIN / MIND*Lab*

Photos: Changsi Cai

FUNCTIONAL HEMODYNAMICS

Capillary Speed Heterogeneity And Tissue Oxygen in Acute Hypertension

by Eugenio Gutiérrez Jiménez

Introduction

During 2012, I was fortunate and grateful to be accepted in the optics Division, Athinoula A. Martinos Center for Biomedical Imaging where I worked under the guidance of Sava Sakadzic and David Boas. Below I report on the work I did with sophisticated methods developed there.

Angiotensin II (Ang II) has been shown to alter the coupling between cerebral blood flow (CBF) and neural activity.[1] *In vitro* studies show that retinal capillaries constrict when exposed to Ang II, owing to widespread pericyte constractions.[2] We hypothesized that Ang II may disturb neurovascular coupling by increasing baseline capillary transit time heterogeneity (CTTH). Elevated CTTH, in turn, is predicted to alter the O_2 extraction efficacy (OEFmax).[3] If cerebral hemodynamics remain coupled to the metabolic needs of the tissue, we would predict Ang II infusions to result in elevated resting CBF and vasodilator responses for mild increases in CTTH, attenuated CBF responses to vasodilators as CTTH increases further, and reduced tissue oxygen tension levels if CTTH reaches malignant levels.[3] The aim of this study is to evaluate the effect of Ang II injections on the capillary speed (CS), capillary speed heterogeneity (CSH) and oxygen availability in mouse brain tissue; both during rest and during vasodilation induced by hypercapnia (HC).

Methods

Animal Preparation
To image the cortical microvasculature, we anesthetized C57BL/6 mice (male, 25-30g, 10-12 weeks old) with isofluorane (2% induction and 1.25% for general surgery anesthesia, FiO_2 30%). Temperature was regulated by homeothermic pad and rectal probe to maintain 37 °C body temperature. A catheter was placed in the femoral artery to monitor the mean arterial pressure (MAP, 75-85 mmHg), extract arterial blood gases sample (pCO_2: 36-39 mm Hg, pO_2: 110-160 mm Hg, pH: 7.30 – 7.40), and in the vein for the administration of dyes and angiotensin II. Afterwards, the mouse was tracheotomized and ventilated mechanically in order to monitor end-tidal CO_2 ($ETCO_2$) and to induce hypercapnia.

A closed cranial window in the parietal bone, 4 mm x 4 mm in size was prepared for imaging. The bone and dura mater were removed and the cranial window was filled with a solution of agarose 2% in artificial cerebrospinal fluid (aCSF) and covered with a glass coverslip (5 x 5 mm) and sealed with dental acrylic.

For tissue pO_2 measurement, a small amount of the dye PtP-343 (~50 l) was applied by microinjection into the cortex before the cranial window was sealed. The area selected was a few millimeters from a diving artery.

Acute Hypertension Induction
We used a model of acute hypertension by Angiotensin II (Ang II acetate: Sigma-Aldrich). To reach an increase of MAP of 20 to 30 mmHg (100 – 110 mmHg), we infused a dose of 1 ± 0.02 g/kg/min. This dosage was administrated over 10 – 15 minutes until a stable increase was reached.

Speckle Intensity Variation (SIV)
To measure capillary speed (CS) and capillary speed heterogeneity (CSH) of red blood cells, we performed optical coherence tomography (OCT) SIV imaging[4] of the cerebral cortex during Normotension/Hypercapnia (NTHC), hypertension/normocapnia (HTNC) and hypertension/hypercapnia (HTHC). Hemodynamic responses of the cerebral blood volume (CBV) were measured by a CCD camera with a separate light source (570±5 nm).

Hypercapnia was induced by increasing [CO_2] by 5%, while simultaneously acquiring physiological signals, CCD video, and OCT. Then, CO_2 was decreased and after ~10 min (recovery) Ang II infusion was initiated. After a delay of ~7-8 min, we acquired data for 20 min, to analyze the slope of MAP and hemodynamic changes and then induced hypercapnia to analyze the same parameters.

Tissue pO_2 by Two-Photon Microscopy during acute Hypertension
The phosphorescent oxygen sensing probe, PtP-C343, was injected into the interstitial space, before closing the cranial window (n=3 mice). The ROI was chosen in a region with a diving artery. We excited phosphorescence by trains of femtoseconds light pulses and acquired and averaged decays from multiple excitation cycles.5 We selected a FOV 100-110 µm below the brain surface (Temp. res.= 0.16 x single-point of pO_2, ~18 min total scan time). We measured tissue pO_2 in two regions, the periarteriolar region and close to the vein drainage (tissue). We induced hypertension and hypercapnia before performing the pO_2 measurements. We made a structural image of the cortical vasculature, using a dextran-conjugated dye and two-photon fluorescence imaging.

Results

Capillary Speed heterogeneity by SIV
For HTNC, data from 6 mice that showed stable baseline time courses were analyzed. HTNC, producing ΔMAP = 31.2±23.6 mmHg, was associated with increase in CBV (-ΔI/I = 3.5±2.6%). Hypertension led to increases in CS (Δμ/μ = 3.4±2.7%) and CSH (Δσ/σ = 6.6±8.2%).

For analysis of NTHC and HTHC I used five animals that exhibited the expected CBV increase. NTHC (ΔpCO_2=12.0±3.3 mmHg, n=4) was associated with CBV increase (-ΔI/I = 3.2±1.6%), but inconsistent responses of the CS and CSH. Three of four cases, where CS increased, exhibited increase in CSH (14.2±5.1%). HTHC (MAP=96±5 mmHg), which produced ΔpCO_2 =13.0±1.2 mmHg, was associated with a CBV increase (- ΔI/I = 4.0±1.2%, n=4). CBV response was not significantly different from NTHC (p=0.34). CS increased over all cases (3.2±1.4%). CSH also increased (7.3±13.5%), although the CSH response was less clear than CS.

Overall, hypercapnia caused increases in both CS and CSH, whereas neural activation led to CS increase but CSH decrease (data not shown). The identical direction of CS and CSH responses to hypecapnia can be understood as passive responses of the capillary network to arterial supply changes (see Figure 1).

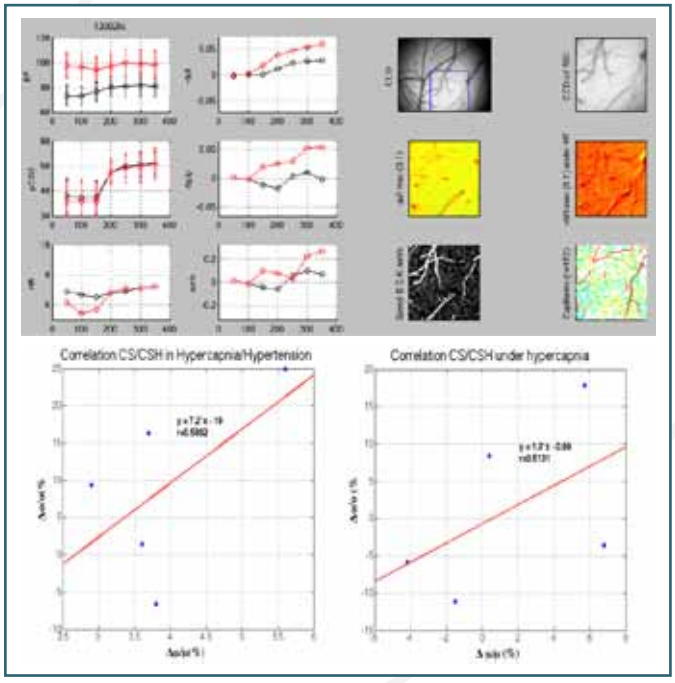


Figure 1
A) Example of analysis of SIV showing changes in CBV (ΔI/I), CS (Δμ/μ) and CSH (Δσ/σ) in respective to physiological parameters (BP, pCO_2 and HR) during NTHC (black) and HTHC (red).
B) Correlation between CS and CSH in NTHC and HTHC.

Tissue pO_2 by Two-Photon Microscopy in acute hypertension
We performed pO_2 measurements in 3 mice (25-28 grs) at 500-550 locations in the tissue during baseline (NTNC), HTNC and HTHC.

In the periarteriolar parenchyma, pO_2 showed an increase from baseline (44.02 ± 8.87 mmHg), to HTNC (54.7 ± 8.56 mmHg) (MAP=98.03 ± 5.46 mmHg; pCO_2= 37.93 ± 1.39 mmHg) and to HTHC (64.17 ± 10.18 mmHg) (MAP=94.49 ± 3.23 mmHg; pCO_2= 55.70 ± 1.73 mmHg) among all experiments.

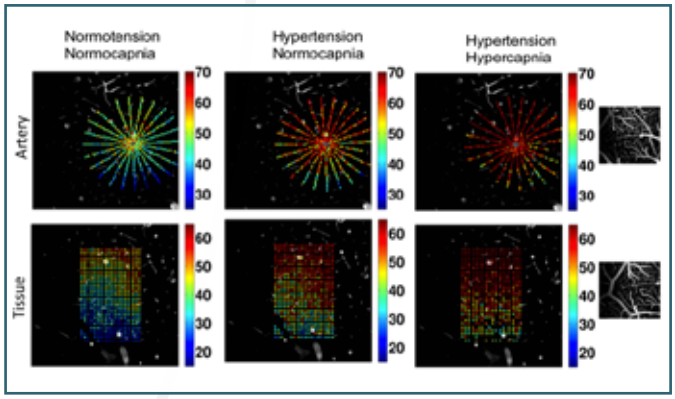


Figure 2
Individual animal pO_2 values (color bar scale) overlaid with the grayscale phosphorescence intensity image at 113 mm depth. We selected 500-550 point to measure phosporescence decays.

Away from the diving arteriole region pO_2 also showed an increase during the three physiological states, from baseline (34.96 ± 8.53 mmHg), to HTNC (50.18 ± 10.99 mmHg) (MAP=95.29 ± 4.51 mmHg; pCO_2= 38.39 ± 1.01 mmHg) and to HTHC (55.19 ± 11.38 mmHg) (MAP=92.81 ± 2.92 mmHg; pCO_2= 55.66 ± 3.18 mmHg) (see Figure 2 and 3).

Discussion

Injection of angiotensin II was associated with increased CSH, an index of CTTH. The increase in CSH was paralleled by increased CS, an index of blood flow, suggesting that CBF adjusts to maintain tissue oxygen availability according to the metabolic needs of the tissue. The data are consistent with the notion that capillaries can contract in response to vasoactive substances, but contradict that changes in CTTH are passive effects of the level of blood flow through the capillary bed.

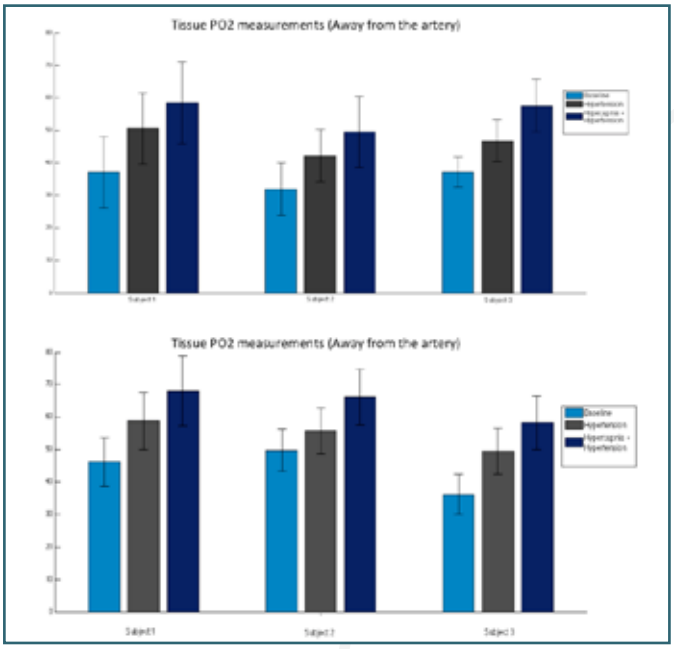


Figure 3
Bar graph showing changes on tissue pO_2 from baseline to HTNC and HTHC.

We observed only mild increases in CSH. The parallel increases in CS and in tissue oxygen tension confirmed that CTTH did not reach malignant levels. In fact, the elevated pO_2 levels suggest that increased blood-tissue concentration gradients significantly improve tissue oxygen availability as CTTH increases. The demonstration of the malignant CTTH phenomenon may require the use of more powerful means of eliciting capillary constrictions.

Conclusions

Angiotensin II injections in mice increases the heterogeneity of capillary flows. The heterogeneity of capillary flows does not appear to be a passive effect of increases in blood flow, suggesting an active regulation.

Eugenio Gutiérrez Jiménez working in the Surgery Lab at CFIN / MIND*Lab*.
Photo: Changsi Cai

Reduction of OEFmax by mild increases in CTTH (capillary dysfunction) appears to be compensated by elevated flow, consistent with a preserved neurovascular coupling mechanism.

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NEW FACE AT CFIN

Nina Kerting Iversen, MSc, PhD was employed as a post doctoral researcher in February 2012. She holds a Master degree in Biology within comparative cardiovascular physiology, and a PhD degree in Nanoscience from the Faculty of Science and Technology, Aarhus University. Her PhD project was part of a EU-funded project with the aim of developing magnetic nanoparticles for a targeted tumour therapy. This research area combined animal physiology and clinical research and inspired her to continue into the field of medical sciences.

Her current research focuses is on the role of capillary dysfunction in acute stroke. She will examine the Capillary Dysfunction hypothesis in animal experimental stroke models by studying the connection between increased capillary flow heterogeneity and the fate of the penumbral tissue after ischemic stroke. This will be done by use of the Two Photon Microscope and the Sidestream Darkfield setup recently installed at CFIN.

FUNCTIONAL HEMODYNAMICS

Two-Photon Laser Scanning Fluorescence Microscope Facility at CFIN

by Eugenio Gutiérrez Jiménez, Changsi Cai & Nina Kerting Iversen

The Two-Photon Microscope (TPM) technique has in recent years become an indispensable tool for *in vitro* and *in vivo* imaging in neuroscience. It allows for live imaging at high-resolution of neuronal activity and hemodynamics within living brain tissue. The advantages of this two-photon excitation include 3-D imaging, more precise localized excitation, higher signal to noise ratio, improved imaging depth down to 1000 µm and confined photo-damage.

The CFIN / MIND*Lab* Two-Photon facility was established and installed this year, with funding from the Institute of Clinical Medicine, the Faculty of Health, and the UNIK grant from the Danish Ministry of Science, Technology and Innovation. This facility provides us with access to a state-of-the-art combination of two-photon microscopy, confocal microscopy, uncaging technology, and electrophysiology.

The core facility is based on the Ultima IV system from Prairie Technologies Inc. This flexible system includes a workstation configured for slice physiology and *in vivo* imaging of the intact brain.

The TPM has two Ti:sapphire lasers installed, that can support two-photon imaging at two different wavelengths. This provides unparalleled spatiotemporal control for uncaging of bioactive molecules in tissue, such as glutamate or calcium, as well as for optogenetics applications.

Our equipment comes with an optical parametric oscillator, which converts an input laser wave with a certain frequency, into two output waves of lower frequency. This provide us with the possibility to excite longer wavelengths, up to 1300 nm, thereby increasing the number of different dyes that can be used in the TPM.

The software of our TPM provides control of scanning and image acquisition for optimization of data collection (including control of image size, scan rate, camera settings, laser wavelength and power levels). One characteristic, which is of utmost importance for us, is that this software allow us to perform free-hand line scans, used to track single capillaries and cells in a 2-D plane. (see Figure 2)

CFIN / MIND*Lab* and researchers from across Aarhus University will benefit from this cutting edge technology for a better understanding of the *in vivo* and *in vitro* physiology. The facility is housed in rooms generously made available and renovated by the Danish Neuroscience Center at the NeuroCenter, Aarhus University Hospital, Nørrebrogade.

Sebastian Frische from the Department of Biomedicine is scientific head of the two-photon facility. Nina Kerting Iversen oversees day-to-day operations of the two-photon facility, including animal experiments and maintenance of lab resources in cooperation with Martin Gervais Dahlman, while Changsi Cai oversees the electrophysiology facility. Eugenio Gutiérrez Jiménez undertakes development of the TPM while studying the hemodynamics in Alzheimer's Disease.

Figure 1
Two-Photon Microscopy.

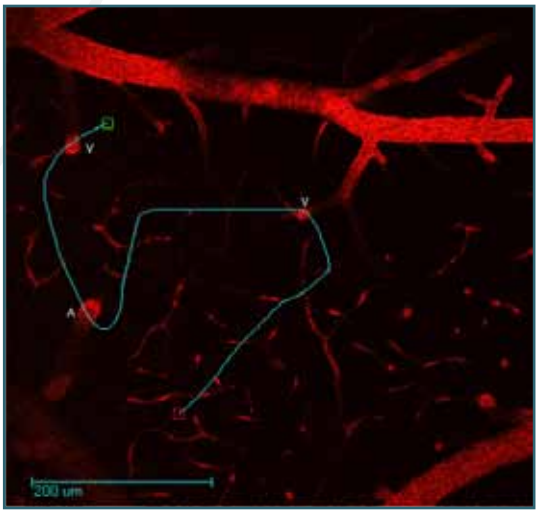

Figure 2
2-D Imaging of the vasculature and the projected "free-hand" line scan over the vascular bed, to perform measurement of mean transit times and red blood velocities.

NEURO-IMAGE PROCESSING

Predicting Alzheimer's disease

by Simon Fristed Eskildsen

Alzheimer's Disease (AD) is the most common form of dementia in the elderly, and the prevalence of AD increases with age. It is the fourth leading cause of death among adults in the Western world. An estimated 35.6 million people worldwide were living with dementia in 2010. This number is estimated to nearly double every 20 years, to 65.7 million in 2030, and 115.4 million in 2050[1].

While the aetiology of AD remains unknown, the disease is characterized by accumulation of extracellular plaques composed of amyloid beta protein (Aβ) and intracellular neurofibrillary tangles consisting of hyperphosphorylated tau in the brain parenchyma, followed by extensive neurodegeneration. Traditionally, the diagnosis of AD has been based on cognitive symptoms, though requiring histopathologic confirmation for a definitive diagnosis[2]. However, with recent advances in neuroimaging, the diagnostic criteria for AD have been revised to include evidence from imaging[3]. Still, the diagnosis of AD is difficult to confirm due to overlapping symptoms with other disorders and the fact that patients often have mixed pathologies. Neuroimaging has the potential to effectively differentiate disorders and identify the various pathologies. With the progress of imaging technology and the wide access to scanners, the role of imaging has become increasingly important in the diagnosis of AD.

The temporal ordering of biomarkers associated with AD is relatively well-established (see Figure 1). For instance, the accumulation of Aβ can be detected by positron emission tomography (PET) years before symptoms appear, and before any structural changes can be detected using magnetic resonance imaging (MRI). However, structural imaging markers are considered more sensitive to change after the first symptoms appear[4, 5]. While the relatively cheap and non-invasive MRI is routinely used for excluding other causes of neuropsychological symptoms, such as tumours or strokes, PET with a radioactive tracer that targets amyloid, is currently perceived as the gold standard for detecting Alzheimer's pathology in patients with dementia. However, recent research shows that the accumulation of Aβ is highly associated with age, and symptom free individuals have been found to have abundant accumulations of Aβ in the brain. In addition, PET is very expensive, which limits its general use in the clinic.

Even though macroscopic changes to the brain seem to occur later than accumulation of Aβ (see Figure 1), the progression of atrophy is closely correlated with the progression of symptoms. At patients' first contact with the health care system, cerebral atrophy has already started. Thus, localized atrophy is generally a better marker than Aβ for disease progression in the transition phase between symptom onset and the established clinical diagnose. The accumulation of Aβ has already reached a plateau at the symptom onset (see Figure 1). Therefore, extensive research is carried out to develop imaging and image processing for accurate measurements of localized atrophy in order to diagnose AD and monitor the disease progression.

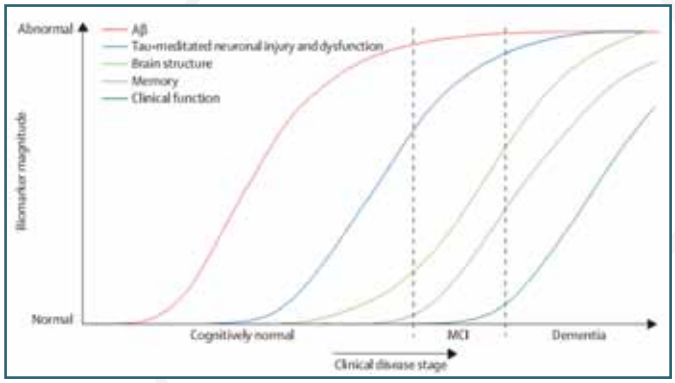

Figure 1
Hypothetical cascade model of biomarkers related to Alzheimer's disease[5].

Structural MRI, primarily T1- and T2-weighted images, has been used to assess cerebral atrophy in the past two decades. During the past 10 years, the technology for quantifying atrophy has progressed rapidly. For example, ten years ago, the standard method for hippocampal volumetry was to calculate the volume from manual delineations of consecutive image slices at relatively low resolutions. Since then, automatic methods have gained widespread use owing to their increasing robustness and accuracy when used with high resolution images. Today, automatic methods for measuring hippocampal subfields are on the verge of becoming sufficiently accurate and reliable to be used as highly sensitive markers for neurodegeneration, with the potential for improvement in diagnosis and prediction[6].

Typical structural alterations measured in AD are grey matter densities, anatomical deformations, cortical thickness, and the volumes of key structures, such as the hippocampus.

Recently, the sensitivity and accuracy of such structural features were thoroughly studied[7]. Results revealed that classical approaches for measuring these features have limitations in terms of their ability to predict AD among individuals with mild symptoms. Prediction accuracies achieved using a single method were less than 65% for all reviewed methods. Accordingly, these methods lack reliability and accuracy when applied on multi-centre studies or in a clinical setting. Accordingly, efforts must be placed in the identification of more sensitive features and more robust feature extraction methods for structural MRI.

In 2012, CFINs neuro-image analysis laboratory in a collaboration with researchers at Montreal Neurological Institute (MNI) and Centre National de la Recherche Scientifique (CNRS) in Bordeaux, published methods for predicting AD using hippocampus volumetry[8] and cortical thickness[9] (see Figure 2). We demonstrated that the improvement of such structural feature extraction methods significantly improves classification and prediction accuracy in AD. Using only cortical thickness features from a baseline MRI scan we were able to predict the development of AD in individuals suffering from mild cognitive impairment (MCI) within a three year window with an accuracy of 74% (see Figure 3). This is the best prediction accuracy achieved so far using a single imaging feature. Combining the structural features with clinical and neuro-psychological data may yield even higher accuracies.

