Center of Functionally Integrative Neuroscience
& MIND*Lab*

ANNUAL REPORT 2017

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CFIN Communications Coordinator and Annual Report editor Henriette Blæsild Vuust during the DHL Relay race 2017 in Mindeparken, 17 August 2017.
Photo: CFIN & MIB

Introduction - 2017 in words

by Leif Østergaard

The Center of Functionally Integrative Neuroscience (CFIN) and our 'sister' center, Center for Music in the Brain (MIB), continue to grow and thrive in the Danish Neuroscience Center (DNC) building at Aarhus University Hospital's (AUHs) Nørrebrogade campus. In recent years, the number of researchers and staff has increased well beyond the intended number of workplaces on the fourth and fifth floor of the DNC building. Although the high density of employees affects working conditions, the group leaders have felt that 'staying together' is crucial for the unique and fruitful interactions among groups and disciplines taking place on the two floors, as well as with the clinical researchers in the adjoining neuro-departments in AUHs Building 10.

In 2017, however, we ran out of options to house new researchers. Therefore, twelve preclinical researchers have had to work out of Building 9, some away from their group leaders and colleagues, until space frees up in the DNC building. While we hope to maintain the proximity of CFIN and MIB researchers in the DNC building, we may not stay close to our experimental infrastructure. The Nørrebrogade campus' new owners plan landscaping, which cuts through our current MRI facility, and construction and renovation work, which will disturb our MEG facility as well as our preclinical imaging facility (PIFa) for extended periods of time. We are therefore planning the move of our MRI, MEG, EEG, and TMS facilities to the AUH Skejby campus some 4 kilometers away, hoping that funding will be ensured to reestablish their current functionality. This relocation will allow us to maintain close proximity to collaborating clinical researchers and to the patients, who help us by participating in our research.

Meanwhile, our technical staff, and CFIN and MIB researchers who prepare and conduct experiments, will invariably be affected by such a move. The planning work has already required hard work and creativity by many of our staff, and I hope for everybody's understanding and support to those involved in, and affected by, this transition as it unfolds over the coming years. Meanwhile, I wish to thank all those who help and support us in the process of finding ways to preserve our precious working environment and infrastructure. Having taken tens of years and millions to establish, they form the backbone of the success we have enjoyed, both in developing original ideas and research, and in attracting grants and bright minds to Aarhus.

We put much effort into securing the safety of the volunteers, who help us understand the brain and its many functions, and the protection of their personal data while they participate in our research projects. Our projects often examine basic brain functions in ways that fall outside the scope of 'biomedical' research. To address participant safety and data protection, we therefore formed an Institutional Review Board (IRB) to evaluate such projects. Read more about this process inside this annual report.

This annual report best illustrates, what makes all the 'house-keeping' concerns and work above worthwhile: The creative ideas being conceived and discussed every day, the cool new methods and exciting results being presented, and the lively social and scientific interactions across ages, nationalities, and educational backgrounds. All made possible by your contributions to our work, and I am sure you will recognize the enthusiasm and dedication of our researchers and staff as you read through the pages – and sense how new discoveries continue to increase our knowledge of the brain and its diseases.

On behalf of our research group leaders, I wish to thank you once again for your collaboration, interest and support.

Leif Østergaard
CFIN / MIND*Lab* director

NEUROPHYSICS 2017

by Sune Nørhøj Jespersen and Brian Hansen

Tissue cannot safely be removed from the living human brain for studies under a microscope, and we therefore lack fundamental knowledge on how neurological disorders develop. Magnetic resonance imaging (MRI) can be sensitized to the cellular and molecular structure of tissue, a factor of 1000 below nominal image resolution, via e.g. micrometer-scale Brownian motion (diffusion) of water and relaxation properties of molecular ensembles. Such virtual MRI microscopy can allow noninvasive 3D characterization of tissue and its histopathology at various disease stages and is therefore crucial for earlier diagnosis of neurodegenerative diseases, at the time when they are still characterized only by subtle tissue changes.

Microstructurally sensitive biomarkers

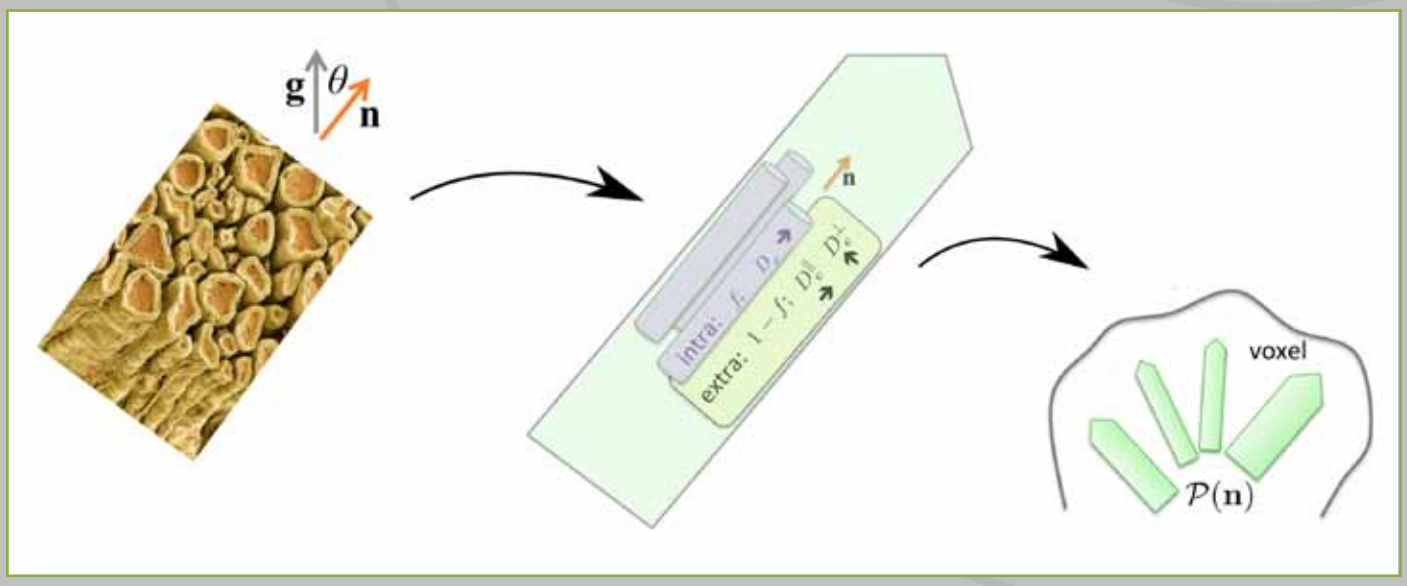
Diffusion is key to sensitizing magnetic resonance imaging to tissue microstructure, orders of magnitude below nominal image resolution. Apparent diffusion constant (ADC) imaging is already established as a sensitive biomarker in e.g. stroke and cancer, but the so-called diffusion kurtosis imaging (DKI) is receiving increasing interest from both basic scientists and clinicians, due to its ability to offer complementary information[1,2].