Using a new concept of grading the hippocampus and the entorhinal cortex (ERC) using a library of labelled images, we were able to automatically classify AD patients and age-matched controls with an accuracies in the range of 90% -

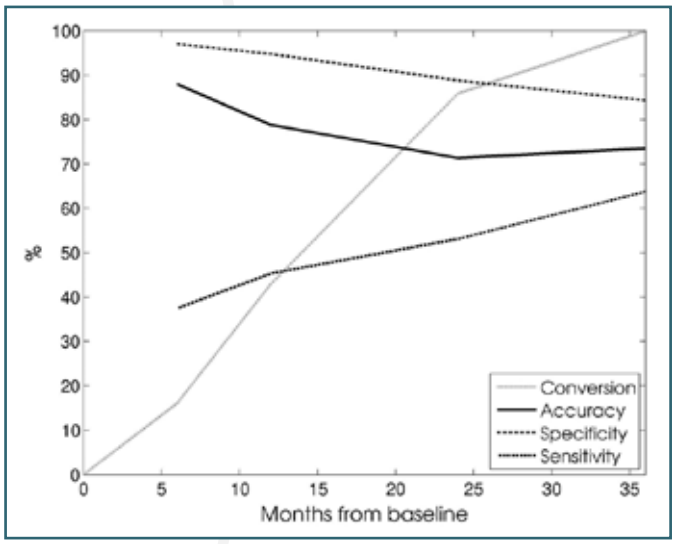

Figure 3
Performance of AD prediction using cortical thickness from baseline MRI. The "Conversion" shows the known conversion from MCI to AD (149 converted after three years). The accuracy, specificity, and sensitivity show the performance of predicting AD within X months from baseline among all the MCI patients (N=283). The three years prediction yields an accuracy of 74% with sensitivity of 64% and specificity of 84%[9]. Based on data from the ADNI study (http://adni.loni.ucla.edu/).

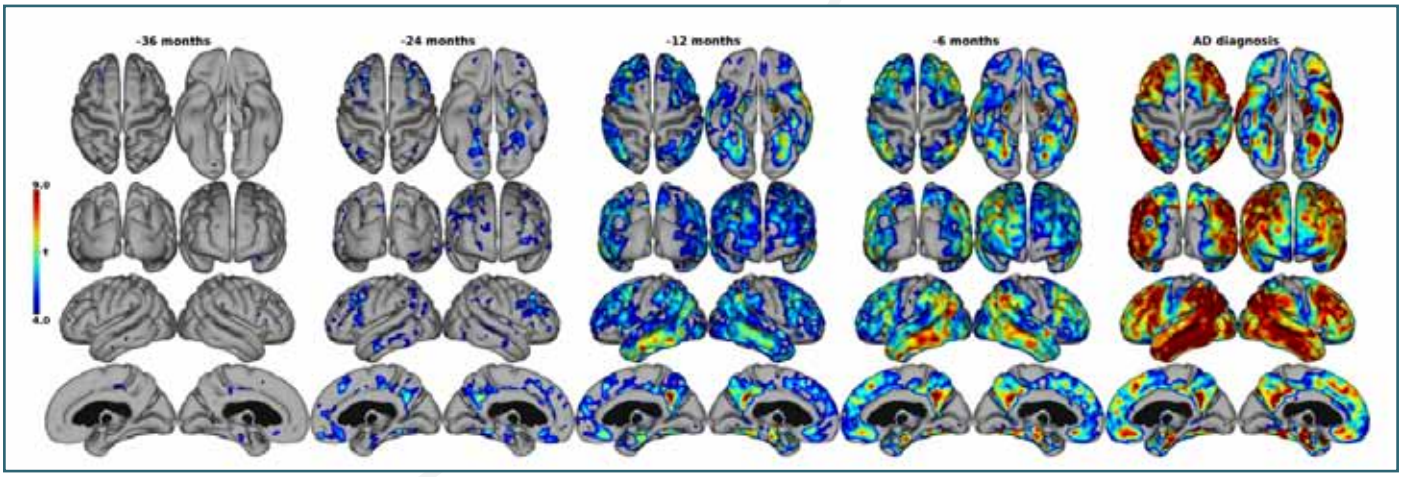

Figure 2
Progression of cortical atrophy in patients with MCI. At three years prior to AD diagnosis, cortical atrophy is present in only few specific regions, such as the parahippocampal gyrus and the precuneus. However, one year later, the atrophy pattern is much more evident and continues to spread across the cortex. Notice how the sensory-motor and visual cortices are spared throughout the course of the disease. Adapted from[9] and based on data from the ADNI study (http://adni.loni.ucla.edu/).

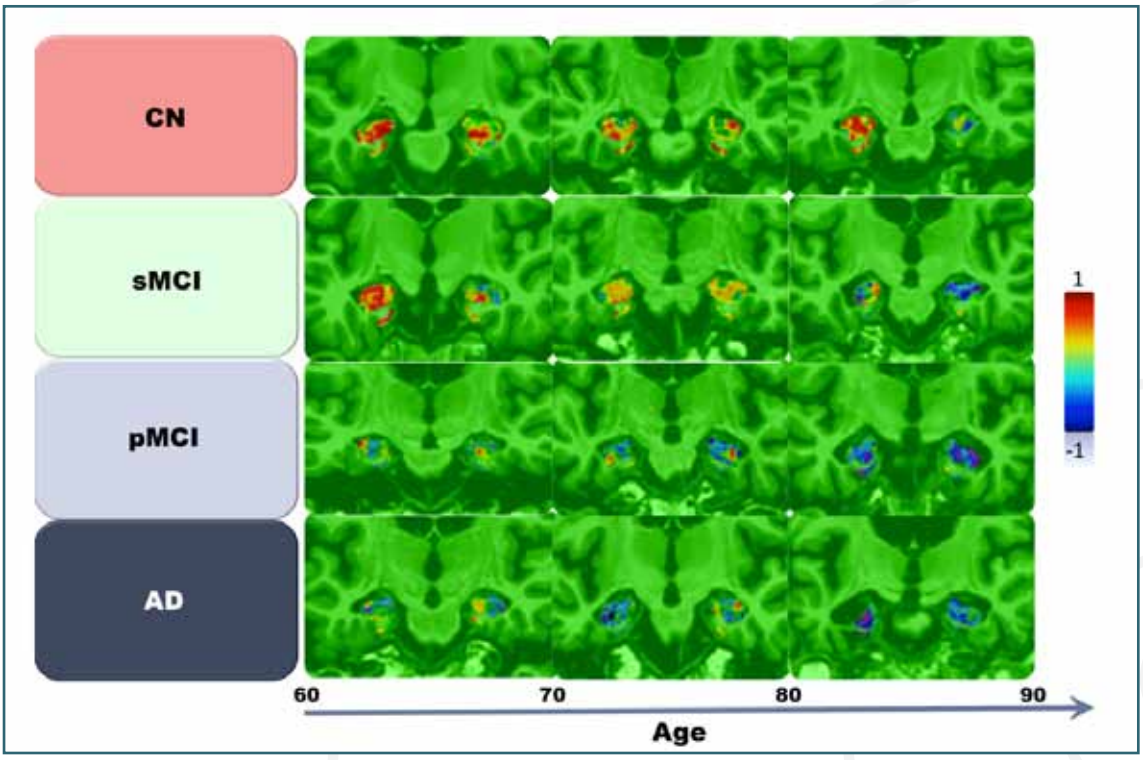

Figure 4
Typical hippocampal and ERC grading maps for cognitive normal (CN) subjects, stable MCI (sMCI) subjects, progressive MCI (pMCI) subjects, and AD patients at increasing age.
Blue indicates pathological structures, while red indicates healthy structures[10].
Based on data from the ADNI study (http://adni.loni.ucla.edu/).

93%[8, 10] (see Figure 4). The grading concept can be applied in all areas where brain structures are modified by a pathological process.

More consistent and accurate measurements can be obtained from longitudinal data acquired over at least six months. With the MNI and CNRS, we are now developing methods[11] that utilize longitudinal imaging data for detecting subtle structural changes and identifying specific atrophy patterns with the aim of predicting the disease and possibly improve patient stratification and AD subtype classification.

Looking forward, we expect to obtain reliable measurements of hippocampal subfields and investigate these in relation to cortical atrophy. The structural measurements will be combined with properties of cerebral vascular flow obtained from perfusion MRI for examining a hypothesis of capillary dysfunction in AD proposed recently by researchers at CFIN[12]. This has the potential to contribute significantly to understanding the aetiology of AD.

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NEW FACE AT CFIN

Simon Fristed Eskildsen, MSc (Engineering), PhD was employed as Associate Professor at CFIN in January 2012. He has more than ten years of research experience within medical image analysis and processing and has been teaching and supervising students since 2004. His main interests are imaging biomarkers for Alzheimer's Disease modeling based on MRI.

Simon was previously employed as Assistant Professor at Aalborg University and more recently worked at the Montreal Neurological Institute as a visiting Professor. Coming back to Denmark, Simon brings international research experience and a large international network of collaborators.

Simon is developing novel methods for quantifying cerebral atrophy and structural alterations within a range of diseases and disorders, such as depression, autism, and dementia. He holds a patent on cortical surface extraction and has released software for many of the processing steps involved in analyzing anatomical MRI.

Simon will primarily be working on detection and prediction of Alzheimer's Disease, investigating the link between neurodegeneration, amyloid plaques, and vascular dysfunction involved in the disease. In addition, he will teach and supervise biomedical engineering students and take part in the Master of Science programme in Neuroscience and Neuroimaging at the Sino-Danish Center for Education and Research.

The Henry Prize

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

The Henry Prize will be awarded every year, during a ceremony taking place at the annual CFIN Christmas 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 2012 The Outreach Henry Prize was awarded to Birgitte Fuglsang Kjølby, and to Jørgen Scheel-Krüger.

NEUROINFORMATICS

by Kim Mouridsen

Kim Mouridsen during the CFIN / MIND*Lab* Retreat at Sandbjerg Manor, 20-22 August 2012.
Photo: Leif Østergaard

The Neuroinformatics group focuses on developing techniques for early detection of pathological changes and for prediction of disease outcome and response to therapy. We do this by carefully modeling physiological mechanisms and utilizing computer intensive methods in large patient databases.

Estimating the volume of salvageable tissue in acute stroke patients has been a main area of research for a number of years. Building on earlier results from our group (Mouridsen et al. 2011, 2013) PhD student Kartheeban Nagenthiraja has developed a complex algorithmic framework that automatically detects tissue areas with reduced blood flow and areas of tissue that are irreversibly damaged by an occlusion of a feeding artery. This highly accurate and standardized procedure is of considerable interest in clinical routine and has led to an international patent application (Nagenthiraja et al., 2012). The techniques developed in this project may also hold potential as a means of identifying tumor volumes. In pursuit of this goal, Kartheeban is currently on a study visit at the Athinoula A. Martinos Center for Biomedical Imaging at Massachusetts General Hospital and Harvard Medical School.

In 2012, our segmentation work was extended by the development of a novel approach in which a wide range of MR images are distilled into a single risk map of the most likely disease progression based on historical data from hundreds of stroke patients. This recent technique utilizes complex statistic methodology to capture the stochastic behavior of disease progression due to unobserved so-called latent factors. Aarhus University has recently acquired the rights to this invention and has submitted a patent application (Mouridsen et al. 2012).

Our group enjoys the privilege of collaborating with many other CFIN / MIND*Lab* researchers on a wide range of projects. In 2012 we worked extensively with ischemic preconditioning (Dupont et al., 2012), cognitive models in pathological gambling (Linnet et al., 2012), imaging of tumor physiology Tietze et al., 2012), brain acetate metabolism and frontotemporal dementia (Lunau et al., 2012).

Our work is founded in a variety of statistical and mathematical frameworks, particularly pattern recognition and dimension reduction. These techniques are widely applicable within neuroscience, and in 2012 our group developed the Statistics in Neuroscience course as part of the Master's program in Neuroscience and Neuroimaging offered through the Sino-Danish Center for Research and Education, which is a collaboration between the Graduate University of the Chinese Academy of Sciences and the Danish universities. As this course presents advanced topics, we also offer a prerequisite course in mathematics and statistics. Both courses are taught at GUCAS in Beijing, China. Targeted especially for graduate students and PhD students in statistics and related fields, we also offer a graduate course in Statistical Learning at the Department of Statistics at Aarhus University.

NEW FACE AT CFIN

Jeanette Bødker Pedersen, BSc (Engineering) joined CFIN in Nov 2012. Her passion is image processing and computer vision and she has worked in this field in private industry for several years. Previous projects includes Machine Vision Quality Control and finding oil spills on ship radar images.

At CFIN Jeanette will be developing new mathematical techniques for the prediction of tissue outcome in acute stroke using MRI as well as CT imaging.

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NEW FACE AT CFIN

Mikkel Bo Hansen, MSc (chemistry), PhD, was employed as a data- and software engineer in the Neuroinformatics group in November 2011.

Mikkel did his PhD and postdoc within quantum chemistry. In this field, his key focus was the development of quantum mechanical theories to describe the interaction between electromagnetic radiation and molecular vibrations, as well as the development of fundamental methods for estimating the quantum mechanical vibrational wave-function, which is central to this field. The toolbox he brings from this background includes mathematics, computer science, basic research principles, physics, and chemistry. Especially the former three are qualities, which he continues to draw heavily on in his work at CFIN / MIND*Lab*.

Kim Mouridsen, Brian Hansen, and Michael Pedersen during the CFIN / MIND*Lab* Retreat dinner, 21 August 2012.
Photo: Alexandra Saragoza Scherman

Mikkel Bo Hansen (center) part of the "Early Bird Retreat Runners" at Sandbjerg during the CFIN / MIND*Lab* Retreat, 21 August 2012.
Photo: Torben Ellegaard Lund

MIND*Lab*

Danish centre for basal ganglia research (DCBR)

by Erik L. Johnsen and Karen Østergaard

The Danish centre for basal ganglia research (DCBR) was established in 2012 from the Translational Unit for Basal Ganglia Research in Aarhus (TUBA) with the aim of conducting clinical research projects on the basal ganglia disorders using the state-of-the-art brain imaging techniques available at the CFIN / MIND*Lab*. With the main focus on Parkinson's disease, the centre aims to improve current treatment options, such as the targeting for deep brain stimulation (DBS, see below) and to elucidate both the pathogenesis of this multi-system disorder (noradrenergic involvement in the disease), and the mechanisms of action of treatments (magnetoencephalography of DBS treated patients).

Deep brain stimulation

Deep brain stimulation (DBS) was introduced as a treatment option for tremor at Aarhus University Hospital (AUH) in 1996 in a close collaboration between the departments of Neurosurgery and Neurology. Later, in 1998 the indications at AUH were opened as a treatment-option for motor symptoms in Parkinson's disease (PD) and dystonia (Østergaard et al., 2000a; Østergaard et al., 2000b; Østergaard et al., 2000c; Østergaard et al., 2002). The clinical benefit of the treatment has now been proved locally as well as internationally in scientific clinical studies, and more than 200 patients have now been freed from disabling tremor, rigidity, bradykinesia or dystonia with this highly advanced treatment. Furthermore, their use of PD medications are reduced significantly, allowing for the patient and their caretaker to live a new life with this otherwise debilitating disease (Haahr et al., 2010; Haahr et al., 2011).

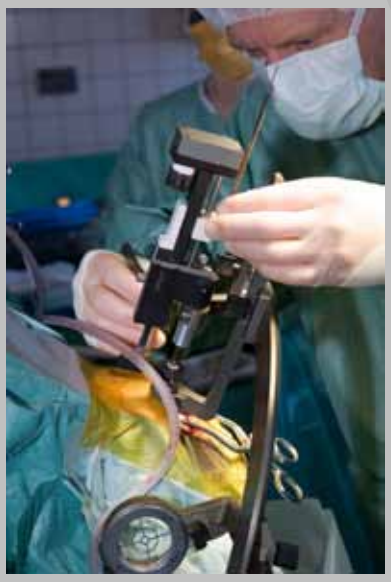

Figure 1a
The DBS-electrodes are implated with a stereotactic precision of less than one millimetre. During surgery, up to five micro-electrodes are placed simultaneously.

Figure 1b
During DBS surgery, the neurologist nurse and neurosurgeon constantly communicate with the awake patient to test for treatment effects and any adverse events.

DBS describes the continuous electrical stimulation through implanted electrodes into functional targets in the brain. Most often – as in PD – the implantation is bilateral and targets either the Globus Pallidus interna (GPi) or the Subthalamic Nucleus (STN) in the basal ganglia. The nucleus of choice is targeted using high-resolution MRI and CT. The target coordinates are extrapolated from the MRI and CT using a head-mounted frame and the electrodes are then descended through a small burr-hole in the skull to the target (see Figure 1a). Optimal positioning of the electrode is verified first by electrophysiological mapping of the target area and then by stimulation with the patient awake to test clinical effect and/or side-effects such as involuntary muscle contractions or speech disabilities (see Fibure 1b). Finally, the patient is sedated and the electrodes are connected to an implantable pulse generator (IPG) in the subclavicular area. The IPG is then programmed by telemetry to deliver pulses of exact frequencies, widths, and amplitudes to the target nucleus in order to alleviate the patient's specific symptoms.

Clinical benefits

Follow-up studies have documented that the clinical benefits of STN DBS are substantial and persistent after several years of treatment (Gervais-Bernard et al., 2009; Krack et al., 2003; Østergaard and Sunde, 2006; Rodriguez-Oroz et al., 2005; Schüpbach et al., 2005; Simonin et al., 2009). However, the course of disease is still progressive (see Figure 2). A study at the DCBR now looks into the persisting effects of stimulation 10 to 15 years after implantation. The study investigates both the effects clinically ON vs. OFF DBS in non-demented patients, and also include an epidemiological study to identify factors that predicted good outcome in the first patients treated in the period from 1998-2003. We hope to use this information to improve outcome in future patients. The study is on-going and conducted by Professor Karen Østergaard, post. doc. Erik L. Johnsen and medical student Margrethe Bang Henriksen with support from the Lundbeck foundation, the Free Danish Research Council and the Foundation of July 2nd 1984.

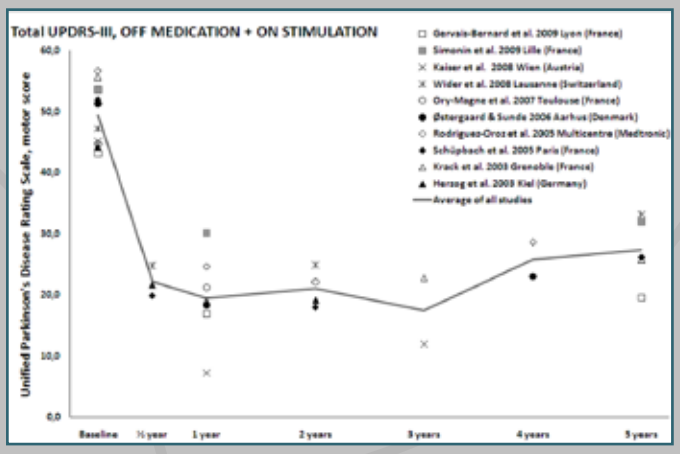

Figure 2
Although the stimulation effect is continued after 5 years, the disease continues to progress, as observed by constant increase in symptom-score (UPDRS-III).

Optimizing the target procedure and optimal electrode position

As mentioned above, the STN is targeted by MRI in combination with head CT. Based on these images, spatial coordinates of the central STN are identified and taken to the operation theatre where the surgeon installs the frame and arc accordingly. Even in PD, the optimal target for electrode positioning is debated; the dorso-lateral STN, the Field of Forell, caudal Zona Incerta among others. A recent study from our group proved the most optimal stimulation site to be within the dorsal half of STN, based on retrospective observations and quantitative gait analyses (Johnsen et al., 2010). This area of the STN can be sought intraoperative by use of multi-channel microelectrode recordings (MER). The microelectrodes pick up spike activity from single neurones as they traverse though electrically silent white matter into grey, active matter. MER has been used for all STN DBS procedures since 2002 and is effective and safe when the extra electrode paths are taken into account during target planning (Johnsen et al., in preparation).

Another aspect of optimizing the target is through improved MR imaging techniques. Diffusion tensor imaging (DTI) and diffusion weighed imaging (DWI) can be used to visualize known anatomical neural paths and fibre tracts. Optimizing the MR protocol to include DWI is currently being initiated at AUH. It is the aim of the study to optimize the electrode position by utilizing that tracts ending in the nucleus may be visualized and thereby targeted by the surgeon. The tracts of

FACTS

Selected ongoing studies:

The effect-mechanism of deep brain stimulation in Parkinson's disease evaluated with magnetoencephalography.
Associated researchers: Professor Karen Østergaard, Postdoc Erik L. Johnsen, Assistant Professor Lars G. Johansen, Assistant Professor Niels Sunde
Funding:Free Danish Research Council, Lundbeck foundation, Danish Parkinsons disease Association

Long-term effect of deep brain stimulation for Parkinson's disease – prospective/ retrospective study with follow-up more than 10 years.
Associated researchers: Professor Karen Østergaard, Postdoc Erik L. Johnsen, MD student Margrethe Bang Henriksen
Funding: Foundation of July 2nd 1984

Evaluation of MR based fiber tracking as a tool in deep brain stimulation for movement disorders.
Associated researchers: Professor Karen Østergaard, Assistant Professor Frederikke Rosendal, Assistant Professor Niels Sunde, Professor Morten L. Kringelbach, MD student Angus Stevner
Funding: Lundbeck foundation

A new method of source localisation in MEG analysis.
Associated researchers: Assistant Professor Dr. Vagn Eskesen, Department of Neurosurgery, University of Copenhagen, Assistant Professor Dr. Frederikke Rosendal, Professor Morten L. Kringelbach, DPhil and Senior Research Fellow at Department of Psychiatry, University of Oxford, Professor Dr. Karen Østergaard, PhD Dr. Erik Johnsen, PhD and research fellow Hamid Mohseni, Oxford Centre of Human Brain Mapping (OHBA)
Funding: Lundbeck foundation

Mestring af ændringer i livet efter Deep Brain Stimulation for Parkinsons sygdom - udvikling og afprøvning af et målrettet interventionsprogram til patienter og pårørende.
Associated researchers: Professor Karen Østergaard, Assistant Professor Anita Haahr, Professor Marit Kirkevold, Prof. Elisabeth Hall
Funding: Aarhus University, Foundation of July 2nd 1984, Danish Parkinsons disease Association

Noradrenergic mechanisms of depression and L-dopa induced dyskinesia in Parkinsons disease.
Associated reseachers: Professor Albert Gjedde, PhD student MD Adjmal Nahimi, Professor Karen Østergaard

Registry. A Huntington database study.
Associated researchers: Consultant Anette Torvin Møller, study-nurse Louise Møller
Funding: European Huntington Disease Network

choice may rely on whether the tracts are active or inactive, as measured by MEG. This complex evaluation requires the combination of the two modalities for optimized patient treatment. The DWI for DBS project is conducted by Associate Professor Frederikke Rosendal and MD-PhD student Mikkel Petersen, and Professor Karen Østergaard in collaboration with Professor Morten L. Kringelbach, affiliated with both Oxford and Aarhus University. The study is supported by the Lundbeck Foundation.