Because the cumulant expansion[3], on which DKI rests, is a general mathematical expansion applied under relatively broad conditions, its parameters cannot be expected to be readily interpretable in terms of specific tissue properties. As such, DKI is an example of a so-called signal representation[4,5].

Although many such representations are possible, we advocate DKI due to its generality and proven applicability for water diffusion in biological tissue.

Despite its lack of specificity, DKI parameters have been observed to have great sensitivity to tissue microstructure, and promises to be a valuable biomarker of pathological changes in several different diseases. In stroke, several studies have pointed towards a complementary role of changes in kurtosis metrics compared to DTI metrics[6-9], potentially facilitating improved sensitivity and specificity for detecting microstructural tissue degradation[10]. For example, the size of the mean kurtosis lesion is often smaller and more heterogeneous than the mean diffusivity lesion, and the magnitude of changes, especially in axial kurtosis, are larger than those of DTI metrics[6,9,11,12]. Furthermore, it has been found that the time evolution of MK changes differs from that of MD[6,7,9,13].

A substantial practical disadvantage of conventional DKI is the rather long acquisition time necessitated by the extensive data required for estimating diffusion and kurtosis tensors. We have succeeded in significantly reducing the amount of data required for DKI by optimizing data acquisition protocols as well as estimation methods (1-3-9 and 1-9-9 protocols)[14,15]. As a result, sufficient data to robustly estimate MKT mean kurtosis, kurtosis fractional anisotropy, as well as axial and radial kurtosis, can be recorded in approximately one minute on clinical scanners[16-18].



These fast DKI techniques have also been applied in the setting of stroke imaging[19-21], and have been shown to offer higher contrast to noise ratio per unit time[20]. The applications of fast DKI to stroke have so far focused on MKT, but in light of the findings that axial kurtosis show greater changes, it would be interesting to apply axisymmetric DKI, which offers robust estimates of axial kurtosis and can be performed using the same raw data as the 1-9-9 fast DKI protocol. Other promising applications have been indicated in Alzheimer's disease[22] and multiple sclerosis[23-25]. Incorporation of kurtosis also improves demarcation of brain tumors[26], and improves cancer grading[27-31]. The fast DKI method promises to reproduce these findings[31].
Intriguingly, former PhD student at CFIN, Erhard Trillingsgaard Næss-Schmidt found indications that fast kurtosis imaging in combination with DTI provides a more sensitive tool to identify injury and predict permanent brain damage as a result of mild traumatic brain injury[32,33].

Another interesting application of the fast DKI protocols was explored by a collaborator and former CFIN PhD student Eduardo Garza-Villarreal, who recruited 54 crack cocaine addicts and 48 healthy controls in order to study the effects of drug abuse on the brain[34]. The DKI results revealed an abnormal decrease in thalamic MKT in the drug addicts, a phenomenon known to happen only at a much later age in the healthy population. The decrease furthermore correlated with cocaine use. Thus, the fast DKI protocols may help reveal accelerated brain aging in cocaine addicts.

The reader is referred to a recent review from our group covering fast kurtosis techniques and their applications for further information[35].

Figure 1
Schematic illustration of the model for diffusion in the brain, modified from (38) (same for graphical abstract). A package of almost parallel axons oriented along some direction $\mathbf{n}$ is probed by diffusion gradients along $\mathbf{g}$. Diffusion in the intra-axonal space with volume fraction f is characterized by and axial diffusivity D_a, whereas diffusion in the extracellular space has axial diffusivity $D_{e,||}$ and radial diffusivity $D_{e,\perp}$. The net signal from a voxel is obtained by convolution of this basic building block with an orientation distribution function $\mathcal{P}(\mathbf{n})$.
(Photo credit to Tom Deerinck and Mark Ellisman at the National Center for Microscopy and Imaging Research for the histology image illustrating a fiber fascicle).

FACTS

Group members, students and collaborators:

- Sune N. Jespersen (group leader, Professor)
- Brian Hansen (head of high field lab, Associate Professor)
- Ahmad Khan (Assistant Professor)
- Andrey Chuhutin (PhD student)
- Hugo Angleys (PhD student)

Events:

- Hugo Angleys (supervised by Sune N. Jespersen and Leif Østergaard) defended his PhD thesis "The role of capillary transit time heterogeneity on oxygen and glucose extraction in the brain" on May 15, 2017. Two world experts on brain perfusion and oxygen extraction, Olaf Paulson and Alberto Vazquez, acted as opponents, and engaged in interesting discussions with Hugo.

Conferences and meetings:

- ISMRM 2017 (May 2017, Honolulu, Hawaii)
- "A Spin Thru' The History of Restricted Diffusion MR", 31.01.17-01.02.17, Cardiff, Wales
- "ISMRM Workshop on Quantitative MRI in White Matter Disorders: Useful, Usable and Used?", 7.2.2017 –12.2.2017, Vancouver, Canada
- "Diffusion DeKay" 13.11.2017, Copenhagen, Denmark
- "EU CONNECT CLUB", 15.03.17-17.03.17, Paris, France
- "European Society for Magnetic Resonance in Medicine and Biology", 19.10.2017-21.10.2017, Barcelona, Spain.

Funding:

- The Lundbeck Foundation (cellular underpinnings of diffusion weighted contrast)
- The VELUX Foundation
- The Augustinus Foundation

Virtual MRI microscopy

To achieve microstructural specificity, it is necessary to apply biophysical modeling[3,4]. Biophysical modeling seeks to identify the relevant microstructural features that shape the MRI signal. The most important part of this process is to create a simplified picture of tissue structure, which can subsequently be combined with the physics of diffusion and MRI signal generation to predict the diffusion signal[4,5]. The neurophysics lab has been closely involved with the development of the first biophysical model to estimate local neurite density in the brain[36,37]. The basic underlying framework which is now extensively applied around the world was recently referred to with tongue-in-cheek as "the standard model" of diffusion MRI in the brain[4] (Figure 1), in analogy to the standard model of physics.

The parameters of this model are difficult to estimate with standard clinical scanners, due to limited time and hardware constraints. Therefore, a great deal of work has been carried out to characterize and potentially circumvent this problem.

Any biophysical model of diffusion has a corresponding diffusion kurtosis tensor, and we have therefore also pursued a strategy of matching the tensors from the models to those estimated with fast DKI[39]. This led to promising *in vivo* estimation of axonal volume fraction as well as intra- and extra-axonal diffusivity in the corpus callosum. We later extended the applicability of this approach to other central nervous system regions, by taking into account axonal fiber dispersion[40]. The method was tested in the spinal cord, and used to estimate time-dependent diffusivities for intra-and extra-axonal water.