STN DBS Action Method

The exact mechanism by which DBS works remains unresolved and is a matter of intense debate. The effect differ according to whether the stimulating electrode is in grey or white matter, and also depend on the distance from the neuronal cell-body to the stimulation electrode. Also, findings have proposed both excitatory and inhibitory effects of HFS on BG signalling.

Four general hypotheses exist with respect to the DBS action mechanism: 1) depolarisation blockade, 2) synaptic inhibition, 3) synaptic depression and 4) modulation of pathological network activity (McIntyre et al., 2004). The interpretation of results obtained in the search for the action mechanism, however, is further biased by different views of the DBS effect; **a)** induction of a functional, reversible ablation versus **b)** stimulation and modification of neural networks (McIntyre et al., 2004).

Overall, the DBS effect on the output from local cells is dependent on the stimulation frequency (low or high frequency stimulation, LFS or HFS) and the position of the neuron relative to the electrode (McIntyre et al., 2004). When applying HFS stimulation directly into the STN, the frequency pattern may resemble γ-band activity over ß-band activity, thus enabling kinesis (Fogelson et al., 2005). This is contrary to LFS that is anti-kinetic when applied to the STN, probably resembling ß-activity (Fogelson et al., 2005). Intracranial local field potential recordings (LFP's) measured after 30 seconds of HFS shows a decrease of β-activity up to 10 seconds after stimulation turn off. Interestingly, 300 seconds of HFS induce β-decrease for 30 seconds. Thus, the activity can be instituted and withheld in the brain circuitry locked to stimulation duration. This may explain the carry-over effect of stimulation observed clinically: when the DBS is turned off, symptoms continue to build-up in up to four hours afterwards (Temperli et al., 2003).

These studies therefore, suggest that the aforementioned hypotheses should be regarded as different aspects of the same process, while the view of the DBS effect termed **b)** above appears most likely.

The effect-mechanism of DBS elucidated with magnetoencephalography.

Intracranial neurophysiological local field potential (LFP) recordings in the human parkinsonian STN have provided new insights into the probable pathology in the basal ganglia. As mentioned above, the STN in PD is dominated by synchronized neural oscillations in the β-band, but these oscillations may also be found in the motor cortex prior to, or during, voluntary movements (Marsden et al., 2001). Thus, activity deep within the brain can be detected on the surface by electroencephalography (EEG) or magnetoencephalography (MEG). Therefore, any modulation of neural networks that involve cortical structures may also be detected by EEG or MEG. MEG also has the potential to localize changes to specific structures.
MEG measures the weak magnetic fields that arise outside the scalp when the pyramidal cell dendrites in brain cortex layers III or V are activated by either an inhibitory or excitatory postsynaptic potential (IPSP or EPSP). The fields to be measured originate from approximately 10.000 activated neurons and their amplitudes are only between one octo (10-18) and one femto (10-15) Tesla. In comparison, the Earth static magnetic field lay around one milli Tesla. This much stronger field must be excluded from the recordings by the magnetically shielded room and special designed software such as beamforming methods (Mohseni et al., 2010) or a temporal signal space separation (Taulu and Simola, 2006). These methods have also proven able to exclude the major artefacts from the DBS hardware and stimulation in previous studies (Airaksinen et al., 2011).

Figure 3
Photo from a MEG in STN DBS-session. The patient is lying in the MEG-scanner, ready for registration.

In our study of the effect-mechanism of DBS, we investigate patients treated or eligible for treatment with STN DBS. The scope of the first study is to follow the hypothesized change of activity over time. As of March 2013, 12 PD patients with STN DBS have been to the MEG-scanner, where we measure the brains cortical activity "off medication and on DBS", "off medication and off DBS" each half hour for two hours, and finally "on medication and off DBS" one hour after a super-optimal dose of levodopa. So far, preliminary results of the first few patients, indicate that a change in frequency bands do occur although the work continues in order to categorize and quantify the changes (see Figure 3). The study is conducted in close collaboration between Professor Karen Østergaard, Postdoc. Erik L. Johnsen and Associate Professor Lars G. Johansen. The studies are supported by the Free Danish Research Council. From the fall of 2013, an engineering PhD student will be assigned to the project.

Noradrenergic contribution to PD symptomatology

With the onset of symptoms originating of PD in the lower brainstem, early symptoms of PD that include sleep disorder, cognitive deficits, depression and autonomic dysfunction, may appear prior to the motor symptoms of PD. These symptoms have been linked to the degeneration of the Locus Coeruleus and subsequent loss of noradrenergic innervations in the peripheral and central nervous systems.

The severity of motor symptoms may also be aggravated by the loss of noradrenaline which normally facilitate the release of dopamine (DA) and the firing of dopaminergic neurons. Similarly, lesions to both dopaminergic and noradrenergic neurons induce more severe motor deficits, compared to lesions of dopaminergic neurons alone. This relation suggests direct and indirect roles for noradrenaline in the emergence and severity of both motor and non-motor symptoms in PD.

In contrast to the possible effects of noradrenaline in some brain regions, non-physiological increase of noradrenaline, after L-dopa administration, may elicit dyskinesia while fluctuations of noradrenaline concentration in other regions may contribute to generation of symptoms of depression. The aim of this project is to examine the mechanisms underlying abnormal noradrenergic neurotransmission in Parkinson's disease (PD) and L-DOPA induced dyskinesia (LID), by means of positron emission tomography (PET) and MIBG SPECT. In the second part of the project, patients

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with or without LID and age matched controls are enrolled to participate in a double-blinded, randomized and placebo-controlled study to determine whether this complication can be influenced therapeutically by selectively targeting the noradrenergic system.

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Electa Neuromag TRIUX MEG scanner facility at CFIN / MIND*Lab*.
Photo: AUH Communication

MIND*Lab*

Self-awareness and conscious experience

by Hans C. Lou & Morten Jønsson

During the past decade we have studied the neurobiology of self-awareness. Self-awareness is a pivotal component of any conscious experience. This is evident already from the fact that any experience requires someone to have that experience. Conscious experience has been likened with a coin, with one face illustrating comparatively stable self-awareness and paralimbic activation, inseparable from the other face, consisting of shifting contents supplied from the outside world through sensory and semantic or procedural sources. During the past decade, the paralimbic neural network that causes self-awareness has been described in detail, using transcranial magnetic stimulation. It includes anterior cingulate/medial prefrontal, and posterior cingulate/medial parietal cortices that interact with bilateral angular gyri at the temporo-parietal junctions and with subcortical structures. This work has been done in collaboration with the Brain Stimulation Laboratory at Columbia University, New York.The network is located medially in the two hemispheres at the interface between information from emotions, memory, and body via the limbic system, and from the environment via neocortical and trans-modal association regions.

Using the new magnetoencephalographic equipment at CFIN we have demonstrated that the paralimbic network interacts by gamma synchrony which increases with the degree of self-awareness in conscious experience. Our recent data link gamma synchrony to self-awareness and conscious experience, and, in default, to developmental neuropsychiatric disorders involving deficient self-awareness and self- control. An example is our recent publication in PNAS on pathological gambling.

Rømer Thomsen K, Jønsson M, Lou HC, Møller A, Gross J, Kringelbach ML, Changeux JP. Altered paralimbic interaction in behavioral addiction. Proc Natl Acad Sci U S A. 2013; 110: 4744-9

Linking consciousness and emotion

In his PhD project *Linking consciousness and emotion* Morten Jønsson (MSc Electrical Engineering) is looking at communication within a paralimbic medial circuit involved in self-awareness. In a PET-study from 1999 the regional cerebral blood flow was measured in a state of Yoga Nidra (Yogic sleep). Despite a great variation in the content of the meditation (ranging from image visualizations to abstract thinking) 3 regions were active across all conditions: the

medial parietal cortex, medial prefrontal cortex and striatum. The same regions were found to be involved in a subsequent fMRI study investigating episodic retrieval of trait-adjectives with various degree of self-reference. This lead to a hypothesis that the paralimbic regions were involved in binding of experience from a minimal self (as seen in the Yoga Nidra study) to an autobiographical self (as seen in the fMRI study). To support the correlational studies transcranial magnetic stimulation (TMS) of the network (targeting precuneus) was found to causally eliminate the self-enhancement effect, where participant typically are better at recalling previous judgment of one-self compared to others.

With established knowledge of this network we were able to tap into the communication between its regions. MEG measures the electromagnetic signals generated mostly from the post synaptic activity of pyramidal cell columns tangential to the scull surface. By combining the recorded electromagnetic activity from 306 sensors with a head model based on a structural MR of the individual participant, we were able to model the source currents at our regions of interest. The interaction between the individual sources can then be quantized using functional connectivity measures such as phase locking and Granger causality.

Using this approach we have shown that the paralimbic regions predominantly communicate bi-directionally in the lower gamma frequency band. Using trans-cranial accumulating current stimulation (tACS) we tried modulating this network with external stimulation in the gamma range, but were not able to generate significant changes in the ability to recall previous judgment using this approach. In a recently published study we looked at the same network, a group comparing of healthy controls with a group of pathological gamblers of which some in addition had drug addiction (amphetamine). Using the MEG-system we found, that the self-referential network was dysfunctional in the group of gamblers independent on drug use and that they in addition performed poorer in a response inhibition task. This is to our knowledge the first MEG study looking at behavioral addiction, and given the interesting results we hope to carry out a longitudinal study, to verify the current results and to see if the apparently dysfunctional self-reference network is restored during cognitive treatment.

MIND*Lab*

Pain studies

by Troels Staehelin Jensen

Pain is defined as an unpleasant sensory and emotional experience associated with actual or potential tissue or described in terms of such damage. Pain is clearly a subjective phenomenon with complex interactions between sensory, emotional and cognitive functions. The use of brain scanning techniques have provided an excellent opportunity to look into the role of specific brain structures in processing and modulating noxious information both in health and in disease.

The imaging group at CFIN / MIND*Lab* consists of Nanna Finnerup, Lone Knudsen, Lene Vase, Emilia Horjales, Peter Svensson and Troels S. Jensen. We represent different disciplines, ranging from neurology, pain physiology, neurobiology, to psychology. Together, we have taken up the challenge to look at different aspects of pain.

Examples of studies in the pain group

Pain and religion:
Post doc Else Marie Jegindø has examined how praying may influence experimental pain in religious and non-religious healthy people and whether endogenous opioids are involved in this pain modulation. In ongoing studies, the brain areas that are involved are being examined.

Pain in amputees:
The cortical structures activated in patients with and without phantom pain in their missing limb are being examined following stimulation of the amputation stump. The hypothesis is that patients with pain have larger cortical areas than those without pain. This study is a joint project between Nanna Finnerup, Lone Knudsen, Lene Vase, Lone Nikolajsen, Peter Svensson and Troels S. Jensen

Neuropathic pain in spinal cord injury:
In a project involving patients with spinal cord injury, Nanna Finnerup examines the hypothesis that microglia activation in the thalamus may be involved in spinal cord injury neuropathic pain. This is examined in a PET study using the ligand PK11195 (see Figure 1).
The study is a collaborative study between Nanna Finnerup, Joel Aanerud, Per Borghammer, Per Munk, Troels S. Jensen and researchers in London: Federico Turkheimer, Imperial College London and Qi Guo, Centre for Neuroimaging Sciences, King's College London UK.

Catastrophizing and Pain:
Catastrophizing is a phonomen that may augment pain perception. Currently we are testing whether the degree of catastrophizing can change pain perception and pain thresholds. In upcoming studies we will examine to what extent this is also reflected in brain areas activated as determined by fMRI scans.

Function and Connectivity in the spinal cord and brainstem:
Nanna Finnerup has a collaborative grant with Dr. Jonathan Brook from the Clinical Research and Imaging Centre at University of Bristol, UK to examine connectivity in spinal cord and brainstem in patients with neuropathic pain. This study is planned to start in 2013.

The pain group also have a planned collaboration with Luis Garcia Larrea, Director of Research, Inserm, Head, Central Integration of Pain Unit - U879 INSERM & University Lyon on the common European reference system for optimal diagnostic and therapeutic procedures in refractory neuropathic pain (NP).

Pain clearly is a multidisciplinary topic, which spans from molecular biology, via genetics to psychology and different clinical disciplines such as neurology, dentistry, anesthesiology etc. To understand how noxious stimuli are processed and in the end result in the complex experience called pain, it is often necessary to interact across disciplines. The research project described by Emilia Horjales in the next section (see page 40-41) is in fact an example of a multidisciplinary study with collaboration between CFIN, Danish Pain Research Center, Department of Psychology, Department of Oral Physiology and the Department of Biomedicine and Centre for Integrative Sequencing, all at Aarhus University.

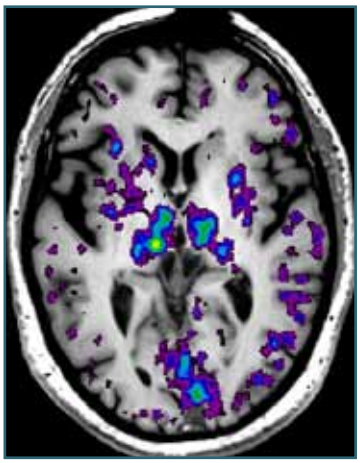

Figure 1
The PET tracer [11C]PK11195 can visualize neuroinflammation in the central nervous system. We are at the moment examining the hypothesis that patients with spinal cord injury have inflammation in the thalamus, thus contributing to their chronic pain.

MINDLAB COLLABORATORS

Danish Pain Research Center (DPRC) at Aarhus University Hospital

The Danish Pain Research Center (DPRC) conducts research in neuropathic pain with national, foundation and industry funding. The Center was founded in 1994 as a university-based clinical research unit by neurologist Troels Staehelin Jensen, who is Director of the Center. The mission of the research is to understand the mechanisms of neuropathic pain to improve treatment. The Center has a close collaboration with the Neuropathic Pain Clinic.

Investigators in the DPRC integrate a wide range of methods from pharmacology, neurophysiology, animal behavioral studies, fMR imaging and clinical observations, and the Center has all the equipment and resources required to perform clinical trials according to Good Clinical Practice including the instruments and experience necessary to carry out quantitative sensory testing using thermal, electrical, tactile and vibratory stimuli.

Current areas of research interests include spinal cord injury pain, postoperative pain, poststroke pain, complex regional pain syndrom, painful peripheral neuropathy and pain and depression.

The DPRC is located in the beautiful old Building 1 at Aarhus University Hospital, Nørrebrogade.

Troels Staehelin Jensen, Nanna Finnerup, DPRC

Peter Svensson,
Department of Dentistry, AU

Professor Peter Svensson, **Section of Clinical Oral Physiology, Department of Dentistry, Aarhus University** has collaborated with DPRC for a number of years in particular in relation to the understanding of the trigeminal nociceptive system. Orofacial pain mechanisms are being studied with a variety of different techniques spanning from advanced psychophysical assessment of somatosensory sensitivity in the face and oral cavity, autonomic measures of jaw muscle pain, adaptation of jaw motor function during pain using EMG, reflex studies and kinematic tests and several other physiological measures in humans. The research carried out at Clinical Oral Physiology can be considered a type of neuro-odontology with strong relationships to cognitive neuroscience, neurology, psychology and classical dental subspecialities.

Pain studies - relation between pain perception, emotions and genes

by Emilia Horjales

Everyone will experience acute pain at some point in their life: stubbing a toe, burning a finger or cutting themself. The ability to experience acute pain is vital for our survival and well-being. Pain generates a drastic deviation from the homeostatic balance, which serves to warn us about dangerous and tissue-damaging circumstances. Thus the brain activates the defensive behavior and - after the acute situation - allows protection of the damaged body part while it heals. Therefore, acute pain functions are of great importance as a warning system.

Pain is the most commonly reported symptom in clinical settings. However, in many cases, pain conditions are still difficult to diagnose and treat. This is in part due to the high variability of pain sensitivity and pain expression within and between patients. The expression and perception of pain are determined by a mosaic of gender, cultural, neurobiological, genetic and emotional factors. Recent studies have reported associations between specific genes variations and pain perception.

Serotonin (5-HT) is a neurotransmitter highly involved in a wide range of behaviors such as mood and nociception[1, 2]. The serotonin transporter (5-HTT) is a key player in 5-HT signaling as it regulates the uptake of serotonin into the presynaptic neuron for recycling or degradation after serotonin has been released, thus playing a critical role in determining the duration and intensity of serotonin communication. The serotonin transporter is coded by a single gene (SLC6A4) located on the long arm of chromosome 17. The combination of two well-described polymorphisms on the promoter region of the gene appears to influence the efficiency with which the 5-HTT returns serotonin to the presynaptic neuron. The combination of these two polymorphisms is referred to as “tri-allelic” 5-HTTLPR, and permits a functional division of individuals into high (LA/LA), intermediate (LA/LG; SA/LA) or low (SA/SA; LG/SA) expression of the serotonin transporter protein. Subjects with a low expression of 5-HTT have been associated with higher scores of neuroticism, anxiety traits[3-5], and a higher predisposition for depression, eating disorders and attention deficit disorder[6-8].

In a previous behavioral study we showed that participants with the genotype corresponding to a high expression of the 5-HTT are able to modulate the perception of pain by their emotional state, reporting higher intensities of muscle pain during negative emotions (generated by watching unpleasant pictures) and lower muscle pain intensities during positive emotions (generated by pleasant pictures), see Figure 1; behavior that is not present in participants with the genotype corresponding to a low or intermediate expression of the protein. It is then imaginable that the emotional modulation of pain perception observed in these participants is generated by a different brain-activation pattern.

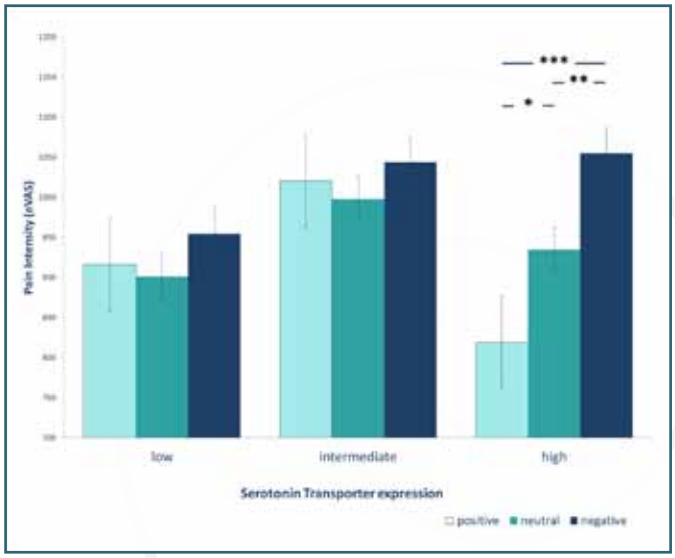

Figure 1
Pain intensity reported during visual stimuli presented by triallelic 5-HTTLPR. In the high expression group, positive pictures (white) decreased pain intensity (area under the curve) compared with neutral (gray) and negative pictures (black). Negative pictures (black) increased pain intensity compared with neutral pictures (gray). No differences were observed in the low and intermediate 5-HTT expression groups. *P < 0.05; **P < 0.005; ***P < 0.001 (two-way analysis of variance).

In our most recent study, we have been able to elucidate for the first time, the brain areas involved in the interaction between positive and negative emotions and deep muscle pain. As showed in Figure 2, the emotional modulation of deep muscle pain perception involves the dorsolateral prefrontal cortex and near to or in the depths of the intraparietal sulcus.

In addition, we have been able to compare the brain response to emotional modulation of deep muscle pain between individuals with the genotype corresponding to the low and the high expression of 5-HTT. We found no significant differences between the genotypes, which indicates that the emotional modulation of muscle pain observed in participants with a high expression of 5-HTT might be regulated in subcortical areas.

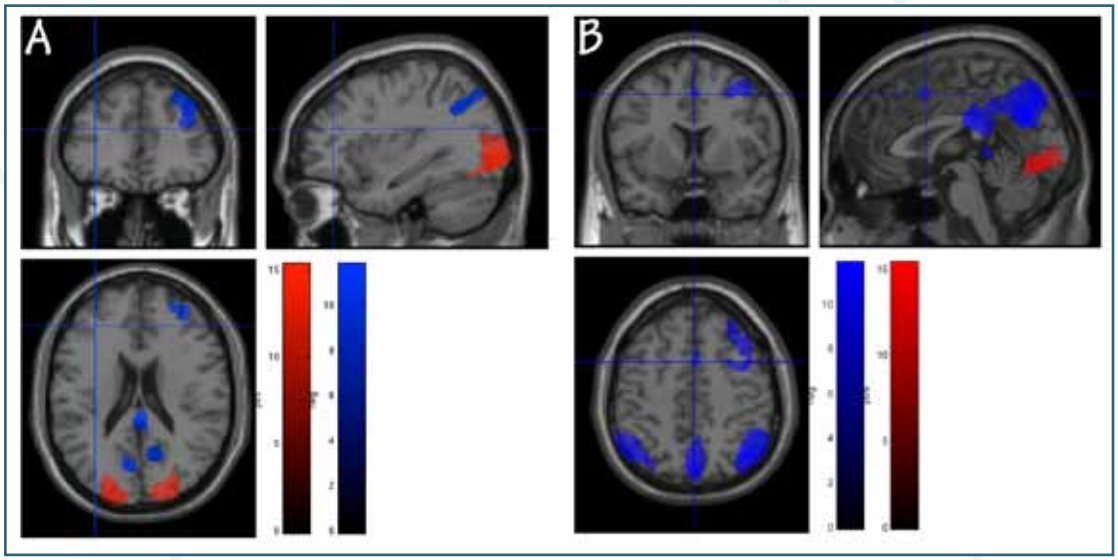

Figure 2
Brain areas involved in the relation between emotions and deep muscle pain perception. Areas with significantly greater activation during negative pictures and pain stimulation in red, and during positive pictures in blue. FEW $P_{corrected}$ < 0.005. VLPFC, ventrolateral prefrontal cortex; FCC, frontal cingulate cortex; PCC, posterior cingulate cortex.