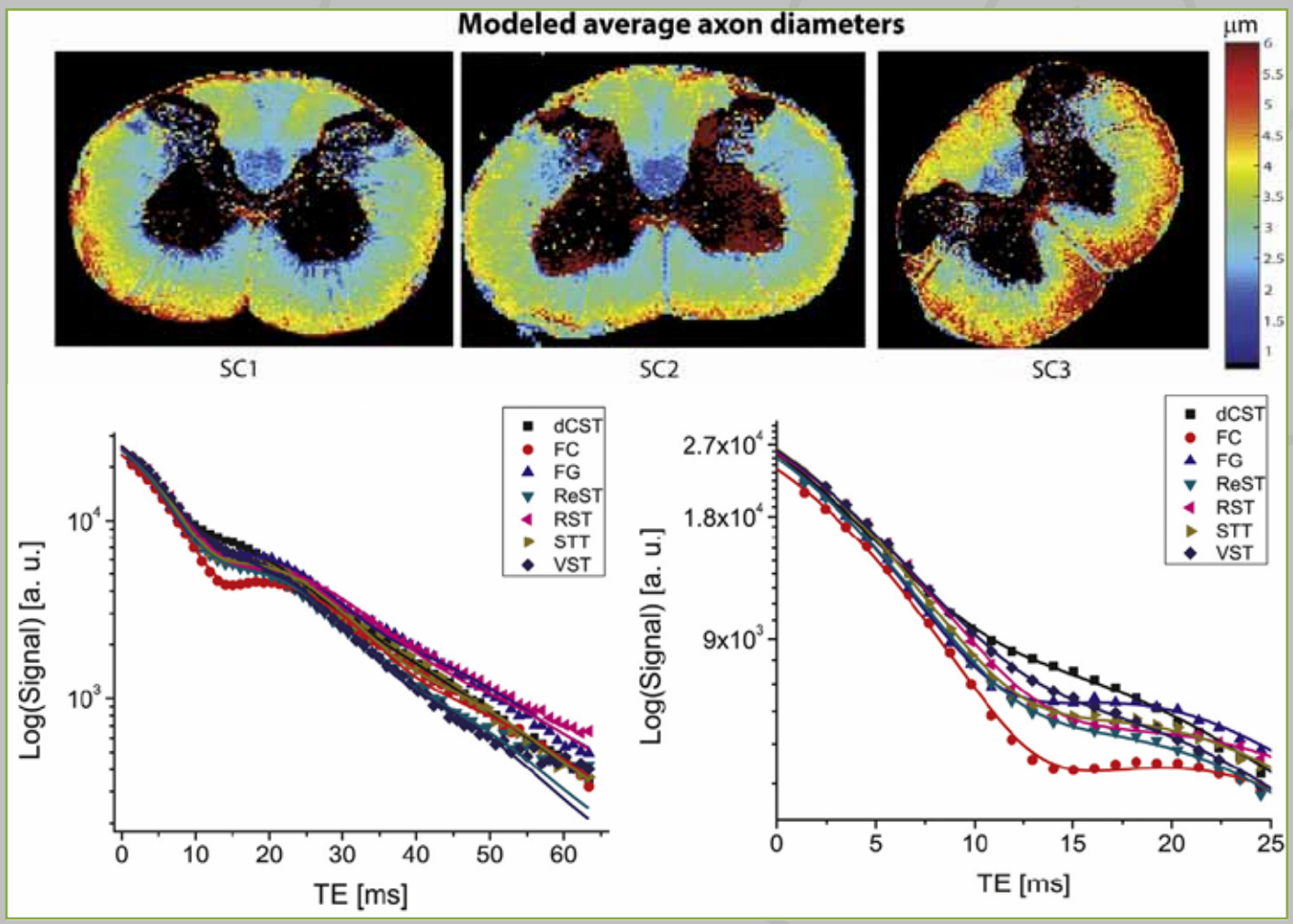


Figure 2
Voxel wise averaged axon diameters (top) as inferred by modeling T2* decay (bottom), from (42).

These approaches, so-called moment matching, rely on very careful estimation of diffusion and kurtosis tensors. PhD student Andrey Chuhutin carried out a systematic study of the influence of experimental protocol on the precision and accuracy of kurtosis estimation, and identified the optimal choice of parameters in different types of brain tissue[41]. Another inherent problem in these approaches is that, quite fundamentally, the diffusion kurtosis tensors do not supply sufficient information to unambiguously determine microstructural parameters, such as the parameters of the "standard model"[38]. Current thinking about this problem suggests that it is necessary to supplement conventional diffusion measurements by "orthogonal" that is, independent measurements of tissue microstructure. One such approach is generalized diffusion gradient waveforms, a framework to which the neurophysics lab has previously made contributions, but another approach exploits the versatility of MRI and incorporate modeling of other biophysical contrast sources. A promising candidate is T2* which is a relaxation measure affected by myelin content and geometry. In a collaborative project with the lab of Noam Shemesh, we used modeling of gradient echo relaxation data to estimate the density of myelin in mouse spinal cord, as well as axon radius (Figure 2)[42]. We hypothesize that the combination of various sources of contrast will enable us to robustly estimate microstructural tissue parameters, bringing us closer to *in vivo* virtual MRI microscopy.

High Field Lab

The high field lab supplies data to a growing range of research projects outside of neurophysics. Examples of recent contributions include data acquisition and analysis for zoological studies[43] and highly resolved (80µmx40µmx40µm) anatomical data suitable for morphological analysis for phenotyping of psychiatric animal models, Qvist et al. in review[44]. This latter study is the result of a collaboration with Simon Fristed Eskildsen's AIM group at CFIN and iPSYCH. Another succesful collaboration with the Functional Hemodynamics group shed light on the effects of sub-arachnoid hemorrhage based on histological analysis and MRI-based volumetry[45]. Current efforts in the lab are aimed at establishing perfusion imaging and chemical shift imaging as tools for characterization of the growing number of animal models utilized at CFIN.

FACTS

Invited talks:

- Ahmad Khan:
  - Diffusion DeKay (Danish/Swedish diffusion MRI network)
- Sune Jespersen:
  - "A Spin Thro' The History of Restricted Diffusion MR", Cardiff, 31.01.17-01.02.17
  - "EU CONNECT CLUB", Paris, 15.03.17-17.03.17
  - "European Society for Magnetic Resonance in Medicine and Biology", Barcelona, 19.10.2017-21.10.2017
  - Diffusion DeKay (Danish/Swedish diffusion MRI network)
  - LUF Neuroscience Survey, Aarhus, 12.06.17

Activities:

- Teaching MR physics at engineering school (Sune N. Jespersen, Brian Hansen and Andrey Chuhutin), and organizing and teaching MR physics master's course at the Department of Physics and Astronomy, (Sune N. Jespersen and Brian Hansen).
- Brian Hansen visited the Advanced Magnetic Resonance Spectroscopy and Imaging (AMRIS) Facility at the University of Florida as a member of the user committee for the National High Magnetic Field Lab.

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'NEW' FACE at CFIN

Simon Jeppe Bjerg, Scientific Coordinator

Simon is not really a new face at CFIN: He has been employed here since 2013! We have somehow failed to introduce him in the previous annual reports, so it's about time to do so!

Fundraising support

Simon Jeppe Bjerg, Scientific Coordinator has been working with research administrative support at CFIN since 2013. During this period the main focus has been helping the researchers to attract external funding for their projects. This involves counselling regarding research ideas, development of funding strategy, coordination of the fundraising process, preparation of applications, research plans and budgets, securing that all formalities are met, etc.