It is thus likely that the emotional pain modulation associated with the 5-HT pathway is regulated at the spinal cord level. A modulation of nociception by emotions at a spinal cord level has previously suggested by Rhudy and colleagues[9] and Roy and colleagues[10]. However, further brain imaging studies are required in order to investigate where the emotional modulation of muscle pain regulated.

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NEW FACE AT CFIN

Emilia Horjales, MSc. Biol., Lic. Med., PhD student, Danish Pain Research Center.

Emilia holds a MSc in Biology from Universidad Nacional Autonoma de Mexico from 2007, and has since continued her education for Lic. Med. at Karolinska Institutet in Stockholm, Sweden, 2010.

Her primary research interest are within effects of emotions in pain perception, and she is currently working on her PhD: Studies on the relation between pain perception, genes and emotions at the Danish Pain Research Center, Aarhus University Hospital.

Hedonia: TrygFonden Research Group

2012

by Morten L. Kringelbach

One of the highlights of 2012 was the publication in Scientific American of our article "The joyful mind" about the emerging new science of pleasure. In Hedonia: TrygFonden Research Group we continue the search for the neurobiological underpinnings of human pleasure. For this, we use a wide range of scientific tools from psychological tests and neuroimaging to deep brain stimulation and computational modelling, which allow us to make new discoveries.

In previous annual reports we have described many of the different aspects of the research from e.g. the impact of the cuteness of infant faces and sounds to the alleviation of human suffering with deep brain stimulation. This year we will briefly describe the use of computational modelling for understanding the role of spontaneous brain activity in generating adaptive behaviour. We are fortunate to be able to collaborate on this research with one of the great pioneers in the field, Professor Gustavo Deco (Barcelona).

Resting or on stand-by

Someone who is awake but not performing any task, physical or mental, is said to be resting. In this state, unlike sleeping, the person is conscious and ready to respond promptly to any sort of external stimulation or cognitive requirement. One could say that the person is somehow on stand-by: although still and quiet, she is awake, ready to suddenly chase a fly that lightly lands on her arm, or to immediately turn her head towards a disturbing sound. Notably, while the person is resting and the body is static, the brain instead seems to be actively engaged, exhibiting spatiotemporally organized fluctuations of neuronal activity. These resting-state fluctuations emerge spontaneously during quiet wakeful rest and vanish either when triggered by a task or when attention to the external environment fades and the person falls asleep (Larson-Prior et al., 2011).

Several studies have speculated on the link between this resting brain activity and underlying high-order cognitive processes such as moral reasoning, self-consciousness, remembering past experiences or planning for the future (Buckner et al., 2008; Lou et al., 1999; Morcom and Fletcher, 2007; Saxe and Kanwisher, 2003; Wagner et al., 2005). However, findings of resting brain patterns in anesthetized monkeys (Vincent et al., 2007) and, more recently, in rats (Lu et al., 2012), points to a more fundamental origin of resting brain activations (see Figure 1) (even if animals may also have a need for self representations).

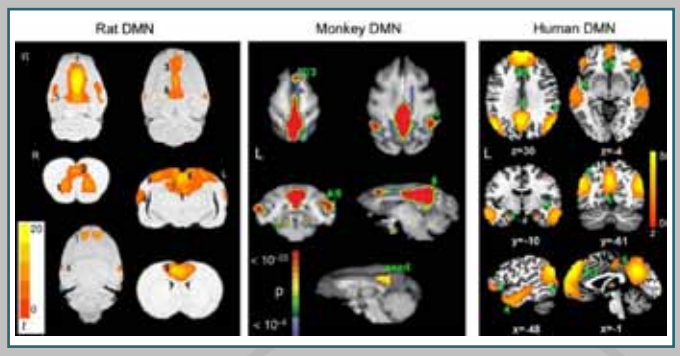

Figure 1
Comparison of the Default Mode Network (DMN) in rats, monkeys and humans. The regions composing the DMN exhibit correlated neuronal activity during rest. Adapted from Lu et al. (2012).

Evidence of coordinated brain activity during rest has been detected primarily with functional magnetic resonance imaging (fMRI) (Biswal et al., 1995), but also with optical imaging (Arieli et al., 1996), positron-emission tomography (PET) (Raichle et al., 2001), electrophysiology (Leopold et al., 2003), electroencephalography (Laufs et al., 2003; Mantini et al., 2007) and, more recently, magnetoencephalography (Brookes et al., 2011; de Pasquale et al., 2010). This consistency across imaging techniques, which provide more or less direct measures of neuronal activity, strongly suggests a robust intrinsic brain dynamics happening at multiple time-scales.

Resting-state activity

Explorations into the organization of resting-state activity in the brain have revealed the existence of temporally correlated activity between spatially segregated brain structures, defining the so-called Resting State Networks (RSNs). Most of these RSNs have been shown to greatly overlap with functional architectures present during goal-directed activity, such as vision, language, executive processing, and other sensory and cognitive processes. On the other hand, one particular set of regions spatially distributed over the medial prefrontal, parietal, and posterior cingulate cortices has been found to exhibit correlated activations especially during rest, and therefore this specific RSN has been labelled as 'default-mode network' (DMN).

To investigate the origin of the co-activation patterns defining RSNs, several studies have inspected their relationship with

the underlying map of long-range axonal connections using imaging techniques that allow the detection of white matter pathways in the living brain (Hagmann et al., 2008; Sporns et al., 2000) Although a remarkable match has been found between the neuroanatomical network and resting-state functional connectivity patterns, anatomical information alone does not uncover the dynamical mechanisms governing resting-state activity in the temporal and spectral domains.

Instead, to investigate how the resting-state dynamics unfolds from the neuroanatomical network, we need to explore the way segregated brain areas (built of millions of highly interconnected neurons) interact. To do so, it is useful to use reduced dynamical models of cortical regions. Following different reduction lines, a number of theoretical studies have attempted to reduce the complexity of the Nobel prizewinning work of Hodgkin and Huxley (1952) on action potentials to describe parts of neural population dynamics using only a few differential equations (Breakspear et al., 2003; Fitzhugh, 1961; Nagumo et al., 1962; Wilson and Cowan, 1972; Wong and Wang, 2006). These equations represent models of neural masses and are particularly useful for large-scale brain models, because they allow simulating the global dynamics of large neuronal ensembles at low computational costs. When these neural pools are embedded in the neuroanatomical network, they interact with each other through excitatory-to-excitatory connections. Furthermore, if we consider axonal conduction speed to be finite, these long-range interactions are time-delayed, which, together with noise naturally present in the brain, introduce additional degrees of complexity to the system. To explore this complex network dynamics, computational models are valuable tools since they allow exploring the non-trivial relationship between structural and functional connectivity, not simply by comparing the corresponding spatial maps, but by considering the interaction of dynamical cortical units.

The brain as a dynamical system

To understand the natural mechanisms permitting the exploratory dynamics observed in the wakeful resting state, one can look at the brain as a dynamical system. Indeed, the complex space-time structure of the brain's wiring diagram, together with a myriad of biochemical processes, form a dynamical framework capable of holding an infinite number of mental states over which cognition unfolds (Kelso, 2012; Tononi et al., 1994). The existence of different input-dependent stable states in the brain has been evident since the first

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  Do crying babies make you sharper?
- BBC, Pleasure: four part documentary, 1 November 2012
  Documentary on the pleasures of sugar, alcohol, opiates and tobacco

Science writing:

- *For crying out loud!*, Old Members, The Queen's College Newsletter, 2012
- *Dyb hjerne stimulering for lindring af kronisk smerte* (with I. Engell & M. Jønsson), BestPractice, 2012
- *Fødselsdepressioner*, videnskab.dk, 2012

Art:

- *Early psychoanalysis, surrealism and shellshock'*
  (dialogue AS Byatt), The Queen's College, 4 December 2012
- *On balance* (with dancer Subathra Subramaniam),
  De La Warr Pavilion, Bexhill, 21 July 2012

human electrophysiological recordings, which revealed that strong Alpha rhythms (8–13 Hz) were substituted by Beta rhythms (13-30Hz) when subjects opened their eyes (Berger, 1929). From the perspective of complex systems' science, this phenomenon can be seen as a transition between two stable states, triggered by an external input. In other words, while the eyes are closed, we can imagine the brain finds a stable equilibrium in a regime in which Alpha (8-12Hz) oscillations emerge. Opening the eyes provokes a dynamical transition in phase space and another equilibrium point is found, in which Beta (12-30Hz) oscillations appear. However, the genesis of these oscillations, as well as the transition between brain states, remains incompletely understood, even today.

Over the years, electrophysiological studies have identified characteristic brain rhythms ranging from <0.1 to 100Hz that appear and disappear according to the mental state in which the brain in engaged. Moreover, with the improvement of neuroimaging techniques, it became possible to map the sources of such rhythms across the brain, resulting in a temporal and a spatial pattern for each brain regime. Notably, consistency was found in the spatio-temporal signature of brain states across healthy humans. Although many brain states are activated by means of stimulation, such as a sensory perception or a mental operation, other brain states, like resting and sleeping, occur spontaneously from intrinsic brain processes. Still, little is known about the biophysical mechanisms underlying the spatio-temporal patterns of different brain states and the dynamical transitions between them.

Among all brain regimes, the resting state is particularly interesting from the perspective of dynamical systems because it exhibits not one, but several coexisting spatio-temporal patterns. These findings suggest that, during rest, the brain is routinely exploring different brain states, resulting in a multistable stationary regime. Deco and colleagues (2009) proposed that this spontaneous switching between brain states could be due to noisy transitions from one equilibrium point to another in the state space of the brain. Furthermore, the authors provided a useful analogy to explain this behaviour: 'the resting state is like a tennis player waiting for the service of his opponent. The player is not statically at rest, but rather actively moving making small jumps to the left and to the right, because in this way, when the fast ball is coming, he can rapidly react'. On receiving an external stimulus, the stability of the state involved in processing that input increases with respect to the others, allowing a rapid switch between brain states at the onset of a task (see Figure 2).

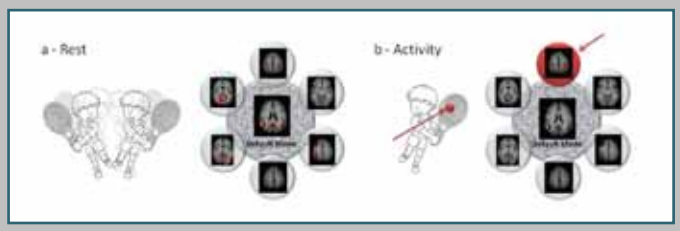

Figure 2
Allegorical illustration of resting-state versus active-state. (a) During rest, the brain is in a multistable regime exploring different available mental states, like a tennis player who jumps from left to right while waiting for the service of his opponent. (b) In this way, upon receiving a stimulus, the brain can rapidly react and engage the regions in charge of processing the stimulus. (Based on Deco et al. 2009).

While the real mechanisms underlying resting-state activity remain unclear, a fruitful way to explore this intriguing dynamics is to combine existing concepts of theoretical physics and experimental electrophysiology with brain-inspired network structures and, by means of computational models, investigate the natural conditions under which such type of nonlinear complex dynamics could emerge.

NEW FACE AT CFIN / HEDONIA

Angus Stevner is a research year student from the Faculty of Health and Medical Sciences at University of Copenhagen, affiliated to Department of Neurosurgery, Aarhus University Hospital and Hedonia: TrygFonden Research Group based both at CFIN, Aarhus University, and in the University Department of Psychiatry, Oxford. He is a medical student at University of Copenhagen and is currently working on his BSc thesis, which is part of his research project at CFIN. His research is focused on analysis of magnetoencephalography (MEG) data. Specifically he is interested in improving the localisation of sources of neural activity from MEG measurements. Additionally he is interested in the analysis of functional connectivity in MEG and its application to resting state data in clinical settings, such as Parkinson's Disease and Sleep disorders.

NEW FACES AT CFIN / HEDONIA

Joana Cabral is a post-doctoral researcher investigating the physical mechanisms underlying brain function with Professors Gustavo Deco and Morten Kringelbach. Her research uses computational models to test theoretical predictions of the brain's network dynamics.

Henrique Fernandes is a PhD student in Hedonia: TrygFonden Research Group. He holds a Master in Biomedical Engineering from New University of Lisbon in Portugal. His PhD project focuses on developing sophisticated computational models of resting state networks in the human brain in health and disease, by combining measures of neuroanatomical connectivity (Diffusion Tensor Imaging) and functional activity (magnetoencephalography and functional magnetic resonance imaging). His research aims to not only to elucidate the principles of deep brain stimulation but also to produce models that can predict new potential DBS targets and hence optimize the balance of the brain.

Mikkel Petersen is a PhD student currently stationed in Oxford, UK. His PhD is a collaboration between the Department of Neurosurgery, Aarhus University Hospital, CFIN, Aarhus University and the Oxford based Hedonia: TrygFonden Research Group. His research is focused on patients treated with Deep Brain Stimulation for Movement Disorders. In these patients he will explore the brain connectivity through the use of Diffusion Tensor Imaging and network analysis. His long term goal is to implement these techniques as a part of the pre-surgical planning for DBS patients. In 2014 he will go back to school for a short period to finish his degree in medicine at Aarhus University.

FACTS

Talks - Professor Morten L. Kringelbach:

- *Scars of War*, The Queen's College, Oxford, 5 January 2012
- *The neuroscience of the parental brain*, Dept. of Psychiatry, Oxford, 10 January 2012
- *Neurobiology of pleasure*, FHS, Dept. of Psychiatry, Oxford, 20 January 2012
- *Deep brain oscillations*, Oxford Synoptics FHS lecture, 24 January 2012
- *The neuroscience of the pleasure of musical rhythm*, Psychiatry, Oxford, 21 February 2012
- *Pleasure and psychosurgery*, Dept. of Psychiatry, Oxford, 16 March 2012
- *Finding pleasure*, KCL Public lecture, London, 13 March 2012
- *Developmental aspects: Origins of psychiatric disorder*, MSc Lecture, Oxford, 2 May 2012
- *Pleasures*, invited lecture, University of California Riverside, USA, 4 May 2012
- *Neuroimaging of olfaction*, Keynote lecture, Danish rhinologists, Denmark, 11 May 2012
- *Combining DBS and MEG*, DBS conference, Aarhus, Denmark, 24 May 2012
- *The neuroscience of olfaction: implications for development*, Psychiatry, 29 May 2012
- *Forandringens hjernerum*, PPE12, Denmark, 18 June 2012
- *Pleasures of the brain*, De Montfort University, UK, 25 June 2012
- *Pleasure and pain in the human brain*, Presidential lecture, IASR, Portugal, 9 July 2012
- *On balance*, De La Warr Pavilion, Bexhill, UK, 21 July 2012
- *Using DBS-MEG to understand chronic pain*, Biomag 2012, Paris, 27 August 2012
- *Pleasure principles*, University of Michigan, USA, 18 September 2012
- *A joyful mind: pleasure systems in the brain*, Max Planck, Munich, Germany, 30 October 2012
- *Pleasure principles of food intake*, Royal College of Psychiatrists, UK, 2 November 2012
- *The pleasure of love*, Foundation Brocher, Switzerland, 5 November 2012
- *Den nydelsesfulde hjerne*, Helenekilden, Cairos, Denmark, 15 November 2012
- *Pleasures of the parental brain*, University of Reading, UK, 29 November 2012
- *Making sense of shellshock* (with AS Byatt), Scars of War Series, 4 December 2012

Discovering eudaimonia for the Hedonia group on a beautiful summer's evening in Sandbjerg, August 2012. Photo: Hedonia: TrygFonden Research Group.

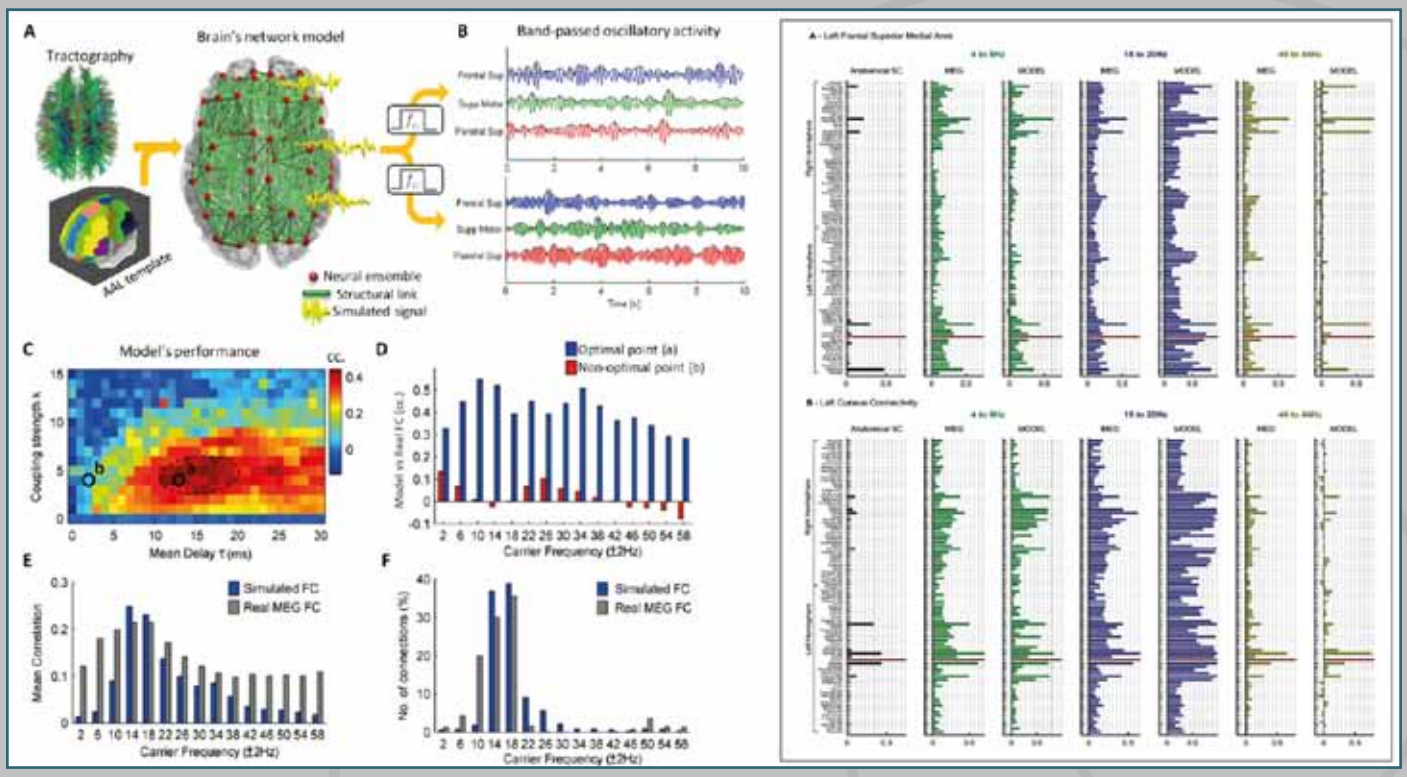

Figure 3
Pilot data: Computational modelling closely matches the data from resting state networks (measured with MEG) using data from the underlying structural connectivity (measured with DTI). The figure shows the oscillatory network interactions and frequency-dependent functional connectivity for simulated and real data (A-F). In the box is shown the close match between the frequency-specific seed-based connectivity maps from the Frontal Superior Medial area (A) and the left Cuneus (B) with all other regions in the brain (rows) (Cabral et al, in review).

Overall, resting state networks are not just important for understanding the fundamental dynamics of the healthy brain. Over the last decade, a large number of studies have reported altered resting brain activity in a wide range of mental illnesses. Such results not only illustrate the importance of balancing resting-state dynamics for an optimal cognitive function, but also provide insights to understand the intrinsic mechanisms leading to and potentially treating the diseased brain (Kringelbach et al., 2011). One particular hypothesis that we are currently pursuing is that the activity in the default mode network is modulating the activity in other RSNs and that this network must be modulated in order to help alleviate anhedonia.

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Media News:

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- Reuters, *Babies' cries get a speedy response* (Kate Kelland), 11 January 2012
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- Baby cry story ran in a total of 78 news outlets around the world, 11 January 2012
- Daily Telegraph, *Why screaming babies are so hard to ignore* (Nick Collins), 21 January 2012
- Videnskab.dk, *Babyers gråd skærper vores reaktionstid* (Ditte Svane-Knudsen), 5 February 2012
- dr.dk, *Babys gråd får os på dupperne* (Dorthe Boss Kyhn), 6 February 2012
- Sciencenordic.com, *Baby cries shorten our reaction time* (Ditte Svane Knudsen), 10 February 2012
- Videnskab.dk, *Hvorfor bliver man træt efter en orgasme?* (Ditte Svane-Knudsen), 16 February 2012
- BBC Focus Magazine, *Cute on the brain* (JV Chamary), 1 March 2012
- Wall Street Journal, *Infant distress* (Ann Lukits), 27 March 2012
- På Vej, *Forandringer kan være fulde af lyst* (Kirsten Weiss), 18 June 2012
- Kristelig Dagblad, *Nydelse pirrer alle vores sanser og er helt vor egen* (Annette Hagerup), 22 June 2012
- Jyllands Posten, *Lykkejagten på samvær, sex og god mad styrer vores handlinger* (Tea Krogh Sørensen), 3 July 2012
- The Guardian, *Why crying babies are so hard to ignore* (Alok Jha), 17 October 2012
- The Times, *Brain is wired to respond to baby's cry* (Tom Whipple), 17 October 2012
- Daily Telegraph, *Why you will never sleep on a plane if a baby is crying* (Nick Collins), 17 October 2012
- The Daily Mail, *Why you can't get a baby's cry out of your head (even if you don't have children)* (Fiona Macrae), 17 October 2012
- Sun News Network, Canada, *Baby mysteries unravelled* (Thane Burnett), 18 October 2012

TrygFonden

MUSIC IN THE BRAIN

by Peter Vuust

The Music In the Brain group (MIB) is an interdisciplinary research group situated uniquely between musical excellence at Royal Academy of Music, Aarhus/Aalborg and the outstanding neuroscientific facilities at CFIN. MIB aims to foster breakthroughs in our understanding of brain function and plasticity in relation to music, with the aim of influencing music education and the clinical use of music. Meanwhile, we aim to uncover mechanisms fundamental to music perception, brain plasticity, learning and neurorehabilitation.

MIB research evolves from two central questions:

1. How is music perception and experience guided by underlying predictive brain mechanisms and networks and how are these shaped by long-term music training and expertise?
2. How can music inform our understanding of prediction as a fundamental brain principle?

The research approach of the MIB group is centered around the Predictive Coding of Music hypothesis (PCM) formulated by Peter Vuust and colleagues in 2009.[1] PCM states that music, based on the concept of anticipation, reflects fundamental survival-related brain mechanisms associated with predicting future events. This principle has been demonstrated in relation to auditory pre-attentive processing[2] and to processing of musical pleasure in the dopaminergic pathways[3] (see report on the following pages), tying music anticipatory processes to emerging models of brain function.[4,5]

Central to the predictive coding theory is the idea that the brain tries to minimize the error between input and anticipatory model. At each level, the sensory information is matched to the internal predictive model. If there is a mismatch between the model and the sensory input at any level of this hierarchy, a prediction error occurs and a neuronal error-message is fed forward to higher, more integrative levels. Here the prediction error is evaluated and depending on the degree, to which it violates the internal prediction, the brain either changes its internal model or it changes the way it samples information from the environment. Hence, the predictive coding theory is a model for both musical perception and learning (see Figure 2 on page 50). This is directly applicable to studies of music processing using EEG or MEG to measure the mismatch negativity, a negative deflection of the event-related potential (ERP).

A promising lines of research within the MIB group research is the recent development of the musical multi-feature paradigm which studies sound deviations in melodic patterns.[6] This EEG/MEG paradigm tests pre-attentive processing of 6 different types of deviants embedded in a melodic context and may be used to distinguish between musicians from different musical genres and between musicians and non-musicians.[7,8] It is also correlated to measures of musical competence.[9,10] This idea is now being investigated in populations with various difficulties in music processing including Cochlear Implant users at Aarhus University Hospital[11] and Hannover Medical School, in people with autism spectrum disorder at Aarhus University Hospital, in individuals suffering from amusia at Goldsmiths College, London, and in monkeys at Laboratory of Neuropsychology, NIMH, National Institutes of Health, Washington.

Musical expertise is a special interest for MIB. In 2012, Anders Dohn successfully defended his PhD thesis concerning one of the most remarkable and rare musical abilities of all: Absolute pitch ability (AP). Using a specially designed tone production device, he showed, that the quality of the absolute pitch ability is dependent on the amount of musical practice, and that AP possessors are more accurate in their production of the white than the black keys on the piano. A surprising finding of this investigation was the discovery of a link between AP and autism, revealing that the AP ability is associated with personality traits of the autism spectrum disorder.[12] Hence, even though AP is considered the trademark of the highest musical expertise, it may come at the expense of other cognitive abilities.

Findings such as these ties the MIB research on fundamental brain processing[13] to clinical questions. One of the main aims of the MIB group is to use the refined understanding of the fundamental principles behind brain processing of music as a means to influence both music education and the clinical use of music. Clinical applications of music are studied intensively in the MIB group. Music has great potential in rehabilitation after stroke and for treatment of other cognitive, sensory, and motor dysfunctions resulting from disease of the human nervous system. MIB is currently investigating the effect of musical training on linguistic skills in cochlear implantees, the influence of music on pain perception,[14] on sleep quality in traumatized refugees,[15] and on patients suffering from autism spectrum disorder in close collaboration with clinicians at AUH. This research may later be extended to studies on the influence of music on patients suffering from a multitude of disorders such as stroke, anxiety, stress, depression and schizophrenia.

In 2012, we welcomed several new researchers in the Music In the Brain group and initiated new international collaborations. Mads Hansen, Kira Jespersen and Niels Christian Hansen all began their PhD studies with the MIB group. Mads Hansen on the musical multi-feature paradigm in collaboration with Elvira Brattico from Jyväskulä in Finland and Lauren Stewart from London, Kira Vibe Jespersen on music in individuals suffering from sleep disorder in collaboration with Eus Van Sommeren from Amsterdam and Morten L. Kringelbach from Oxford, and Niels Christian Hansen on modeling of behavioral and brain responses to music in individuals from different musical genres in collaboration with Marcus Pierce from London. PhD student Line Gebauer spent 6 months at Krista Hyde's lab in Montreal, specializing in morphological measures of brain anatomy. The research of the MIB group was also represented by lectures and posters at important international conferences, workshops and institutions within the field of neuroscience and music such as the ICMPC in Thessaloniki, Symposium on the Neurophysiology of Interval Timing in Mexico, University of Monterey, Mexico, ISMIR in Portugal, Goldsmiths College, UK, Helsinki University, Finland, The Brain Prize Meeting, Sandbjerg, Denmark, and many more. Furthermore, the MIB group hosted visits by prominent international researchers including Vickie Williamson, Andrea Halpern, Lauren Stewart and Eckart Altenmüller.

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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
- Gitte Westphael
- 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

MUSIC IN THE BRAIN

Musical pleasure cycles: listen, like, learn

by Line Gebauer

Music is consistently rated to be among the top ten things people find most pleasurable in life.[1] Consequently, researchers have suggested that music listening is rewarding in itself.[2,3,4] Like other rewards (such as food, sex and money), pleasurable music activates structures in the dopaminergic reward system, but how music manages to tap into the brain's reward system is less clear.

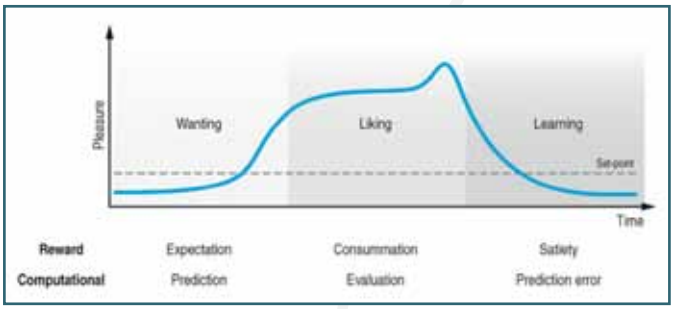

Figure 1. Pleasure cycles.
Pleasures are associated with a cyclic time course. Rewarding moments go through a phase of expectation or wanting for a reward, which sometimes leads to a phase of consummation or liking of the reward, which can have a peak level of pleasure (e.g. musical chill, encountering a loved one, a tasty meal, sexual orgasm, drug rush, winning a gambling bet). This can be followed by a satiety or learning phase, where one learns and updates predictions for the reward.

In a recent paper, we proposed a novel framework for understanding musical pleasure, suggesting that music conforms to the recent concept of pleasure cycles with phases of 'wanting/expectation', 'liking' and 'learning' (see Figure 1). We argue that expectation is fundamental to musical pleasure, and that music can be experienced as pleasurable both when it fulfils and violates expectations. The structure of music is highly repetitive and governed by statistical regularities.[5,6] The creation of musical expectations in the listener (of for instance, meter and tonality) seems to happen within the first few seconds of listening to a musical piece, and without a conscious cognitive effort.[7,8] Musical anticipation can be formulated according to Bayes' theorem, which is the cornerstone of Bayesian statistics and fundamental to the predictive coding theory.[9,10] Obviously, the brain cannot make up models or predictions *de novo*, but needs to rely on prior experience to model expectations for the future. This prior experience gives a prior probability, describing how probable an internal hypothesis of i.e. the musical structure is to be true. Prior probabilities are context-sensitive and hierarchical, hence we have a range of possibilities available to us where some are more likely to be correct than others and they change according to the context. Consequently, these predictions are products of the interplay between the subject's prior experience and the available sensory information. In this way, our predictions are built on prior experience and learning, but are still dynamic and context-sensitive (see Figure 2).

Dopaminergic neurons in the midbrain represent expectations and violations of expectations (prediction errors) in response to rewards.[11] Music is, however, not a concrete reward like money or foods, where value or magnitude can be calculated exactly. However, it was recently found, that the majority (60-90%) of dopaminergic neurons also show burst responses to different types of sensory events that are not directly associated with rewarding stimuli.[12,13] These responses are suggested to depend on a number of neural and psychological factors, including direct sensory input, surprise, novelty, arousal, attention, salience, generalization, and pseudo-conditioning.[14,15] An underlying alerting signal or incentive salience has been proposed to be the cause of these burst responses by dopaminergic neurons to sensory events.[13, 16] Thus, we argued that the human brain treats music as an alert/incentive salience signal, and suggest that the activity of dopamine neurons represent aspects of musical expectation and musical learning, but not directly the phase of music liking. Musical anticipations are hierarchically organized and based on prior experiences but are still highly context-sensitive. Dopaminergic neurons represent musical anticipations according to statistical regularities learned through musical exposure. For music, the wanting or expectation phase can be defined as the anticipation of a specific (pleasurable) musical

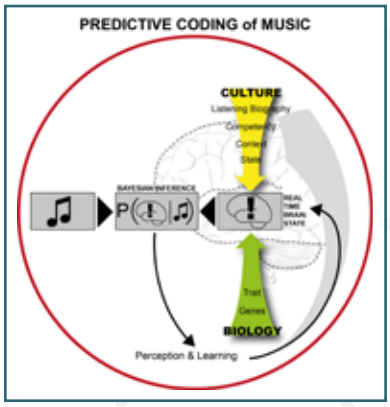

Figure 2. Bayesian predictive coding framework for musical perception and pleasure.
Music listening takes place in a dynamic interplay between structures in music and the predictive brain on the other. The real time brain model is dependent on cultural background, personal listening history, musical competence, context, brain state (including attentional state and mood), and innate biological factors. Our hypothesis suggests that the brain is constantly trying to minimize the discrepancy between its interpretation model and the musical input by iteratively updating the real time brain model (or prior) by weighting this model with the likelihood (musical input) through Bayes' theorem.

structure. The liking phase includes moments of peak pleasure corresponding to time intervals where the pleasure of the music is experienced most intensely; this can for instance be a certain chord progression, strong emotional responses or the time window around music-induced chills. A distinction between the wanting/expectation phase and the peak pleasure part of the liking phase is further corroborated by the finding of different neural responses to the two during music listening.[17] The learning phase is also a crucial part of musical pleasure, since it changes musical expectations,[5] and thus ultimately changes both the wanting/expectation phase and the liking phase for future listening experiences. Failed anticipations are linked to dopaminergic anticipatory firing followed by a prediction error. There is probably an individual optimum for when an unanticipated musical sequence is experienced as a pleasurable surprise, that result in increased dopamine firing and thus a higher dopamine release than a fully predicted musical sequence, and when it is too strange and results in a prediction error manifested as a depression of dompaminergic firing. Repeated exposure (and thus learning) of a musical piece increases liking, but only up to a certain point of satiety or even over-exposure, where the music is perceived as less pleasant.[18, 5, 19]

Pleasurable responses might be seen as evaluations of how well our brain predicts the future, but not in a black or white manner where correct predictions result in pleasure and failed predictions in aversion. Rather we believe the pleasure cycle serves as a motivational guide, directing our attention and behaviour towards potentially rewarding stimuli. Thus music is attributed high significance because it continues to stimulate our expectations, by being on the one hand highly predictable and on the other hand continually changing, resulting in minute prediction errors. The anticipatory interplay between the listener's expectations and the structure provided by the music is not a one-way process with a beginning and an end but continues throughout the musical pleasure cycle (see Figure 2). The anticipatory interplay is a continuous dynamic transaction, where new information in the musical structure continually influences the expectations of the listener and the expectations influence the perception of the subsequent music. Subsequently, the musical brain is shaped by cultural influence and training over the span of a lifetime, such that the anticipatory mechanisms guiding musical experience gradually change. This has dramatic effects on the way we experience music as evidenced by large differences between musicians and non-musicians in brain processing of auditory stimuli,[20, 6] and in brain structure.[21]

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MUSIC IN THE BRAIN

Behavioral and neuroanatomical correlates of absolute pitch ability

by Anders Dohn

Absolute pitch (AP), the ability to identify or produce a musical tone correctly without the aid of an external reference, represents a unique musical faculty that has puzzled scientists for decades. AP is a rare ability with a prevalence of around 0.01% of the general population, and the fact that AP cannot be learned in adulthood (unlike several other musical abilities such as relative pitch) has given rise to much speculation about its etiology[1, 2].

Absolute pitch and autism

Although AP is commonly considered to reflect musical giftedness, it has also been associated with certain disabilities after findings of a high prevalence of AP in individuals with autism. Consequently, we examined whether individual autistic traits are present in people with AP by quantifying subclinical levels of autism traits using the Autism-spectrum Quotient (AQ)[3]. We found a significantly higher degree of autism traits in musicians with AP (APs) than in musicians without AP (non-APs) and non-musicians, and the AQ scores were significantly correlated with pitch identification scores.

The group differences emerged however on subscales that are not part of the diagnostically crucial autism impairments, indicating that although AP is linked to autism, AP is most

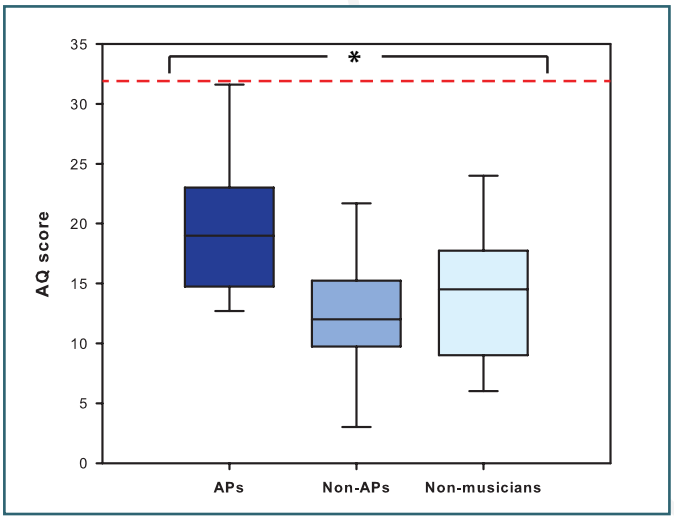

Figure1
Box plot showing the autism-spectrum quotient (AQ) score of absolute pitch possessors (APs), musicians without absolute pitch (non-APs), and non-musicians. The red dashed line shows the proposed AQ cut-off for distinguishing individuals who have clinically significant levels of autistic traits, according to Baron-Cohen[3].

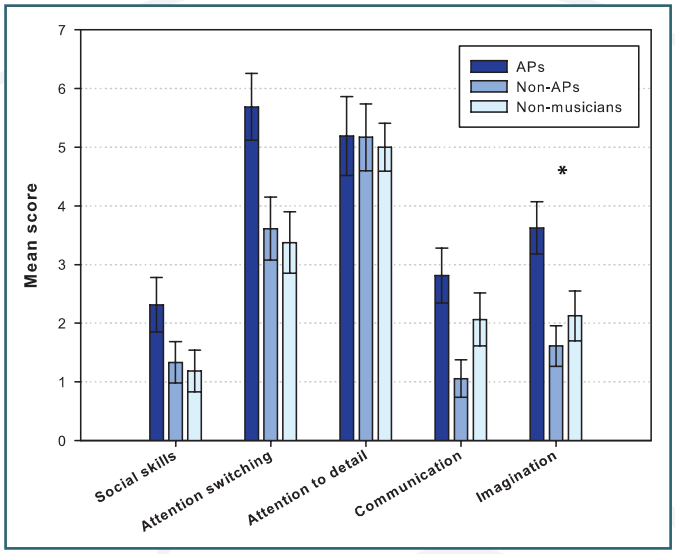

Figure 2
Bar plot showing the mean autism-spectrum quotient (AQ) factor score of all groups. The error bars indicate the standard error of the mean.

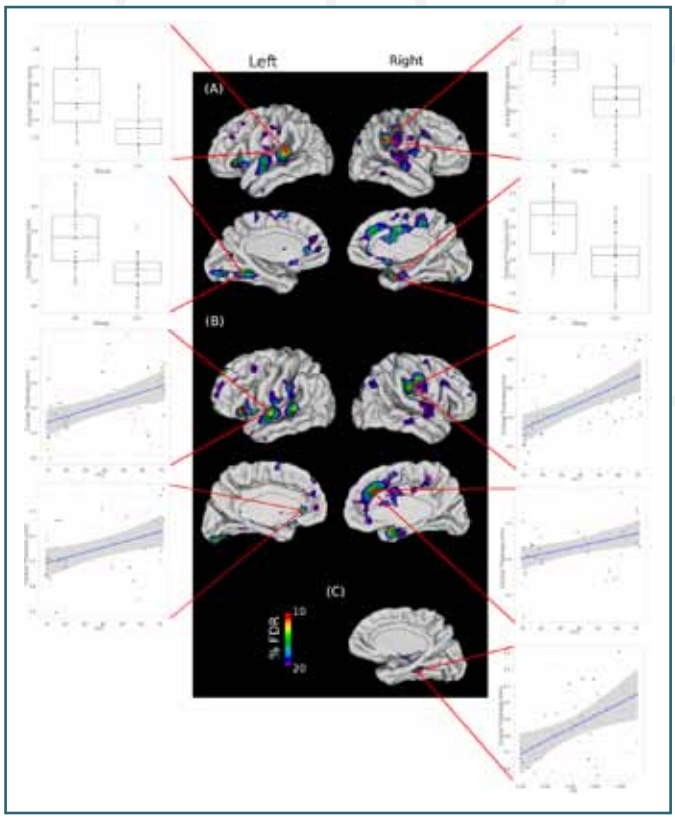

Figure 3
t-Statistic maps showing the cortical thickness findings. (A) shows the contrast of APs > non-APs. (B) shows the regression of AP performance score (in the PIT) onto the cortical thickness. (C) shows the regression of cortical thickness onto individual FA-values in the WM cluster.

strongly associated with personality traits that vary widely within the normal population[4].

The neuroanatomical correlates of absolute pitch

AP has been studied for more than a century, yet its neural underpinnings remain unclear. We investigated the gray and white matter anatomy on closely matched groups of musicians with and without AP using structural magnetic resonance imaging (MRI) and diffusion tensor imaging (DTI). We performed cortical thickness analysis on the whole cortex from T1-weighted images to probe for group differences in gray matter and we analyzed the fractional anisotropy (FA) and performed tractography from the DTI images to probe for group differences in white matter. We found significant increased cortical thickness in APs compared to non-APs in a number of cortical areas, including the left superior temporal gyrus, the left inferior frontal gyrus, the right supramarginal gyrus, and the right parahippocampal gyrus.

Furthermore, we found increased FA in APs compared to non-APs in a cluster within the inferior fronto-occipital fasciculus, the uncinate fasciculus, and the inferior longitudinal fasciculus in the right hemisphere.

The mean FA in this cluster was also found to correlate with cortical thickness in the parahippocampal gyrus (see Figure 3C). These findings indicate a specialized neural network in APs and since findings from previous studies on musicians have pointed toward similar areas, this may suggest a link between AP and musical expertise in general. However, given the close matching of the groups on musical training and musical aptitude, these findings are not likely to derive from neuroplasticity but may instead indicate a component of predisposition.

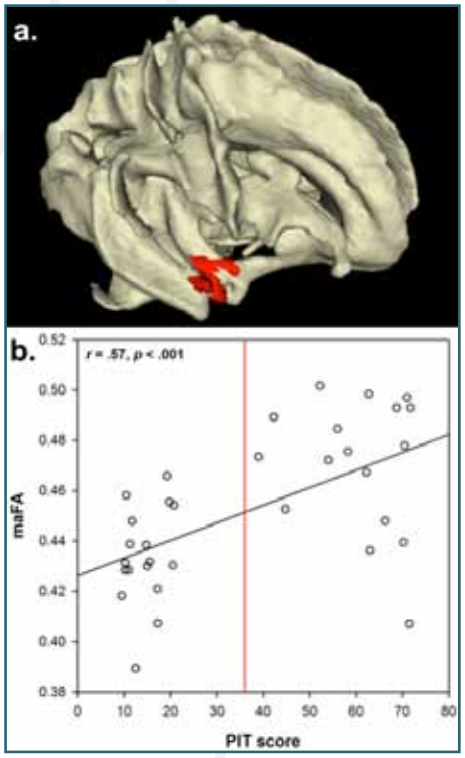

Figure 4
a) render image of the template FA map. The mask (red) represents the inflated Tract-Based Spatial Statistics (TBSS) significant cluster. b) Scatter plot of the correlation between the FA value in the individual TBSS cluster (maFA), and the pitch identification test (PIT) score for each subject. The red vertical line represents the cut-off for AP ability.

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NEW FACE AT CFIN

Kira Vibe Jespersen, PhD student, is MSc in Psychology with an additional bachelor degree in music therapy. Her interest in sleep problems has developed through her clinical work with traumatized refugees.

Kira has been affiliated the Music in the Brain research group since 2009, and in September 2012 she started her PhD at CFIN. The purpose of the PhD is to investigate the impact of music on sleep and the potential mechanisms involved.

The PhD project is financed by Aarhus University.

Read about Kira Vibe Jespersen's PhD project on the next page.

MUSIC IN THE BRAIN

Music for sleep improvement

by Kira Vibe Jespersen

Sleep problems are highly prevalent in modern society with about one-third of the general population experiencing insomnia symptoms[1]. Insomnia is associated with a number of psychiatric disorders such as depression and anxiety disorders as well as decreased immune functioning and medical problems such as cardiovascular disorders, hypertension and chronic pain[2, 3]. In addition, insomnia in itself can have a number of negative daytime consequences, and can affect important areas of life such as occupational function and social relations[4]. As such, it is a condition with great costs for both the individual and society.

Studies find that listening to music is often used as a self-help intervention to improve sleep[5]. Needless to say, music as an intervention to improve sleep offers potential advantages of easy administration, low cost and safety. Research on the impact of music on sleep has evolved during the last 20 years, and positive effects on sleep quality have been found in different populations. However, the studies are generally small and suffer from methodological shortcomings. Therefore, more research is needed to establish whether there is a true effect of the music that can be used clinically[6].

One group of people that is often severely affected by the negative consequences of persistent sleep problems is traumatized refugees, and difficulties initiating sleep as well as recurring nightmares are a part of the diagnosis for post-traumatic stress disorder (PTSD)[7]. In a clinical study we aimed at determining whether the subjective sleep quality of traumatized refugees could be improved by listening to music at bedtime, and if such an improvement would affect the experience of trauma symptoms and well-being. A repeated measures design was used, and the dependent variables, including subjective sleep quality, trauma symptoms and well-being, were measured by standardized questionnaires (see Figure 1).

Fifteen traumatized refugees with sleep problems participated in the study. Participants were recruited consecutively, and assigned to the intervention or control condition based on gender. To match for gender, every other male participant was given the intervention condition, and the same approach was used with the female participants. The intervention group received a music player designed to be used in bed every night for three weeks, and an ergonomic pillow (see Figure 2). The control group received only the pillow. The music used had a slow tempo of 52 bpm and was characterized by stable dynamics and a simple structure.