Simon holds a Master in Sociology (2007) from Aalborg University. He has previously been working with register-based labour market research at Center for Labour Market Research (CARMA) at Aalborg University.

Up until his CFIN employment, he worked in the education and research administration at Aarhus School of Architecture with statistics, evaluations, workflow procedures, quality assurance, and fundraising.

FUNCTIONAL HEMODYNAMICS

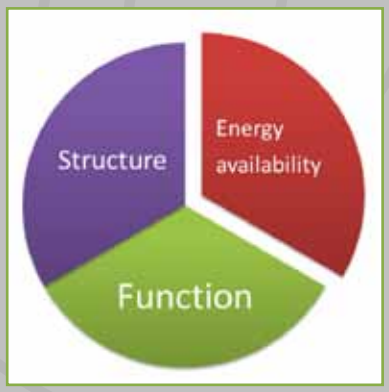
2017

by Leif Østergaard

In some ways, brain function is all about energy. Weighing only 2% of our body mass, the brain accounts for 20% of our body's oxygen utilization during rest. In the brain, oxygen is mostly spent on oxidative phosphorylation of glucose, breaking it down into carbon dioxide, water, and adenosine triphosphate (ATP) molecules, the 'currency' in which energy is stored and transported within cells. Brain functions' energetic demands is highlighted by the fact that we lose consciousness within seconds of cardiac arrest, as the brain runs out fresh oxygen and glucose supplies via the bloodstream. Even with a steady supply of nutrients, however, energy availability limits the number of new synapses, the brain can form and maintain as we learn new skills and form new memories: Almost 40% of the brain's total ATP utilization is spent on reversing ion fluxes through postsynaptic receptors, and the number of postsynaptic receptors on dendritic spines is thus limited by their energy usage. During long-term potentiation (LTP), the first step towards consolidation of e.g. new memories, synaptic strength is enhanced by an increased number of postsynaptic receptors, which again is associated with a proportionate increase in ATP expenditure. Several mechanisms therefore regulate the number of postsynaptic receptors according to local ATP availability, while seeking to ensure the optimal functioning of both individual synapses and neuronal networks.

For neurons to maintain sufficient energy supplies at all times, a range of neurovascular coupling mechanisms are known to regulate arteriolar diameter such that local blood supply is adjusted according to local metabolic demands. We have argued that, much closer to individual cells, neuro*capillary* coupling mechanisms adjust the flux of blood through individual capillaries, such that local blood supply, downstream of the arterioles, is distributed according to cellular demands, while ensuring efficient oxygen extraction. The interdependence between neuronal function and energy demands is particularly evident as groups of neurons increase their activity due to external or internal stimuli: Local blood supply immediately increases, allowing us to detect brain activity indirectly, either as an increase in blood supply, or through the related increase in blood-oxygen-level-dependent (BOLD) signal intensity.

The functional interrelationships between brain cells and the brain vasculature is perhaps most intimate during brain development, where the proliferation and differentiation of parenchymal cells depend on the parallel development of brain microvasculature, not only for nutrient supply, but also for the release of critical growth factors. Indeed, local hypoxia within the growing brain seemingly drives the proliferation and differentiation of both vascular and parenchymal cells, with vascular endothelial growth factor (VEGF) acting both as a stimulant of vessel formation (angiogenesis), and as a neurotrophic factor that supports the growth, survival and differentiation of neurons. The human hippocampus retains the ability to generate neurons from granule cell precursors throughout life. This adult neurogenesis takes place in the dentate gyrus and depends on active angiogenesis, during which endothelium (the inner, cellular layer of microvessels), glia cells, and neurons develop from a common proliferative focus. Notably, endothelial cells seemingly produce brain derived neurotrophic factor (BDNF) during adult neurogenesis, stimulating the growth, differentiation, and synapse formation of new neurons.



Given the importance of brain energy homeostasis, it is perhaps not surprising that dwindling ATP levels and decreasing tissue oxygen tension trigger a broad range of cellular responses, aiming to restore energy homeostasis while protecting cells, and ultimately their host, from immediate harm. Indeed, tissue hypoxia and disturbed energy homeostasis are increasingly implicated in poorly understood, early disease phenomena such as low-grade inflammation, failing trophic support, failing DNA repair, and epigenetic programming. Increasing research outputs in these research areas may therefore shed light on the biological consequences of threatened energy homeostasis at the molecular and genetic level.

The Functional Hemodynamics group seeks to understand how the microcirculation ensures the supply of energy substrates to support brain functions, and whether disturbed microvascular function might contribute to aging and disease. Whereas research into cerebral hemodynamics and metabolism typically utilizes neuroimaging methods to create maps, in which each image voxel contains an index of local cerebral blood flow, glucose metabolism, or oxygen

utilization, our group is particularly interested in the function of the thousands of capillaries *within* each image voxel, which ensure that blood is well distributed at the microscopic level. The complexity of fluid transport in microvascular networks and the subsequent diffusion of molecules into tissue is such that we try develop 'simple' models and methods that capture salient features of microvascular function and allow us to understand their behavior in biological systems. To this end, we work closely with several other CFIN groups: We utilize *biophysical modeling* to understand how capillary blood flow patterns affect the regional uptake of oxygen and glucose uptake in tissue in collaboration with Sune Jespersen and the Neurophysics group, *kinetic modeling* of indicator dilution data to characterize capillary blood flow patterns from magnetic resonance imaging (MRI) and two-photon microscopy (TPM) data in collaboration with Kim Mouridsen and the Neuroinformatics group, *human neuroimaging studies* of capillary dysfunction with a range of clinical collaborators and the expertise of the Neuroinformatics group and Simon Fristed Eskildsen's Applied Imaging and Modelling (AIM) group, and *optical imaging studies* in rodents in collaboration with the TPM Laboratory, with the collaborators David Boas, Sava Sakadžić, and others from the Optics Division at the Martinos Center for Biomedical Imaging at Harvard Medical School and the Neurophotonics Center at Boston University.

With the generous support of the VELUX Foundations and Aarhus University, several projects on capillary function and –dysfunction were completed and published in 2017 – including three PhD projects, of which two are described in the following pages. Funded by the VELUX Foundation's ARCADIA center grant, Hugo Angleys finalized his PhD thesis on the effect of capillary transit heterogeneity (CTH) on oxygen and glucose extraction in tissue, and on the BOLD signal, which is used to map the brains functional organization and connectivity patterns – See also Pages 16-17. Among other fundamental insights, Hugo Angleys' work resulted in a more detailed model of oxygen transport in tissue, which serves as a means of estimating oxygen availability in tissue based on recordings of the the two 'summary parameters' we use to characterize capillary flow patterns: The *mean* transit time (MTT) of blood as it passes through the microcirculation, and the *standard deviation* of capillary transit times across capillaries, dubbed capillary transit time heterogeneity (CTH). Figure 1 shows an example of how hemodynamic recordings from young, old, and old Alzheimer-like mice can be entered into a surface plot derived from Hugo Angleys model and compared in terms of the oxygen metabolism,