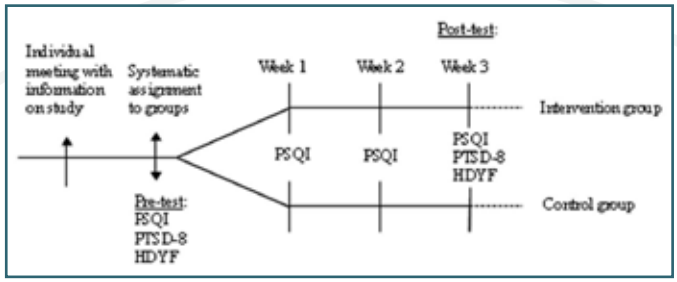

Figure 1
Study design. Questionnaires pre- and post-intervention included the Pittsburgh Sleep Quality Index (PSQI), the PTSD-8 trauma questionnaire and the 'How do you feel?' well-being questionnaire designed specifically for refugees (HDYF).

Figure 2
The music player and pillow.

Statistical comparisons showed a significant improvement of sleep quality in the music group, but not in the control group. A significant increase in well-being was found only in the intervention group, but there were no reliable changes in trauma symptoms in either of the groups. These results indicate beneficial effects of music listening at bedtime on sleep quality in traumatized refugees[8]. The project was implemented in collaboration with Integrationsnet – part of the Danish Refugee Council, with financial support from Trygfonden and the Danish Ministry of Refugee, Immigration and Integration Affairs.

To further investigate the effect of music as intervention to improve sleep quality in subjects with poor sleep, we will conduct additional studies using randomized controlled trials design and objective measures of sleep such as polysomnography (EEG, EOG and EMG). Polysomnography is the gold standard of sleep measurement, and based on this measure we will be able to determine changes in standard sleep measures as well as changes in specific sleep stages. Furthermore, we will look into the potential neurological, physiological and psychological mechanisms that may be involved in the impact of music on sleep. Through this work we wish to contribute to an improved evidence base for the potential clinical applications of music.

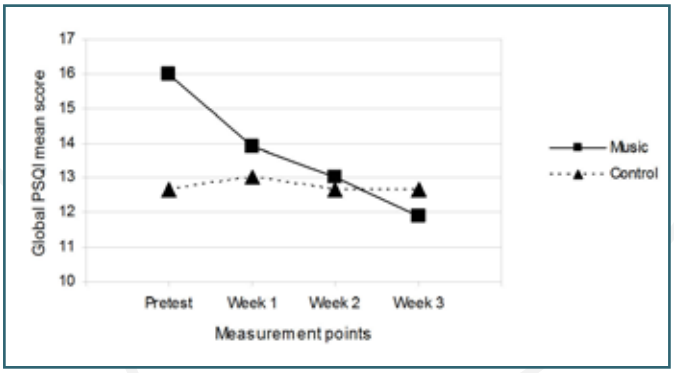

Figure 3
Global PSQI mean scores during intervention (higher scores indicate more sleep problems). Data showed a significant pretest difference between the groups. Still, both groups suffered from considerable sleeping difficulties with PSQI scores well above the score 5 which separates 'good' and 'poor' sleepers[9]. To control for this pretest difference we calculated a change score for each group, and statistical comparisons revealed that the music group experienced significantly more improvement in sleep quality than the control group.

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NEW FACE AT CFIN

Niels Chr. Hansen (MSc, MMus, BA) joined the Music in the Brain Group at CFIN formally in October 2012 working on a PhD project titled "Musical expectation mechanisms and statistical learning" under the supervision of Peter Vuust and Marcus Pearce. Prior to this, he had just returned from two years in London where he was employed as a research assistant at the Centre for Digital Music, Queen Mary, and received his MSc in Music, Mind & Brain from Goldsmiths College awarded with distinction for a project establishing Shannon entropy as a model of predictive uncertainty in melodic pitch expectation. During his time there, Niels Christian also found time to work as primary organist for the Danish Church in London.

Niels Chr. Hansen has previously collaborated with CFIN researchers on a survey study on sensation-seeking in professional musicians and has actively participated in the activities of the Music in the Brain Group since its inauguration, being a student at the Royal Academy of Music Aarhus/Aalborg (RAMA) since 2004. From RAMA he gained his BA and MMus in classical piano and music theory. Niels Christian has performed Central Javanese gamelan music for a number of years and has played concerts as a pianist in DK, SE, PL, NL, DE, UK, LV, and IT. His music theory research has been published in peer-reviewed journals such as Dutch Journal of Music Theory, Danish Yearbook of Musicology, and Journal of Music and Meaning.

In his PhD project, which is a collaboration with RAMA and the Department of Aesthetics and Communication at Aarhus University, Niels Christian investigates behavioural and neural correlates of the expectations that novices and professional musicians have when listening to music. More specifically, his preliminary findings – using computational modelling and behavioural experiments – suggest that experts make predictions with lower entropy due to a more optimised internal predictive model. Musical learning can thus be modelled as a continuous process of uncertainty reduction leading to establishment of, possibly multiple, increasingly specific predictive models. Amongst other things, Niels Christian's research will explore potential triggers for appropriate model selection in musical contexts.

CNRU

by Morten Overgaard

Cognitive Neuroscience Research Unit, CNRU, is an interdisciplinary research group, performing experimental and theoretical research within cognitive neuroscience, neurorehabilitation, and philosophy of mind and science. We find it to be an essential feature of basic research in cognitive neuroscience not just to explore interesting topics and expand our current understanding of the human mind, but to also contribute to clinical disciplines. In parallel, we find it fundamental that the development of such clinical methods for assessment and treatment are based upon cutting-edge basic research and conceptual analysis.

Below, we present some highlights of CNRU's contribution to these matters in 2012.

Basic research goals

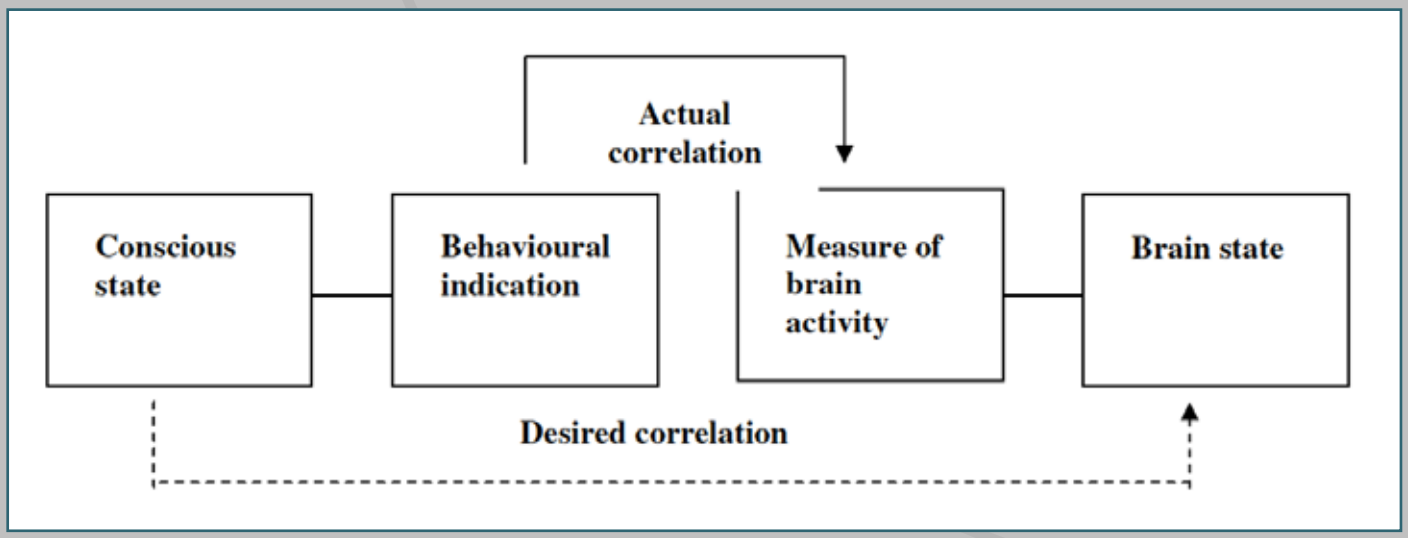
At the heart of CNRU research is the ambition to unravel the relation between mental and neural states. This issue is more than purely theoretical. It is an underlying question in many clinical areas such as cognitive neurorehabilitation, psychiatry, and coma research. Thus, the question of how the mind relates to the brain is fundamentally interdisciplinary, with important potential collaborations between psychology, philosophy, neuroscience and several other disciplines.

The interest entails the invention of experimental paradigms that reliably study the contents of subjective consciousness and that are able to relate such findings to objective measures of brain activity or behaviour. As illustrated in the figure below, correlations between neural activity and conscious experience relies completely on the behavioural indications we have of a given conscious experience (such as a verbal report) and the measure of the brain state we use (such as a scanning technique). However, should any of those measures be unreliable, so would the desired correlation be.

So far, CNRU has primarily worked on the "left part" of the figure of perception paradigms: The otherwise untangible question how to measure subjective states. As a result, a direct, introspective measure was developed, which is still applicable to a variety of experiments. The PAS-scale is the result of healthy subjects creating their own categories to describe visual experiences, so that one description or "scale point" matched a felt difference in visual consciousness. The method is now applied by many research groups world-wide.

Motor control and action

Consciousness is, as mentioned above, typically defined as subjective experience: A basically non-functional definition that in itself does not entail that we have to be conscious in order to perform any cognitive or motor function. Cognitive psychology has in several experiments found dissociations between conscious experience and almost every possible cognitive function. Nevertheless, most people entertain the idea that consciousness is somehow related to action, e.g. as "free will", or that we at least by way of being conscious cause certain actions, if nothing else then verbal reports such as "I am conscious". However, if there is any truth behind such ideas, states of subjective consciousness must be in some or other causal relationship to functional and physical states.



In 2012, The Danish Council for Independent Research/ Humanities (FKK) granted 6.254.816 DKK to the CNRU project “Phenomenal Consciousness and Cognitive Motor Control”. The research project seeks to address questions about volition and consciousness in a new way. Our strategy is to combine expertise in the field of vision research and the field of motor control research. If phenomenal consciousness is indeed crucially related to control, then the domain of motor control would be a natural domain for consciousness research.

Based on this grant, Mikkel Vinding and Mia Yuan Dong were hired as PhD students and Michael Nyegaard Pedersen as engineer. They are working closely with Lau Møller Andersen who also started his PhD in 2012 on the same problems of volition and consciousness based on a faculty stipend.

CNRU currently employs 14 full time researchers and several more student helpers with different backgrounds in psychology, medicine, philosophy and engineering. Morten Overgaard, head and founder of CNRU, was appointed professor in cognitive neuroscience December 2012 at the Department of Clinical Medicine, Aarhus University. Thus, this interdisciplinary field of research is now a formal part of Health Sciences in Aarhus.

Clinical applications

Different ongoing experiments are currently investigating disorders of working memory following brain injury. PhD student Jonas Lindeløv, investigates effects of computerized cognitive training programs in healthy subjects and patients with cognitive impairments. In another, larger, study, Jonas Lindeløv and Rikke Overgaard investigate the effect of hypnotic inductions on brain injury. This study was completed in 2012 after more than two years of work.

In other, even more severe clinical cases, patients have seemingly lost consciousness after neural injury. Research year student Bochra Zareini has conducted a study on 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 whereas the minimally conscious are not. In 2013, when analysis is complete, we will know whether the three groups of patients in fact differ in ways that support or go against this understanding.

FACTS

Cognitive Neuroscience Research unit (CNRU)

http://www.cnru.dk/

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- 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

In the attempt to increase theoretical understanding of the neural processes underlying regeneration and recovery, Morten Overgaard and Mads Jensen published an edited book with Frontiers in Psychology entitled Consciousness and Neural Plasticity.

Theoretical modelling

The entire field of cognitive neuroscience, from basic to clinical research, is producing an increasing amount of experimental investigations each year. However, overarching theoretical models to explain mind-brain relations are developing at a much slower pace. One reasonable explanation of this could be that most experiments can be theoretically explained from several different perspectives. Stated as a critique, many experiments in cognitive neuroscience may say nothing or very little about how we might conceive of mind-brain relations. From 2011, and throughout 2012, Morten Overgaard started a theoretical attempt to construct overarching models, showing how theories of mind-brain relations can be put to a direct empirical testing.

Masters program in Cognitive Neuroscience

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

Students from the programme have been frequent guests with CNRU in Aarhus during 2012. The close collaborations between CNRU in Aarhus and the cognitive neuroscience programme in Aalborg is an important aspect of the integrative approach – between disciplines, research and education, and different universities.

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CNRU
Cognitive Neuroscience Research Unit

NEW FACE AT CFIN

Thomas Alrik Sørensen, PhD, joined the Cognitive Neuroscience Research Unit at CFIN in 2012. He is an assistant professor at the Department of Communication and Psychology, Aalborg University. He has earned his Masters from the University of Copenhagen, where he also finished his PhD by investigating the relationship between visual attention and memory, particularly focusing on the capacity limitations in visual processing and short-term memory. More specifically how expertise, training, and varying degrees of arousal affect these limitations.

His current research focuses broadly on aspects of visual perception, attention, and memory. He currently pursues several lines of inquiry, such as synesthesia, processing of facial features, and more clinical avenues focusing on amnestic syndrome and confabulations. The general aim of these projects is to explore the diversity of subjective experiences by employing an experimental approach, which aims to measure subtle behavioral differences in both normal observers and specific clinical subgroups.

NEW FACE AT CFIN

Mark Schram Christensen joined the Cognitive Neuroscience Research Unit in 2012 as part of the collaborative project Phenomenal Consciousness and Cognitive Motor Control.

He is affiliated with CNRU and is associate professor at Department of Neuroscience and Pharmacology, University of Copenhagen. He holds a MSc degree in engineering physics from the Technical University of Denmark and did his PhD from the Faculty of Science, University of Copenhagen in collaboration with Danish Research Centre for Magnetic Resonance (DRCMR) at Hvidovre Hospital. His postdoc was carried out in the Copenhagen Neural Control of Movement research lab headed by professor Jens Bo Nielsen in collaboration with DRCMR. His major area of interest is cognitive motor control and he has mainly contributed with and increased understanding of how central motor commands influence sensory processing and influence sensation of movement in the absence of sensory feedback using both TMS and fMRI.

ELITEFORSK TRAVEL SCHOLARSHIP

Jonas Lindeløv from the Cognitive Neuroscience Research Unit (CNRU) received The Danish Agency for Science, Technology and Innovation's EliteForsk Travel Scholarship of DKK 300.000.

Jonas Lindeløv's research is within rehabilitation of working memory after brain damage.
The prestigious award was presented to Jonas on Thursday 7 February 2013 at an event in Ny Carlsberg Glyptoteket in Copenhagen with participation from the Danish Minister of Education Morten Østergaard.

Jonas Lindeløv (front row, middle) at the EliteForsk Conference in Copenhagen, February 2013.
Photo: Lars E. Andreasen/EliteForsk

COGNITION RESEARCH

by Andreas Roepstorff

Interacting Minds Centre

Since 2007, Chris and Uta Frith from UCL, London have been associated with MIND*Lab* and CFIN as visiting professors. The collaboration, known as the Interacting Minds project, has been funded primarily by the Danish Research Foundation, and it has been key in developing interdisciplinary research on social cognition at Aarhus University. The Interacting Minds project formally ended medio 2012. At the same time, Aarhus University established the Interacting Minds Centre (IMC) as one of five new transfaculty interdisciplinary initiatives. IMC brings together researchers from all four faculties in an investigation of human interaction. IMC has been provided with refurbished office space in the Nobel Park and with a core grant for research and key staff. Establishing IMC is an example of how complex, externally funded projects over time can find space, support and indeed a home inside the university system, and it provides a platform for the continued collaboration with 'the Friths' for the next five years.

IMC
INTERACTING MINDS CENTRE

Interacting Minds researcher Josef Bulbulia (with computer) during field experiment on rituals and social cohesion in Mauritius.
Photo: Dimitris Xygalatas

Cognition and Behavior Lab

One side effect of the neurocognitive turn, which in Aarhus has been spearheaded by MIND*Lab* and CFIN, is a new conceptual space for investigating human behavior, cognition and interaction. It is as if the opening of the brain to functional investigations, with fMRI, EEG, MEG etc., has also changed the way one studies the mind. In Aarhus and elsewhere, we are thus seeing a new wave of somewhat low-tech experimental investigations that uses high analytical rigor to study relatively open-ended situations of behavior and interaction. In 2012, the Faculty of Business and Social Sciences established the Cognition and Behavior Lab at Aarhus University. The Lab, which will become fully functional medio 2013, includes state-of-the art facilities for studying cognition and behavior in individuals and in groups. It contains rooms, which allows for detailed control of stimuli and responses, an econlab, where a group of people may interact mediated by computer interfaces, and flexible spaces, which can be used for more open-ended investigations. This infrastructure complements the neuroimaging facilities at MIND*Lab* and a close collaboration between technical and management staff at the two labs ensures that projects and people may move relatively easy between methodologies and sites.

Are we in this together?

The last years have seen a shift in research projects away from mainly studying individuals in isolation while they react to very simple stimuli, towards also studying people that face complex information, often in interaction with others. With the new tools, which allow us to study the effect of coordination in brains, bodies and behaviors, a new set of questions arises. If interactions with concrete or abstract others affect our patterns of predictions, anticipations and action, what, then, determines and modulates these patterns?

2012 saw a number of papers coming out, which examined such topics. Does methylphenidate, a prescription drug widely used to treat ADHD, affect how much one is affected by others opinion? Are there neural markers that distinguish between whether one observes or participates in an action? Will individual values and cultural background affect how the brain processes information related to "self" and "other"? Does it matter to the brain responses when cheating, whether one is in risk of being caught or not? Can data recorded in one brain be used to say anything about what goes on in another

Constructing shared worlds in collaboration with Lego Learning Institute, October 2011.
Photo: Kristian Tylén

brain? Based on the publications below, the answer to all of these questions is a tentative 'yes'. There is much to follow up on, but these experiments reactivate a classical conundrum. How does an understanding of humans as people acting, perceiving and interacting square with an understanding of humans as containers for brains processing information? Stay tuned for more on this in the future.

Selected publications:

Campbell-Meiklejohn, D., Simonsen, A., Jensen, M., Wohlert, V., Gjerløff, T., Scheel-Kruger, J., Møller, A., Frith, CD., Roepstorff, A. (2012) Modulation of Social Influence by Methylphenidate Neuropsychopharmacology 37, 1517–1525.

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COGNITION RESEARCH

Mental Training and Neuroplasticity

by Micah G. Allen

In the past decade, reports concerning the natural plasticity of the human brain have taken a spotlight in the media and popular imagination. In the pursuit of neural plasticity nearly every imaginable specialization, from taxi drivers to Buddhist monks, has had their day in the scanner. These studies reveal marked functional and structural neural differences between various populations of interest, and in doing so, drive a wave of interest in harnessing the brain's plasticity for rehabilitation, education, and even increasing intelligence (Green and Bavelier, 2008). Under this new "mental training" research paradigm investigators are now examining what happens to brain and behavior when novices are randomized to a training condition, using longitudinal brain imaging.

Figure 1
Mental Training

These studies highlight a few promising domains for harnessing neural plasticity, particularly in the realm of visual attention, cognitive control, and emotional training. By randomizing novices to a brief 'dose' of action video game or meditation training, researchers can go beyond mere cross-section and make inferences regarding the causality of training on observed neural outcomes. Initial results are promising, suggesting that domains of great clinical relevance such as emotional and attentional processing are amenable to training (Lutz et al., 2008a; Lutz et al., 2008b; Bavelier et al., 2010). However, these findings are currently obscured by a host of methodological limitations.

These span from behavioral confounds (e.g. motivation and demand characteristic) to inadequate longitudinal processing of brain images, which present particular challenges not found in between-subjects or cross-sectional design (Davidson, 2010; Jensen et al., 2011). The former can be addressed directly by careful construction of "active control" groups. Here, both comparison and control groups receive putatively effective treatments, carefully designed to isolate the hypothesized "active-ingredients" involved in behavioral and neuroplasticity outcomes. In this way researchers can simultaneously make inferences in terms of mechanistic specificity while excluding non-specific confounds such as social support, demand, and participant motivation.

We set out to investigate one particularly popular intervention, mindfulness meditation, while controlling for these factors. Mindfulness meditation has enjoyed a great deal of research interest in recent years. This popularity is largely due to promising findings indicating good efficacy of meditation training (MT) for emotion processing and cognitive control (Sedlmeier et al., 2012). Clinical studies indicate that MT may be particularly effective for disorders that are typically non-responsive to cognitive-behavioral therapy, such as severe depression and anxiety (Grossman et al., 2004; Hofmann et al., 2010). Understanding the neural mechanism underlying such benefits remains difficult however, as most existing investigations are cross-sectional in nature or depend upon inadequate "wait-list" passive control groups.

Figure 2
Meditation on the brain

We thus investigated functional and structural neural plasticity before and after a 6-week active-controlled mindfulness intervention. To control demand, social support, teacher enthusiasm, and participant motivation, we constructed a "shared reading and listening" active control group for comparison to MT. By eliciting daily "experience samples" regarding participants' motivation to practice and minutes practice, we ensured that groups did not differ on common motivational confounds.

We found that, while both groups showed equivalent improvement on behavioral response-inhibition and meta-cognitive measures, only the MT group significantly reduced affective-Stroop conflict reaction times (Allen et al., 2012). Further we found that MT participants show significantly greater increases in recruitment of dorsolateral prefrontal cortex than did controls, a region implicated in cognitive control and working memory. Interestingly we did not find group differences in emotion-related reaction times or BOLD activity; instead we found that fronto-insula and medial-

prefrontal BOLD responses in the MT group were significantly more correlated with practice than in controls. These results indicate that while brief MT is effective for training attention-related neural mechanisms, only participants with the greatest amount of practice showed altered neural responses to negative affective stimuli. This result is important because it underlines the differential response of various target skills to training and suggests particular applications of MT depending on time and motivation constraints.

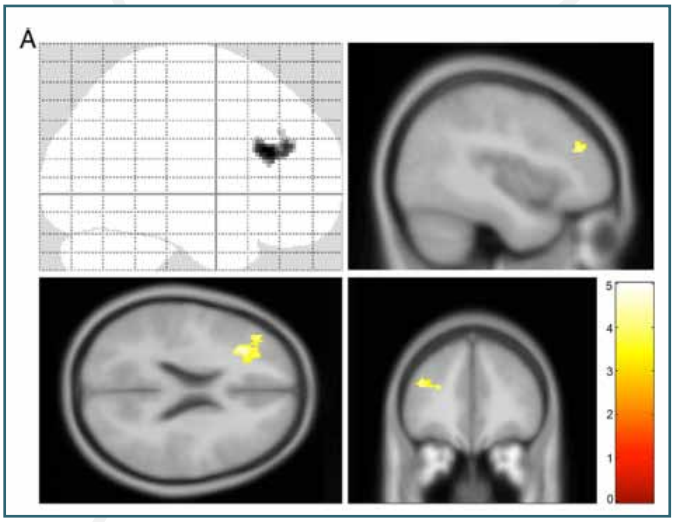

Figure 3
DLPFC activation increases following meditation training.