FACTS

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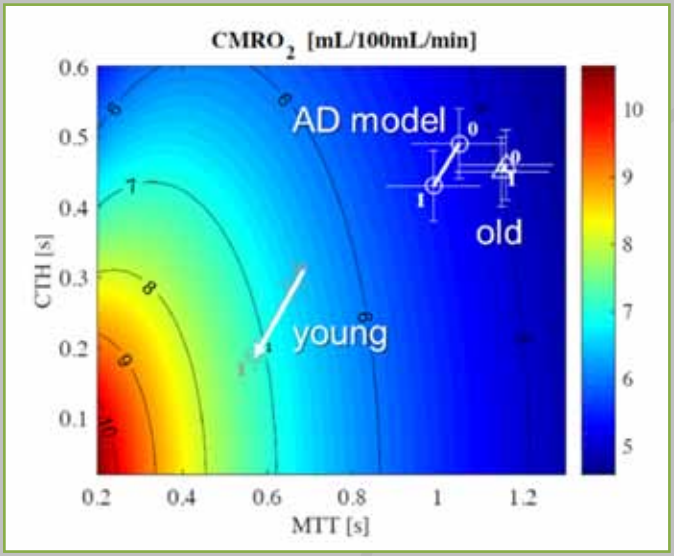

Figure 1
Using Hugo Angleys biophysical model, this contour plot shows the estimated oxygen availability ($CMRO_2$) in color code as a function of the mean (MTT) and standard deviation (CTH) of capillary transit times in the tissue for a normal tissue oxygen tension (PtO2) of 26 mmHg. The arrows connect measurements during rest ("O") and functional brain activation ("I") in young and old (18 months) mice, and in old mice expressing proteins characteristic of Alzheimer's disease. Note, how blood supply is reduced (MTT longer) and the ability to increase blood supply and homogenize capillary flows in parallel (that is, reduce both MTT and CTH) during functional activation is lost in both old and AD model mice. The difference in color allows us to estimate that oxygen availability is reduced by 25% in the latter. From (Gutierrez-Jimenez et al., 2018)

these capillary flow patterns would be able to support (Gutierrez-Jimenez et al., 2018). Hugo Angleys' models of the extraction of glucose and glucose analogs in brain tissue provided biophysical insights into literature findings that have long puzzled neuroscientists: First, the brain produces lactate during functional activation, although the parallel increase in blood supply (functional hyperemia) would seem to provide sufficient oxygen for oxidative phosphorylation. According to Hugo Angleys model, this paradox "aerobic glycolysis" phenomenon (lactate production in the presence of ample oxygen) may in fact be inevitable, because changes in capillary flow patterns affect oxygen extraction more than they do that of glucose during functional hyperemia. Second, direct measurements of glucose metabolism, for example by nuclear magnetic resonance spectroscopy (NMRS) have historically provided lower estimates of the increase in glucose metabolism during functional brain activation than indirect measurements, estimated from the uptake of the glucose analog fluorodeoxyglucose (FDG). Hugo Angleys' detailed modeling suggest that the uptake of FDG differ relatively more from that of 'real' glucose when blood supply is higher, causing this state-of-the-art method to overestimate the increase of glucose uptake during brain activity by as much as 50%. Finally, Hugo Angleys modeled the effects of capillary transit time heterogeneity on the dynamics of the BOLD signal, introducing a dramatic re-interpretation of its biophysical underpinnings: By facilitating oxygen extraction, homogenization of capillary flow patterns (decreasing CTH) *reduces* BOLD signal intensity, while increasing blood supply tends to *increase* it. Until now, negative BOLD transient have been interpreted as oxygen extraction from a 'passive' microvasculature, but according to this extended model, the BOLD signal should be viewed as the superposition of positive contributions, attributable to neurovascular coupling mechanisms, and negative contributions, attributable to tissue oxygen utilization *and* neurocapillary coupling mechanisms. As these predictions are tested experimentally, we note that BOLD signal amplitudes are likely to reflect not only brain activity as currently assumed, but also capillary function in each individual subject, as well as the effects of various neurotransmitters on neurovascular and neurocapillary coupling.

The capillary dysfunction concept was first developed in the context of Alzheimer's disease, in a position paper published in 2013 (Østergaard, Aamand et al., 2013). At that time, the development of methods to characterize capillary function in humans and rodents was still underway, and in 2017, the first tests of this hypothesis were published in leading journals within the field of aging and dementia. With these sensitive methods and his previous insights on the 'normal' behavior of microvascular flows, Eugenio Gutiérrez-Jiménez studied capillary function in aged mice, and in aged mice who express elevated levels of the neurotoxic Aβ protein (APP^{swe}/PS1ΔE9), which is characteristic of Alzherimer's disease (Gutiérrez-Jiménez et al., 2018). Figure 1 shows data from his 2018 paper, in which he demonstrates the failing response of cerebral microvessels to functional activation in both aged mice and in aged mice with Alzheimer-like pathology. A recent comparison of cerebral hemodynamics in patients with AD or mild cognitive impairment (MCI) on one hand, and age matched controls with no history of vascular risk factors, on the other, showed extended areas of capillary dysfunction in the patient cohort. Notably, the degree of capillary dysfunction was positively correlated with white matter hyperintensities and mini mental status examination (MMSE) score in the patient cohort (Eskildsen et al., 2017). In a cross-sectional