In a second study, we utilized a longitudinally optimized pipeline to assess structural neuroplasticity in the same cohort as described above (Ashburner and Ridgway, 2012). A crucial issue in longitudinal voxel-based morphometry and similar methods is the prevalence of "asymmetrical preprocessing", for example where normalization parameters are calculated from baseline images and applied to follow-up images, resulting in inflated risk of false-positive results. We thus applied a totally symmetrical deformation-based morphometric pipeline to assess training related expansions and contractions of gray matter volume. While we found significant increases within the MT group, these differences did not survive group-by-time comparison and thus may represent false positives; it is likely that such differences would not be ruled out by an asymmetric pipeline or non-active controlled design. These results suggest that brief MT may act only on functional neuroplasticity and that greater training is required for more lasting anatomical alterations.

These projects are a promising advance in our understanding of neural plasticity and mental training, and highlight the need for careful methodology and control when investigating such phenomena. The investigation of neuroplasticity mechanisms may one day revolutionize our understanding of human learning and neurodevelopment, and we look forward to seeing a new wave of carefully controlled investigations in this area.

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Micah Allen during his PhD defense in the Palle Juul-Jensen Auditorium (DNC), Aarhus University Hospital, 21 December 2012.

MIND*Lab*

Pain and Coping in the Religious Mind - a PhD thesis

by Else-Marie Elmholdt Jegindø

Religious coping and various religious practices have often been claimed to alleviate mental and physical suffering, but very little empirical evidence exists to support such arguments. The aim of the thesis was to investigate a possible pain modulation by religious beliefs and practises and to quantify potential psychological and physiological mechanisms that might mediate these experiences. The project included two related experimental pain studies in a laboratory setting and two related fieldwork studies during the Thaipusam Festival in Mauritius. The project thus integrates methods from standardised psychological testing, clinical psychophysiology, advanced neuroimaging, neuropharmacology, and classic ethnography. The project is the result of excellent interdisciplinary collaborations, bringing together leading experts from cognitive neuroscience, pain medicine, and the study of religion and culture.

In the experimental pain studies[1-2], we showed that devout Protestants are able to reduce pain sensation and pain unpleasantness during prayer (see Figure 1). Our behavioural results indicate that expectations contribute to large amounts of the effect, but at a neuronal level we found robust decreases in BOLD in attentional and executive systems during prayer. Our findings therefore suggest that, in contrast to current knowledge of descending pain inhibition, prayer might attenuate pain through a reduction in processing of pain stimulus saliency and prefrontal control. As a religious coping strategy, prayer may in some circumstances allow devout subjects to cope with pain by dissociating from part of the negative input of the stimulus and hence decrease the demand for selecting the appropriate response. In addition, by using administration of the opioid antagonist Naloxone, our results suggest that the mechanisms involved rely on non-opioidergic systems.

The Thaipusam Festival in Mauritius is celebrated annually by Tamils and Hindus who engage in physical sacrifice in the form of ritual piercings, that are endured and carried through hours of ceremonial procession (see picture). Interestingly, we found that participants experience very low levels of pain sensation, both during the actual piercing and during the processions. Again, the use of prayer, expectations about pain, and strong religious beliefs contribute to the experience of pain. Moreover, our results indicate that Thaipusam participants experience symptoms of dissociation (e.g. amnesia, depersonalisation, and derealisation), which further helps participants to disconnect from the pain[3].

Ritual piercing during the Thaipusam Festival in Mauritius.
Photo: Jens Jegindø

The thesis also includes a brief introduction to cognitive pain modulation and discusses past research on pain modulation due to religious beliefs and practices as well as the possibilities and limitations of scientific methods one might apply to study these phenomena. The steps taken in this thesis therefore serve as important leads for further investigations of how cultural factors may influence the experience and modulation of pain.

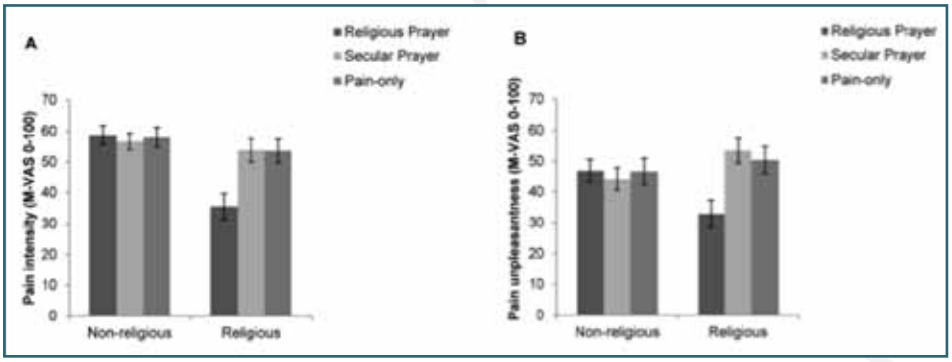

Figure 1
Mean ratings of pain intensity (a) and pain unpleasantness (b) for the non-religious and religious group during the three conditions, "Religious Prayer", "Secular Prayer", and "Pain-only". Religious participants reported a large and significant reduction in both pain intensity and pain unpleasantness[1].

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MIND*Lab*

Prayer on the brain – a series of imaging studies

Uffe Schjødt and Armin W. Geertz

The Religion, Cognition and Culture Research Unit (RCC) at the Department of Culture and Society is a partner in MIND*Lab* and CFIN. The goal of the RCC is to explore experimentally, empirically and theoretically the interactions between brain, body, culture and religion. Through the use of brain imaging, clinical tests, behavioral experiments and fieldwork both in Denmark and various parts of the world, we attempt to gain empirical insight in the workings of religious behavior and thought.

One of the focus areas of the RCC concerns prayer. We discovered very interesting features of prayer through brain imaging, clinical pain tests, and fieldwork in Spain and Mauritius. In contrast to popular neuro-theologians in the U.S., our point of departure is that there are no special areas of the brain dedicated to religious beliefs or behavior. We also assume that there is no generalized "religious experience"[1].

Uffe Schjødt showed in his brain scan experiments that even a simple procedure such as prayer draws on different areas of the brain. Using fMRI, he investigated how religious prayers changed the evoked BOLD response in a group of Danish Christians who are members of the Inner Mission[2]. Like other forms of repeated habits, we hypothesized that praying would activate the striatal reward system. Within the striatum, a main effect was found in the caudate nucleus of the dorsal striatum. The activation of the caudate nucleus supports the hypothesis that prayer may stimulate the dopaminergic system.

In a second study, Schjødt et al.[3] investigated the differences between formalized and improvised forms of prayer, in other words, the Lord's Prayer in contrast to personal prayers to God. It was hypothesized that improvised prayers consisting of conversations with God would activate social cognition and

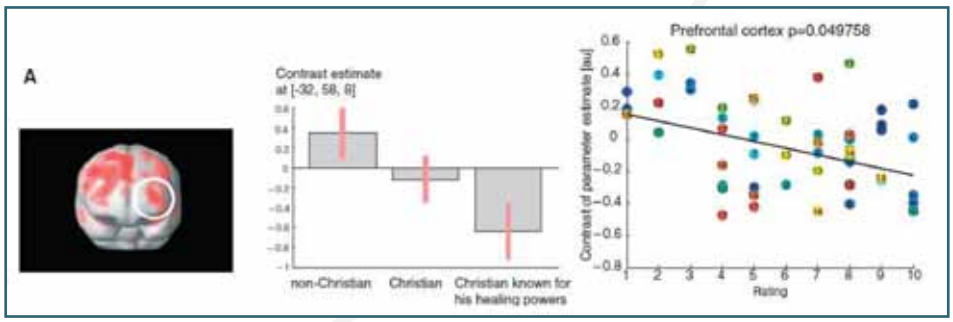

Figure 2
Left: Activations in 'non-Christian' relative to 'Christian known for his healing powers'. (A) prefrontal cortex.
Middle: Effect size of the three conditions compared to baseline.
Right: Effect of listening to the praying speakers (y-axis) as a function of subsequent ratings of the speaker's charisma on a scale from 1-10 (x-axis). A one-sample t-test across subject-specific slopes showed a significant effect for all regions except for the cerebellum (P<0.05).

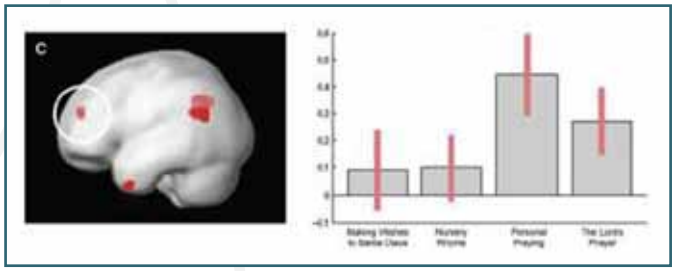

Figure 1
Left: Personal praying relative to making wishes to Santa Claus.
Right: Effect size analysis of the regions of interest in the four conditions relative to baseline (90% CI). Anterior medial prefrontal cortex.

its neural substrates, i.e. areas associated with theory of mind processing (anterior medial prefrontal cortex, the temporopolar region, and the temporo-parietal junction)[4]. It was further hypothesized that these areas were less active in formalized prayers such as the Lord's Prayer as well as in conversations with another invisible interlocutor which participants did not believe to be real (Santa Claus). The results supported these hypotheses (Figure 1).

In a third study, Schjødt et al.[5] investigated how assumptions about speakers' abilities changed the evoked BOLD response in secular and Christian participants who received intercessory prayer. Christian recipients who assumed that the speaker was charismatic down-regulated areas in the medial and the dorsolateral prefrontal cortex bilaterally in response to the intercessory prayer. This down-regulation correlated with participants' subsequent ratings of the speakers' charisma and the experience of God's presence during prayer (Figure 2).

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by Ken Ramshøj Christensen & Mikkel Wallentin

On Broca's area and language processing

One of the most well-studied regions of the human brain is the left inferior frontal gyrus, LIFG, the area also called Broca's area. Yet, it is also perhaps the most widely debated area of the brain. Since Paul Broca described it as the seat of speech in 1861, this region has been at the heart of the debate on the degree to which specific regions of the brain are dedicated to specific tasks. Leaving aside the question about domain specificity versus generality, the function of LIFG in language processing is still a matter of debate. One of the potential causes for what seems to be incompatible results is that researchers use different technologies and/or experimental designs which in turn give rise to two different types of change in brain activation, or 'signal'. LIFG is known to display increased activity during the processing of syntactic complexity, such as word order variation (e.g. in question formation), embedding (e.g. sentences within sentences) and various structural contrasts (Christensen 2008, 2010; Kristensen et al. 2013). The standard method in experiments on syntactic complexity involves contrasting minimally different, well-formed structures (e.g. The professor did not solve the problem vs. What problem did the professor not solve?). The resulting increase in brain activation measured with fMRI is normally taken to reflect an increase in processing cost.

Another approach to language processing is to study what happens when unexpected or incomprehensible linguistic input is processed. This can be studied using oddball paradigms comparing, for example, well-formed and anomalous sentences (e.g., She poured herself a glass of refreshing lemonade / *titanium), and the technology for this type of experiment is usually EEG. The difference between the responses to these two types of words can be observed in the amplitude of the so-called N400 component (400 ms after onset of the word). This type of response reflects a linguistic prediction error, and it is also known to increase activation in LIFG in fMRI studies.

Christensen & Wallentin (2011) sought to investigate whether the two signals, the processing cost signal and the error signal, are the same or whether they can be disentangled. In an fMRI study, participants read or listened to sentences consisting of well-formed and anomalous examples of the so-called locative alternation, e.g. He sprays paint on the wall vs. He sprays the wall with paint. The latter sentence has a more costly order of arguments (naming the location before the object) and comparing the fMRI response for this contrast with the contrast between comprehensible and anomalous sentences (e.g. He pours water on the flowers vs. *He pours the flowers with water), the results provide evidence that the two signals are cognitively distinct (showing differential behavioral patterns) but cortically overlapping in LIFG. Both processing cost due to syntactic complexity and semantic error detection due to anomaly resulted in non-distinct increased activation in LIFG (figure 1). The interaction between the two also engaged premotor cortex (Brodmann area 6).

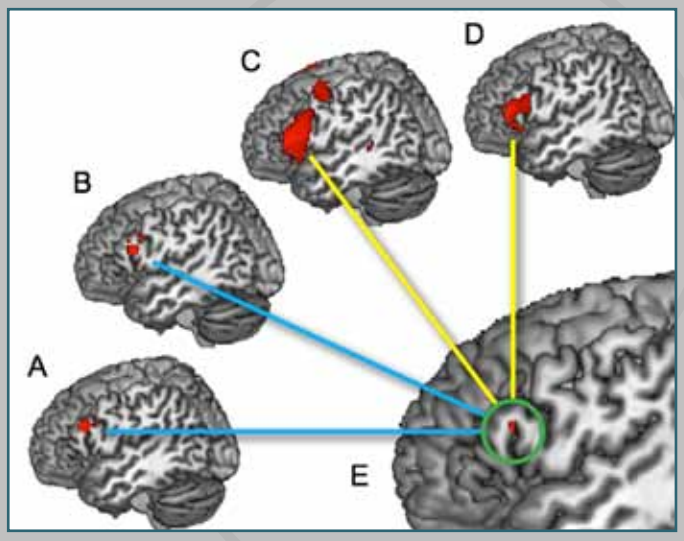

Figure 1
A=Syntactic complexity (ANOVA, ROI). B=Response time (Parametric, ROI). C=Interaction effect (ANOVA). D=Acceptability (Parametric, ROI). E=Overlap. (N=22, p<0.05 FWE). From Christensen & Wallentin (2011).

In a behavioral study, Christensen, Kizach & Nyvad (2013a) investigated the interaction between syntactic structure and working memory on long extraction (moving a question word, such as what or where, out of an embedded clause, e.g. What did they say we should fix?). It is sometimes assumed that certain types of word order variation are ungrammatical due to a domain-specific constraint on language. This constraint blocks extraction of a question word across another question word (e.g. *What did the say where we should fix?), a so-called island-violation. The results revealed, however, that such extractions are constrained by the interaction between working memory and a parsing principle that ensures fast and efficient, but sometimes temporarily erroneous, syntactic processing.

Christensen, Kizach & Nyvad (2013b), aimed to investigate whether LIFG activation was sensitive to increases in syntactic working memory load triggered by multiple extractions from an embedded clause (island violations), using the same stimuli as Christensen et al. (2013a). Event-related fMRI was used to measure the cortical effects of the differences in acceptability, and the neural activation in LIFG was predicted to correlate negatively with the level of acceptability. The behavioral data replicated the results from Christensen et al. (2013a). Ungrammatical sentences were predicted to engage LIFG, potentially overlapping with the effects of acceptability. The behavioral results replicated the findings from an earlier study showing that acceptability correlates negatively with demands on syntactic working memory. However, contrary to prediction, the imaging data showed no significant difference between long extraction and multiple extractions, while both induced a significant increase in activation in LIFG compared to short extraction (e.g. Did they say what we should fix?). The imaging results (figure 2) showed that activation in LIFG, as well as in premotor cortex and a region in posterior temporal cortex, correlated with the crossing of a clause boundary (structural complexity), not with increases in working memory load or decreases in acceptability due to island violations. This suggests that the clause itself is an important processing unit.

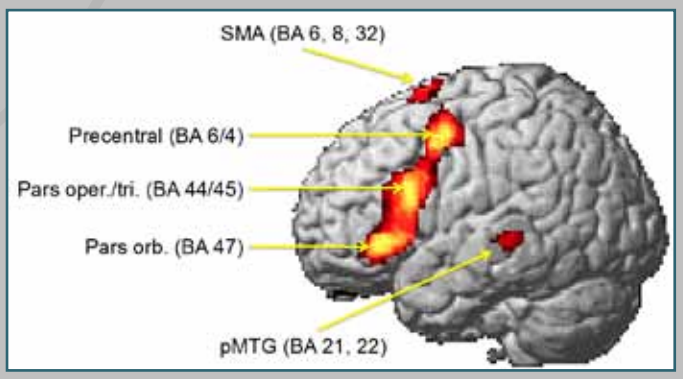

Figure 2
Cortical effect of extraction of a question word out of an embedded clause. (N=30, p<0.05 FWE.) Adapted from Christensen, Kizach & Nyvad (2013b).

Kristensen et al. (2013, submitted) conducted two experiments to investigate the effect of context on the processing of different syntactic constructions. Sentences with the subject in the beginning of the sentence (e.g. She likes him) are usually found to be easier to process than sentences with the object named first (e.g. Him, she likes). This may be due to the structural differences, but it may also be because one type of sentence is more frequent than the other. In Danish, the object-initial sentences are typically found in

FACTS

Teaching

Language and Cognition.
(Ken Ramshøj Christensen, Kristian Tylén, Mikkel Wallentin, Ethan Weed). Co-taught, research-based course offered annually in the Autumn semester for all 2nd year students at Arts ("HUM-fag").

Selected research projects:

Complexity and Parsing Efficiency.
(Ken Ramshøj Christensen, Johannes Kizach, Anne Mette Nyvad). Psycholinguistic (behavioral experiments) and neurolinguistic (fMRI) investigations into the interaction between syntax and, e.g. information structure (given-new), iconicity (mapping between language an perception of events), working memory, and word order.

Information Overload.
(Ken Ramshøj Christensen, Johannes Kizach, Ethan Weed). Does overly complex language fool the anomaly detectors? An EEG/ERP study investigating whether the otherwise automatic N400 effect, reflecting semantic or pragmatic incongruity, can be modulated or cancelled using various types of complexity.

Agrammatism.
(Anne Mette Nyvad, Ken Ramshøj Christensen, Sten Vikner). On the effects on language of trauma to the brain, primarily Broca's aphasia, and the implications for models of linguistic competence.

Linguistic illusions and Shallow Processing.
(Ken Ramshøj Christensen). How we process (or fail to notice) linguistic parallels to optical illusions, for example, garden-path sentences and pseudo-elliptic dead ends.

Foreign Language Acquisition Ability: EEG Models and Neurofeedback Assisted Learning.
(Alexandra Kratschmer). Psycholinguistic (behavioral experiments) and neurolinguistic (EEG) investigations into individual differences in foreign language learning ability (sound distinction, sound production, vocabulary acquisition) and the efficiency of EEG neurofeedback training as a method of enhancing this ability.

Semantic and pragmatic aspects of epistemic modality in the Italian language system: behavioral and neural correlates.
(Alexandra Kratschmer, Valentina Bambini [Pisa and Pavia]). Psycho- and neurolinguistic (EEG, fMRI) investigations of linguistic expressions conveying epistemic modality with particular focus on its scalar nature, regarding semantics as well as pragmatics.

Studying the brain signatures of co-constructed meaning.
(Riccardo Fusaroli, Kristian Tylén, Johanne Stege Bjørndahl).

Voice dynamics in psychiatric pathologies and brain deficits.
(Riccardo Fusaroli, Ethan Weed, Arndis Simonsen, Kristian Tylén).

Narratives in the brain.
(Kristian Tylén, Peer Christensen, Svend Østergaard, Andreas Roepstorff, Merlin Donald, Peter Vuust, Torben Ellegaard Lund, Andreas Højlund Nielsen, Rasmus Høll Nielsen, Ian Rynne, Jákup L.D. Michaelsen, Mikkel Wallentin).

Context influences on word order predictions in Broca's region.
(Line Burholt Kristensen, Elisabeth Engberg-Pedersen, Andreas Højlund Nielsen, Mikkel Wallentin).

Semantic distance metrics in the brain.
(Mikkel Wallentin, Ian Rynne, Jákup L.D. Michaelsen, Rasmus Høll Nielsen).

Investigating lateralization in the light of learning processes.
(Andreas Højlund Nielsen, William B. McGregor, Mikkel Wallentin).

particular linguistic contexts, e.g. when we want to contrast the object to some other members of a particular set (e.g. Linda hates John, Ringo and George, but not Paul. Him, she likes.). Consistent with previous studies on LIFG and syntax, Kristensen et al. found that Danish object-initial clauses yield a higher BOLD-response in LIFG, but they also observed an interaction between appropriateness of context and word order. For object-initial clauses, the effect of an appropriate contrastive context is bigger than for subject-initial clauses (figure 3). This caused Kristensen et al. to argue that factors such as discourse context contribute to the recipients' predictions of upcoming language input, and that increased BOLD-responses in the LIFG reflect the recipients' failure to correctly predict word order. Linguistic prediction errors may thus not only be based on structure and information within the sentence, but is also influenced by the larger context of the ongoing discourse.

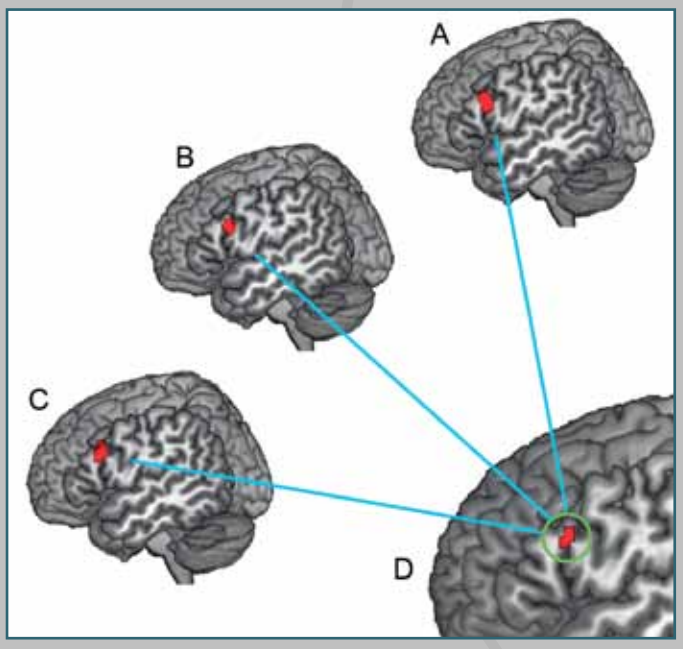

Figure 3
(A) the effect of word order, (B) the effect of context appropriateness, (C) the interaction between context appropriateness and word order, and (D) the overlap between activations in LIFG. (N=32, p<0.05 FWE.) Adapted from Kristensen et al. (submitted).

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- Kristensen L.B., Engberg-Pedersen E., Wallentin M. (submitted). Context influences word order predictions in Broca's region.