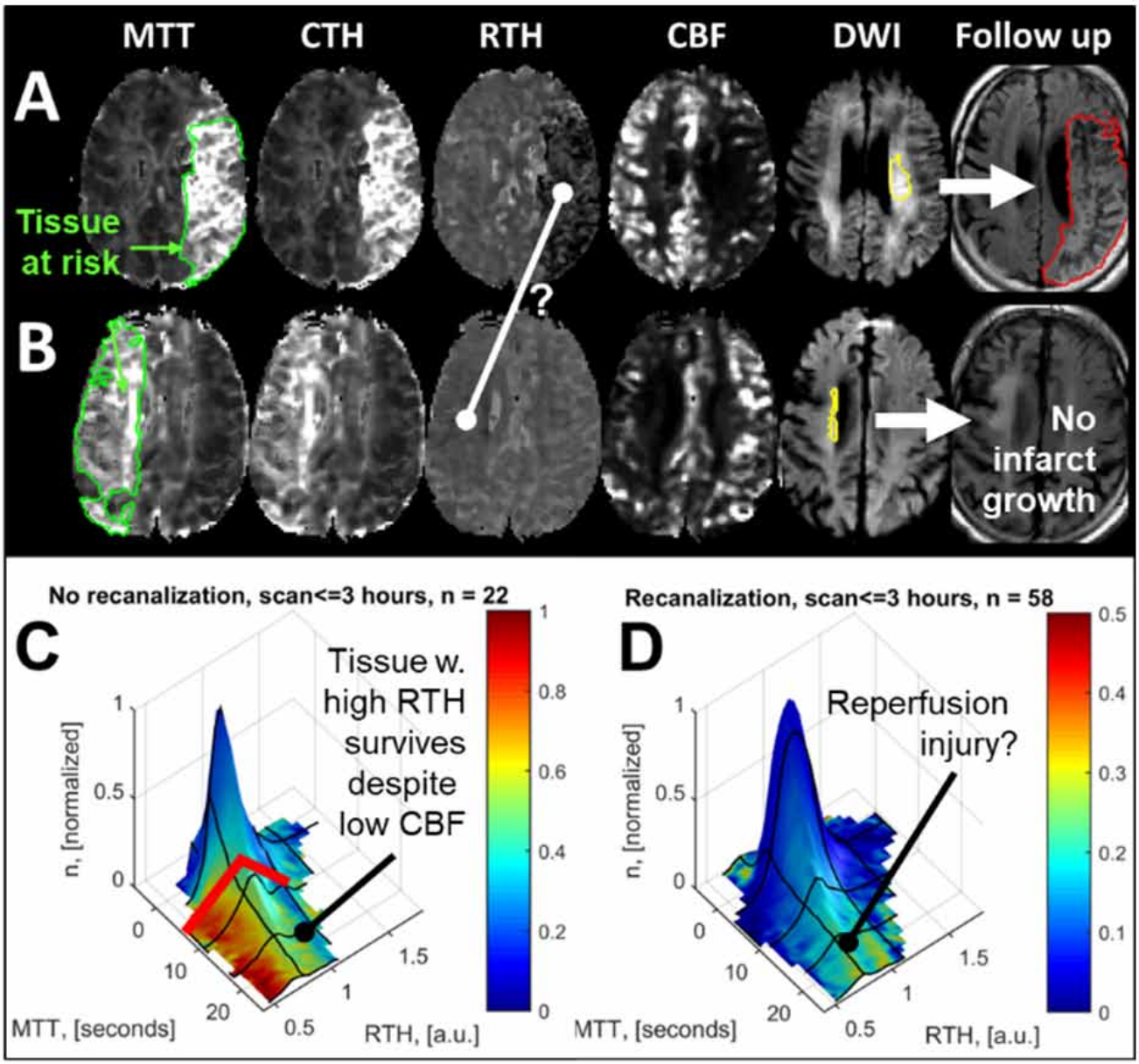

Figure 2

Rows A and B show MRI data acquired in two stroke patients with middle cerebral artery occlusions, none of which re-canalized. The fifth column shows their acute (< 3 hours after symptom onset) diffusion lesion (yellow outline), which is thought to represent irreversible, hypoxic tissue injury. The sixth column shows their final infarct a month later. Note that only patient A suffered severe infarct growth, despite having similar, lasting reductions in blood supply (CBF - fourth column) and prolonged mean transit time (MTT - first column) as patient B. Tissue with prolonged MTT also shows elevated CTH, that is, capillary dysfunction. The CTH:MTT ratio (RTH) was lower in patient A than in patient B. Thorbjørn Engedals simulations suggest this phenomenon may reflect capillary obstructions, and thus explain the subsequent tissue infarction. Using data from 22 patients, whose vessel occlusion did not re-canalize, Panel C shows the risk of infarction for all image voxels with reduced blood supply but normal diffusion characteristics (viable but at risk of infarction), as a function of acute voxel MTT and RTH values. The color indicates the fraction of voxels with a given (MTT, RTH) combination that had infarcted approximately one month later (orange = all tissue), and the height of the plane indicates the number of voxels examined. Note how the infarct risk depends as much on RTH (possibly capillary occlusions, see above) as on MTT, contrary to earlier beliefs that the degree of CBF reduction alone determines tissue outcome in permanent ischemia. Panel D shows similar data from patients where vessel recanalization was achieved. Note that the bluish surface color, suggesting that whatever phenomenon caused infarction in tissue with high RTH, this is mostly reversed by the inflow of blood. From Engedal et al (2017).

study of AD patients, cognitive scores correlated with both the degree of capillary dysfunction and with the calculated tissue oxygen tension across patients (Nielsen et al., 2017). Notably, capillary function had deteriorated 6 months later in this patient cohort, paralleling the decline in their cognitive scores. So far, experimental data thus support our original hypothesis.

In 2017, Thorbjørn Engedal, MD, finalized his PhD work, in which he tested our hypotheses on the roles of capillary function in stroke (Østergaard, Jespersen et al., 2013) and in cerebral small vessel disease (SVD) (Østergaard et al., 2016). In animal models of stroke, ischemia has been shown to cause pericyte constrictions (and hence capillary narrowing) that fail to reverse after reperfusion. By limiting blood's access to cells at the microscopic level, this phenomenon may reduce the success of human stroke therapies that aim to restore blood supply through the artery affected by e.g. a blood clot. Thorbjørn Engedal examined capillary function in a large group of acute stroke patients, whose culprit vessel did not recanalize, and found that tissue survival depends not only on residual blood supply, but also on the degree of capillary dysfunction (Engedal et al., 2017) – See Figure 2. This runs counter to the widely held belief, that blood supply *alone* determines neuronal viability and the reversibility of neurological symptoms after acute stroke. Importantly, these observations open the possibility that brain tissue may be salvaged by therapies, which prevent pericyte constrictions, even in cases where recanalization *cannot* be achieved. This perspective is of great importance to stroke patients, especially those 80%, who are currently ineligible for thrombolytic therapy.

Thorbjørn Engedal also examined whether capillary dysfunction might play a hitherto overlooked role in cerebral autosomal dominant angiopathy with subcortical infarcts and leucoencephalopathy (CADASIL), a genetic form of SVD. Working with data from our colleague Keith Muirs research group at the University of Glasgow, he discovered severe capillary dysfunction in what we otherwise refer to as normal appearing white matter in these patients (NAWM) (Engedal et al., 2015) – See Figure 3. Notably, the degree of capillary dysfunction seemed to partly account for differences in cognitive function among patients, who otherwise had similar neuroimaging findings. Such shared disease features, between Alzheimer's disease (above) and what we refer to as vascular dementia, may prove crucial for our future understanding of how we prevent, diagnose, and manage dementia.

PhD student Maryam Anzabi, MD, also finalized her thesis in 2017, having set out to test our hypothesis that changes in capillary function plays a key role in the development of delayed cerebral ischemia (DCI) and degenerative brain changes after subarachnoid hemorrhage (SAH) (Østergaard et al., 2013), and the possible, primary role of capillary flow patterns in the complex and poorly understood flow changes in relation to cortical spreading depressions (CSD) (Østergaard et al., 2015). Having learned a challenging SAH model with Nikolaus Plesnila's group in Munich, and worked with CSD expert Cenk Ayata and optical imaging experts David Boas and Sava Sakadžić at Massachusetts General Hospital and Harvard Medical School, Maryam Anzabi demonstrated early, dramatic capillary flow changes in both conditions – See Page 18-21. In DCI and CSD, observations of reduced arterial diameters and blood flow have naturally lead to the assumption that vasospasms and hypoperfusion were key targets for the prevention of the accompanying tissue injury. With Maryam Anzabi's impressive thesis work, capillary function and, to our surprise, post-SAH astrocytic function, seem to be fertile areas of future research.

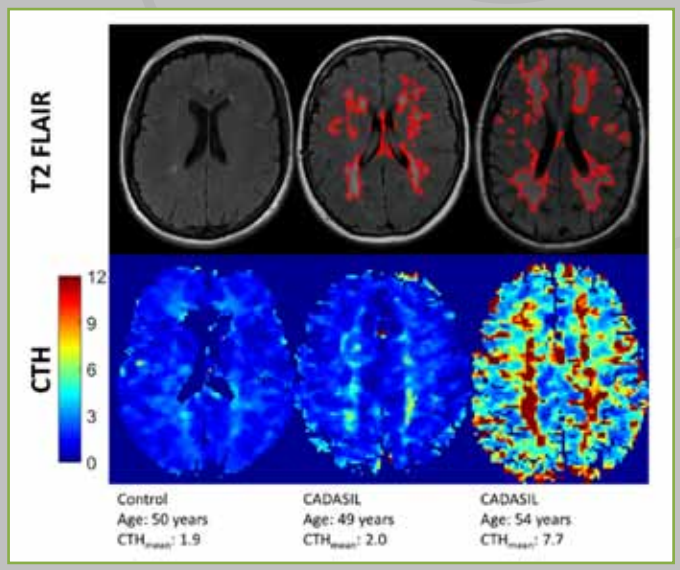

Figure 3
FLAIR images (top row) show distinct WMHs in a middle-aged control subject (left) and confluent areas in two CADASIL patients (middle, right). The rightmost patient suffers from much more severe cognitive deficits than the middle patient, although their WMH loads are similar. The lower row shows measurements of capillary dysfunction, as indexed by capillary transit-time heterogeneity (CTH). Note the widespread, extensive capillary dysfunction in the rightmost patient, as indicated by the warmer colors throughout the brain slice.

The number of microvessel within just a cubic millimeter of brain tissue is enormous – and the task of reporting observations of their functions even greater. As our methods begin to allow us to characterize capillary network topology, the fluxes and velocities of red blood cells through multiple, interconnected capillaries within networks, and recordings of oxygen tension in and around the microvasculature, it becomes essential to develop ways of reporting experimental findings in a consistent way – and perhaps more importantly: To know which data to record, in order to adequately characterize a given microvascular network and its functions. Working with world-leading experts within microvascular function, professors Timothy W. Secomb, University of Arizona and Axel R. Pries, Charité Berlin, using data sets describing blood cell distribution within microvascular networks different sizes from their labs and from our collaborators David Boas, Sava Sakadžić, ARCADIA researcher Peter Mondrup Rasmussen has taken monumental steps towards a solution to both challenges: Using measurements from a subset of capillaries across richly interconnected microvasculature as test data, he developed a framework for estimating key network characteristics, and indeed to guide experimental procedures so as to obtain these characteristics with the desired accuracy across large networks (Rasmussen et al., 2017). While this framework represents a break-through for standardized planning and reporting of experimental studies, it also provides means of evaluating the appropriateness of model assumptions based on empirical data, for example regarding the distribution of hematocrits in individual microvascular segments (Rasmussen et al., 2018). As we go forward, trying to understand how subtle disease changes in individual capillaries affect the distribution of blood across entire capillary networks, and hence local oxygenation, these tools will be of paramount importance to our work.

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FUNCTIONAL HEMODYNAMICS

PhD defense: Hugo Angleys

by Hugo Angleys

The brain's resting metabolism is fueled almost entirely by oxidative phosphorylation of glucose, and normal brain function is therefore contingent on a steady supply of oxygen and glucose. Glucose and oxygen are transported to the brain via the bloodstream and are mostly extracted to cerebral tissues across the capillaries. While sufficient oxygen is vital for the survival of the brain, too much oxygen can potentially be toxic, and risks are therefore involved for all tissues if oxygen levels are not finely adjusted. When neural activity increases, oxygen and glucose metabolism increase, although not to the same extent. Blood supply must therefore promptly adapt to meet the increased demands for oxygen and glucose. This coupling between neural activity and blood flow has been already studied in 1890 by Charles Roy and Charles Sherrington (Roy and Sherrington, 1890), and is now referred to as neurovascular coupling.

It was proposed 25 years ago by Kuschinsky and Paulson (Kuschinsky and Paulson, 1992) that not only the blood flow, but also its pattern plays an important role to regulate tissue oxygenation. This hypothesis was supported by several experimental studies suggesting that the blood flow is actively redistributed at the capillary level. Recently, the classical flow-diffusion (Renkin, 1985) model has been extended to examine this hypothesis, taking capillary transit time heterogeneity (CTH) into account (Jespersen and Østergaard, 2012). This model predicts that blood flow homogenization improves tissue oxygenation by counteracting the inherent reduction in oxygen extraction fraction as cerebral blood flow (CBF) increases. Consequently, it has been hypothesized that impairment of mechanisms controlling homogenization of the blood flow, in particular at the capillary level, could lead to tissue hypoxia, although CBF seems to be normal. This work generated several hypotheses on the effects of capillary dysfunction that are now supported by experimental work.

In this project, we further examined the effects of CTH on oxygen and glucose delivery, based on biophysical modeling.

We first developed a three compartment (hemoglobin, plasma, tissue) model for oxygen extraction, extending the aforementioned model (Jespersen and Østergaard, 2012) to take the effects of oxygen metabolism on tissue oxygen tension and extraction efficacy into account (Angleys et al., 2015). We observed that explicitly modeling oxygen metabolism to alleviate the assumption of a constant extravascular oxygen tension does not qualitatively change the conclusions of the original model and lead to more realistic predictions – see Figure 1. Finally, we showed that the model predictions were largely insensitive to the particular choice of transit time distribution employed.

Then, we developed a model of glucose extraction to examine the extent to which CTH affects glucose extraction (Angleys et al., 2016). We found that, while the cerebral metabolic rate of oxygen (CMRO2) is predicted to be influenced primarily by CTH and only moderately by CBF, the cerebral metabolic rate of glucose (CMRglc) is influenced primarily by CBF and moderately by CTH – see Figure 2. Accordingly, our model predicts that enhanced energy demands accompanied by hyperemia favors glucose uptake over oxygen uptake, leading to lactate production during functional activation.