Anne Mette Nyvad, Ken Ramshøj Christensen and Micah Allen during the CFIN / MINDLab Retreat at Sandbjerg, 20-22 August 2012.
Photo. Alejandra Saragoza Sherman

SINO-DANISH CENTER FOR EDUCATION AND RESEARCH (SDC)

by Kim Ryun Drasbek

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

Master programme in Neuroscience and Neuroimaging

Specialize in solving the mysteries of the human brain

Researchers from both Denmark and China contributed to the development of the SDC Master programme in Neuroscience and Neuroimaging in an intense effort in 2010/2011. The Master programme has its roots at Aarhus University but includes course-organizers and lectures from the other Danish universities as well as several CAS institutes. In the spring of 2012 both Danish and Chinese students signed up for the new programme that started in September 2012 with a total of 20 students for the first enrollment. The students follow a range of courses within molecular neurobiology and clinical neuroscience as well as more technical/engineering courses within neuroimaging. As the education is situated in Beijing, several Danish researchers have taken the trip to China to give lectures and provide the students with an insight into their own research and the latest developments within neuroscience and neuroimaging. As this is the first class of students in the master programme some challenges have arisen but the students and lectures have been very positive and adaptable. Currently we are enrolling students for the 2013 class to start in Beijing in September.

CFIN / MIND*Lab* researchers involved in the Master programme in Neuroscience and Neuroimaging:

- Andreas Roepstorff
- Arne Møller*
- Birgitte Fuglsang Kjølby
- Christopher Bailey*
- Dora Grauballe Zeidler
- Jørgen Scheel-Krüger
- Kim Mouridsen*
- Kim Ryun Drasbek
- Louise Munk Rydtoft
- Simon Fristed Eskildsen
- Simon Lykkemark
- Sune Nørhøj Jespersen
- Søren Baarsgaard Hansen*
- Thomas Alrik Sørensen
- Torben Ellegaard Lund*

People marked with * are course leaders

Kim Ryun Drasbek and Arne Møller on the Great Wall of China, September 2012

MIND*Lab*

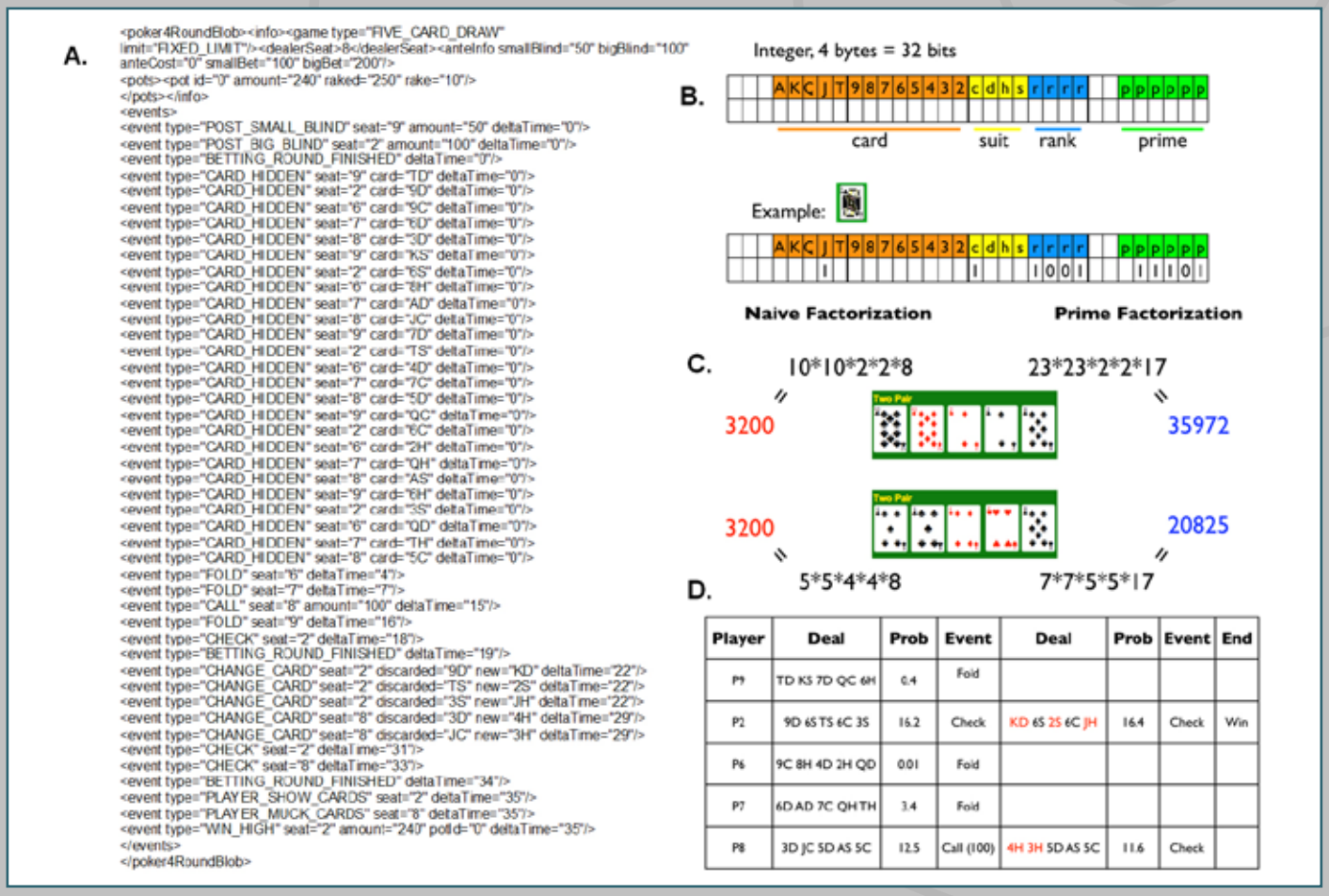
The Research Clinic on Gambling Disorders (RCGD)

by Jakob Linnet

The Research Clinic is rooted in CFIN and now part of The Research Clinic for Functional Disorders and Psychosomatics at Aarhus University Hospital. RCGD integrates research, treatment and prevention of pathological gambling in an interdisciplinary setting in close collaboration with CFIN / MIND*Lab*. For instance, the RCGD is currently collaborating with CFIN on an fMRI investigation of the Cognitive Bias Model developed by Jakob Linnet and Kim Mouridsen[1, 2]. The Cognitive Bias Model is also tested in another project about prospective testing of pathological gambling in online poker.

The online poker project is an international collaboration between the Division on Addiction, Cambridge Health Alliance, a teaching affiliate of Harvard Medical School, the Neuroinformatics group at Center of Functionally Integrative Neuroscience, Aarhus University and the Research Clinic on Gambling Disorders, Aarhus University Hospital. The project received kr. 2.163.139 in funding from the Danish Research Councils. As part of the collaboration Jakob Linnet is appointed Visiting Associate Professor at the Harvard Medical School.
The project analyzes data from more than 17.000 online poker players, and tests the hypothesis that the average winning percentage of played hands can prospectively differentiate players who later developed gambling problems from those who did not.

The poker data are stored in XML files (see Figure 1A). We have developed a simulation routine, which can compute the winning probability from the point of view of each player given the cards dealt. In a two player setting, for instance, 500,000 games can be evaluated per second. A publicly available encoding principle has been developed, which obtains a single index directly from the card combination. Briefly, a single card is represented by 4 bytes = 4x8 bits, see Figure 1B. The card rank is first indicated directly by a single 1 in the first 2x8 bits and its suit is indicated in the following 4 bits. Then, in a parallel representation, the rank is again represented in the



Player	Deal	Prob	Event	Deal	Prob	Event	End
P9	TD KS 7D QC 6H	0.4	Fold				
P2	9D 6S TS 6C 3S	16.2	Check	KD 6S 2S 6C JH	16.4	Check	Win
P6	9C 8H 4D 2H QD	0.01	Fold				
P7	6D AD 7C QH TH	3.4	Fold				
P8	3D JC 5D AS 5C	12.5	Call (100)	4H 3H 5D AS 5C	11.6	Check	

Figure 1 A-D

next 4 bits by its rank in binary form (deuce = 0, trey=1, ..., ace=12) and, in the last 6 bits, as a unique prime number, in binary form, corresponding to rank (deuce=2, trey=3, four=5, ..., ace=41). Figure 1B demonstrates this encoding. Empty fields correspond to zeros, which have been left out for readability.

The use of prime numbers is necessary to avoid aliasing. Figure 1C presents an example where a factorization using straight forward card enumeration leads to identical products for two hands of different overall rank. It can be seen that the native enumeration of the two hands TS, TD, 2D, 2D, 8S and 5S, 5C, 4D, 4H, 8S result in an equal ranking of 3200. In contrast, with the prime number enumeration, distinct products, and thereby indices, are obtained, i.e., the former hand has a bigger value than the latter, consistent with the rules of poker.

Figure 1D shows the simulation algorithm applied to the game in Figure 1A. Figure 1D shows the cards dealt and the computed probability of winning from the perspective of each player. Player 9, 6 and 7 fold their hands. This is consistent with the fact that these players have the lowest probabilities of winning (0.4%, 0.01% and 3.4%, respectively). Player 2, who checks, have a winning probability of 16.2%, and player 8, who calls, have a winning probability of 12.5%. These probabilities are calculated separately based on the information available to each individual player and therefore should not sum to 100%. The behavior in the example is consistent with the data showing that the players with the strongest hands play and the players with the weakest hands fold. After the cards are exchanged in the second betting round player 2 (16.4%) still has a better winning probability than player 8 (11.6%), but neither player has a strong hand. This is consistent with the betting behavior, where both players are checking. Player 2 wins the hand, consistent with having the better winning probability (however, the outcome could have been different, since the two hands have an almost equal winning probability).
The project will detect anomalies in such decision sequences in order to identify potential pathological gamblers.

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2. Linnet, J., L. Gebauer, H.J. Shaffer, K. Mouridsen, and A. Møller, Experienced Poker Players Differ in Estimation Bias and Decision Bias from Inexperienced Poker Players. Journal of Gambling Issues, 2010. 10: p. 86-100.

FACTS

The Research Clinic on Gambling Disorders (RCGD) is a self-financed clinic under Aarhus University Hospital, and a is a collaborative partner of CFIN / MIND*Lab*. The RCGD is headed by Jakob Linnet, Associate Professor, PhD, 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): Line Holger Pedersen Gilibert
Psychologist (prevention): Stine Moldt Jensen
Postdoc: Hanne-Lise Falgreen Eriksen
Phd/postdoc: vacant
Secretary: Pia Brunsgaard Bek

www.forskningsklinikkenforludomani.au.dk

Collaborations 2012:

- 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.

Ongoing Grants:

- Ministry of Health and Prevention, treatment of pathological gambling (2012)
- bwin.party bevilling, project on treatment effects of pathological gambling (2011-2013).
- Danish Research Councils, pathological gambling in online poker (2012-2015)
- Danish Research Councils, fMRI project of pathological gambling (2010-2014)

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Highlights in 2012

CFIN Running Brains I:
Michael Nygaard Pedersen, Mikkel Bo Hansen, Mikkel Wallentin, Anders Dohn & Andreas Højlund Nielsen

CFIN Running Brains II:
Ryan Sangill, Mads Hansen, Lau Møller Andersen, Irene Klærke Mikkelsen & Søren Møller Madsen

CFIN Running Brains III:
Jonas Lindeløv, Yi Ching Lynn Ho, Anne-Mette Pedersen, Mikkel Vinding & Jesper Frandsen

CFIN Walking Brains:
Dora Zeidler, Kristine Rømer Thomsen, Henriette Blæsild Vuust, Leif Østergaard & Bertha Østergaard

Photos: Henriette Blæsild Vuust

DHL Stafet 2012

The DHL Stafet in Aarhus celebrated it's 30th anniversary in 2012. More than 40.000 people participated in the run/walk during 3 days in August in Mindeparken. Aarhus University has a long tradition for participating in the DHL Stafet and in 2012, the university had more than 2.300 employees participating in the run/walk.

The DHL Stafet is a 5 x 5 km. relay race, and CFIN had 3 running teams, *The CFIN Running Brains*, and 1 walking team, *The CFIN Walking Brains* in the race.

CFIN / MIND*Lab* Retreat 2012

The annual CFIN / MIND*Lab* Retreat at Sandbjerg Manor near Sønderborg was held on 20-22 August 2012.

This year CFIN / MIND*Lab* researchers focused on: *Emerging modes of analysis* in a program that featured talks and workshops from both local researchers and invited guests.

The invited key note speakers were:

- Charles L. Webber, Department of Cell and Molecular Physiology, Loyola University Chicago, Stritch School of Medicine, USA : *Theoretical Fundamentals of Recurrence Quantification Analysis*
- Hanneke den Ouden, New York University, Center for Neural Science: *Selective striatal gating of cortical connectivity*
- Lars Kai Hansen, Head of Section Cognitive Systems, DTU Informatics, Technical University of Denmark: *EEG Brain Imaging*
- Gustavo Sudre, Carnegie Mellon University, Center for Neural Basis of Cognition, USA: *Tracking neural coding of perceptual and semantic features of concrete nouns*
- Bahador Bahrami, Institute of Cognitive Neuroscience, University College London, UK: *Optimally Interacting Minds*
- Jakob Hohwy, Monash University, Australia: *The Predictive Mind*












CFIN / MIND*Lab* Retreat 2012 at Sandbjerg Manor, 20-22 August 2012
Photos: Leif Østergaard, Alejandra Zaragoza Sherman, Torben E. Lund

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Cognition Research / Interacting Minds

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

Research Clinic on Gambling Disorders

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Jesper Frandsen,
Lars Riisgaard Ribe, Software Engineer
Martin Snejbjerg Jensen, Engineer
Michael Geneser, Radiographer
Michael Nygaard Pedersen, Engineer
Mikkel Bo Hansen, Software Engineer
Ryan Sangill, MR Physicist

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CFIN / MIND*Lab* researchers at the DHL Stafet, 23 August 2012.
Above: Michael Nygaard Pedersen checking the time just before start.
Below: Mikkel Vinding, Jonas Lindeløv, Ryan Sangill and Dora Zeidler on the look out for fast collegues.
Photo: AU Foto / Lise Balsby

2012 Publications

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Kristian Sandberg, CNRU during the CFIN / MIND*Lab* Retreat at Sandbjerg, 20-22 August 2012
Photo: Alejandra Saragoza Sherman

CFIN Bibliometry - 2012

by Leif Østergaard

Since we first began publishing our Annual Report in 2006, this space has been reserved for a bibliometric analysis in which we keep track of the number of articles published the past year, broken down into the Journal Impact Factors of the journals in which they appeared. Like previous years, tables and diagrams show the development since CFIN was founded in 2001. To allow comparison with previous years, the 2012 figures include only the publications listed on the previous pages, i.e. from researchers directly affiliated with CFIN. As we make the transition to also report from the growing collaborations within Aarhus University's interdisciplinary MIND*Lab* Center in the coming years, we will develop new metrics to monitor our productivity.

From time to time, we have discussed the difficulty of comparing Journal Impact Factors across disciplines with different publication and citation patterns. From 2011, we therefore also introduced the Authority Level analysis introduced by the Danish Government. A range of Danish experts have analyzed over 20.000 publication channels (mainly journals) and assigned them into 'Level 1' and 'Level 2' journals. Within a given research area, 'Level 2' journals are those who experts consider to be the leading, international journals within their field, in the sense that they publish the top-20% of the world's scientific production within that area. Meanwhile, 'Level 1' is assigned to journals who publish the remaining 80% of the World's production within the area. By using this common metric our research output quality can therefore be communicated in a way which is less biased by the number of research fields we represent. Needless to say, we have a strong interest in communicating the value of our research, not only in terms of scientific and societal impact, to our benefactors and collaborators. By this metric, and the number of books, book chapters, theses and patents we produce, this value also becomes tangible in terms of the Government support we bring to Aarhus University.

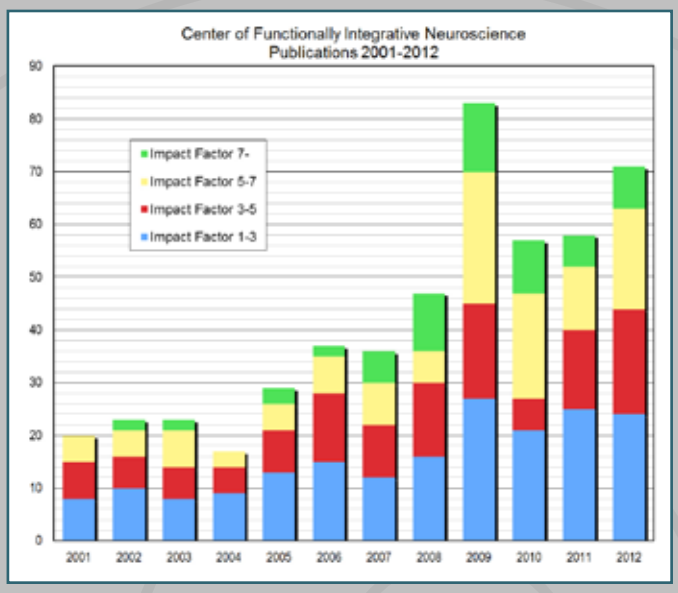

Figure 1
CFIN Publications 2001-2012

The table shows the number of Level 1 and Level 2 CFIN publications 2001-2012 according to the '2012 Authority List' from the Danish Agency for Science, Technology and Education. As noted in last year's Annual Report, 'average performance' by definition corresponds to a scientific production where 80% of the production falls in the 'Level 1' category, and the remaining 20% in the 'Level 2' category. We are very pleased that a high proportion of CFIN articles have been published in the 'Level 2' journals within the fields covered by our research. In recent years, more than half of our manuscripts have thus been published in journals considered among the top-20% by our peers.

	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Impact Factor 0-1	6	4	12	8	8	3	11	9	10	7	21	10
Impact Factor 1-3	8	10	8	9	13	15	12	16	27	21	25	24
Impact Factor 3-5	7	6	6	5	8	13	10	14	18	6	15	20
Impact Factor 5-7	5	5	7	3	5	7	8	6	25	20	12	19
Impact Factor 7-	0	2	2	0	3	2	6	11	13	10	6	8
Total	26	27	35	25	37	40	47	56	93	64	79	81

Table 1
Publication Impact Factor 2001-2012

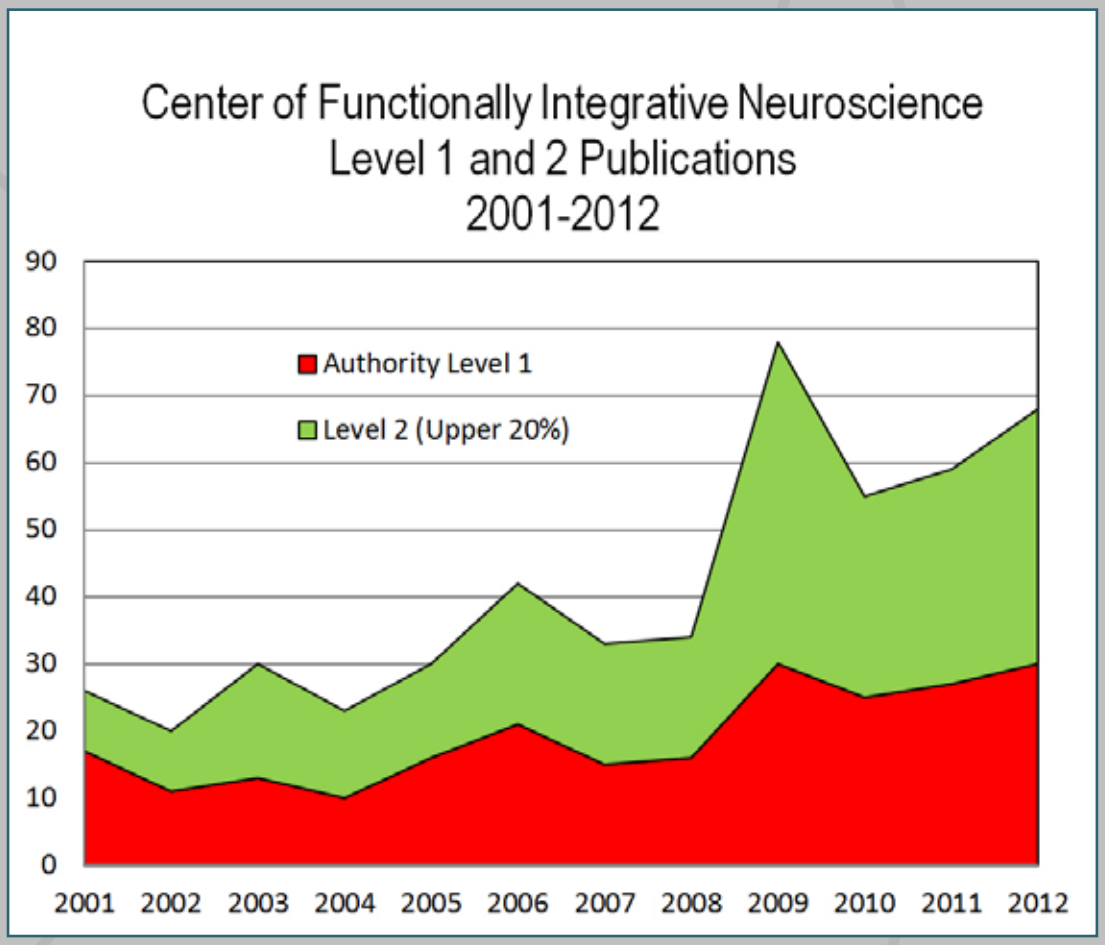

Figure 2
Level 1 and Level 2 CFIN Publications 2001-2012

	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Authority Level 1	17	11	13	10	16	21	15	16	30	25	27	30
Level 2 (Upper 20%)	9	9	17	13	14	21	18	18	48	30	32	38
Level 2 - Percentage	35	45	57	57	47	50	55	53	62	55	54	56

Table 2
Number of Level 1 and Level 2 CFIN Publications 2001-2012

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Augustinusfonden
BayerSchering Pharma AG
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Danish Cancer Society
Danish Council for Strategic Research Programme Commission on Nanoscience, Biotechnology and IT
Danish Council for Strategic Research Programme Commission on Non-ionizing Radiation
Danish Ministry of Culture
Dansk Parkinsonforening
Department of Neuroradiology, Aarhus University Hospital
Department of Nuclear Medicine & PET-Centre Aarhus, Aarhus University Hospital
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neuroinformatics

emotion

functional hemodynamics

neurotransmission

brain

MEG

neuroconnectivity

fMRI

neuroenergetics

subject

stroke

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