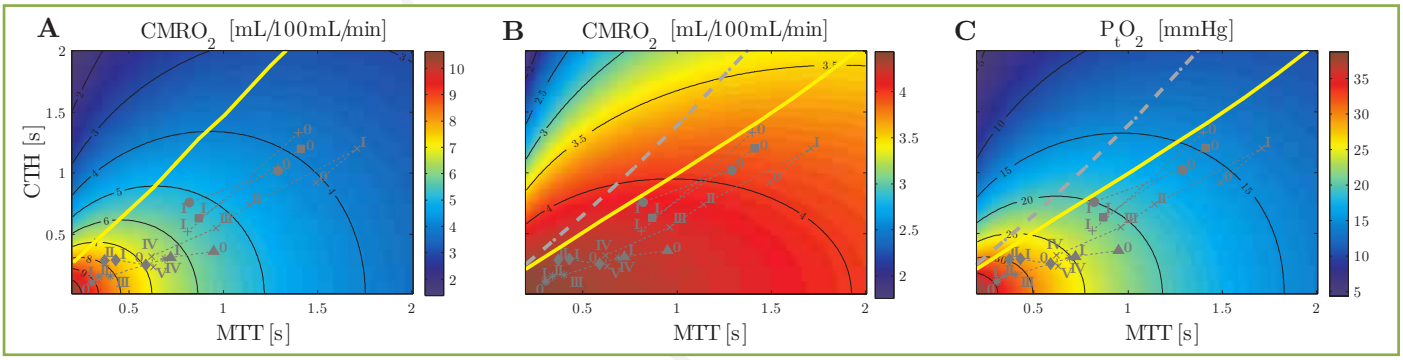

Figure 1
Comparison of the CMRO2 contour plots obtained with the model from (Jespersen and Østergaard, 2012) (A) and our model (B, C). In (A) the predictions are made without explicit oxygen metabolism and with tissue oxygen tension assumed to be fixed and equal to 25 mmHg. The yellow line and the dotted gray line in the three different panels separate states where a flow increase given a fixed CTH will lead to an increased (right side of the line) or decreased (left side of the line) oxygen consumption (A and B) and tissue oxygen tension (C), respectively. The roman numeral accompanying each symbol identifies different physiological conditions. Symbols: x: cortical electrical stimulation; +: functional activation; *: hypotension; ▲ : mild hypoxemia; ♦: severe hypercapnia; ●: Mild hypercapnia; ■: Severe hypoxemia.

Finally, we developed a model aimed at predicting dynamic changes in blood oxygenation and in the blood-oxygenation-level dependent (BOLD) signal, incorporating the effects of dynamic changes in CTH (Angleys et al., 2018). Our model predictions show good agreement with experimental measurements of BOLD signal under these conditions – see Figure 3. In particular, signal transients are consistently reproduced only when CTH is included in the model. Including dynamic changes in CTH provides a way to accurately predict the BOLD signal under a wide range of physiological conditions, based on realistic physiological mechanisms.

Overall, the findings in these three studies emphasize the importance of capillary flow patterns on oxygen and glucose delivery to cerebral tissues. They also provide a framework to evaluate the role of the microcirculation in health and disease for other tissue types.

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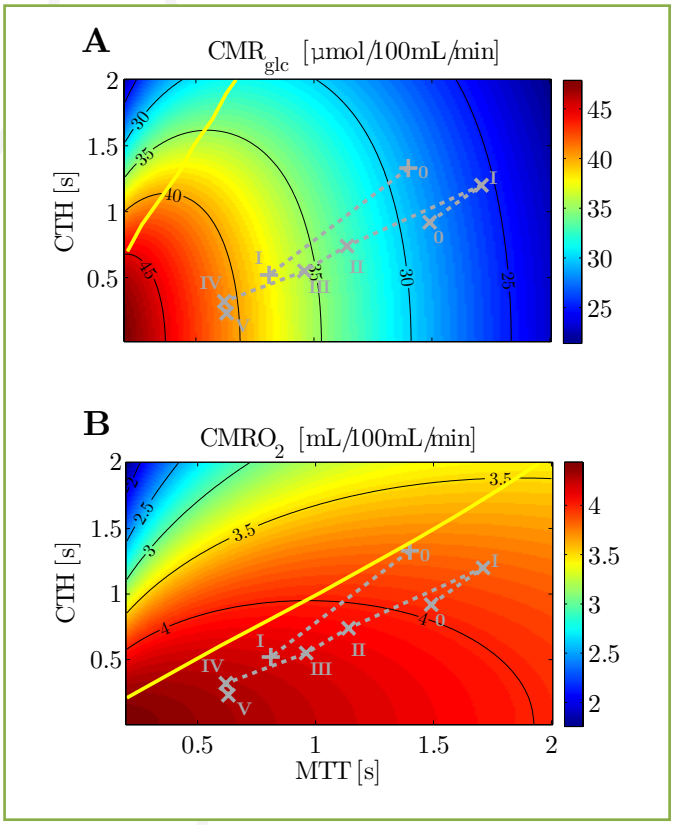


Figure 2
CMRglc (A) and CMRO2 (B) contour plots. The numeral '0' stands for resting state, whereas roman numerals refer to state of altered basal physiology. Note that the CMRglc and CMRO2 iso-contours do not show the same slope for the experimental data used in this figure, indicating that a change in MTT (resp. CTH) will have a strong (resp. moderate) influence on CMRglc , and inversely for CMRO2 . The yellow line separates states where a blood flow increase (decrease in MTT) given a fixed CTH will lead to an increased (right side of the line) or decreased (left side of the line) glucose (A) or oxygen (B) consumption, respectively. Symbols: +, functional activation; ×, cortical electrical stimulation.

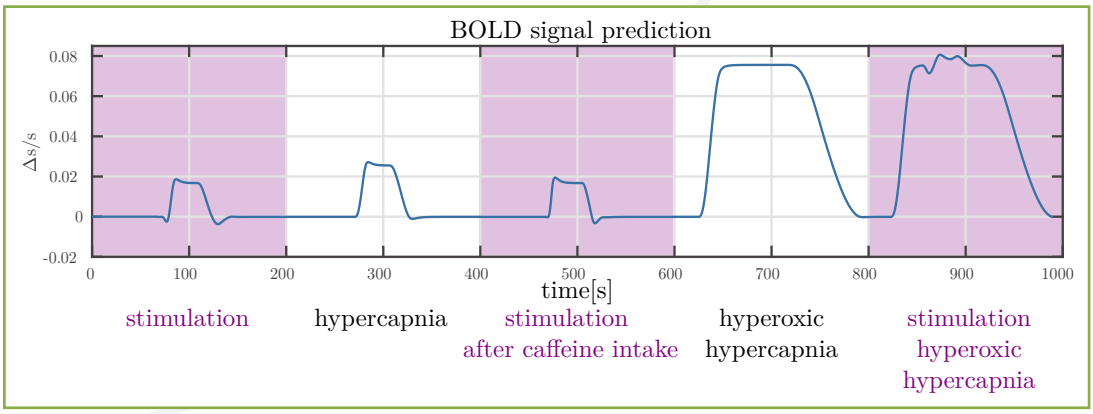


Figure 3
Prediction of the BOLD signal under different physiological conditions. Note the different transients (initial dip and post-stimulus undershoot) predicted.

FUNCTIONAL HEMODYNAMICS

PhD defense: Maryam Anzabi

by Maryam Anzabi

Brain Microcirculation and Tissue Damage after Subarachnoid Hemorrhage

The poor outcome after subarachnoid hemorrhage (SAH) is mainly ascribed to delayed cerebral ischemia (DCI), which is traditionally believed to be the result of parallel vasospasms[1]. This causal relation has recently been questioned; due to observations of discordant cerebral vasospasm and DCI development, and failure of cerebral blood flow (CBF) restoring strategies to prevent DCI[2,3].

The capillary bed flow was recently proposed as a contributor to the brain damage after SAH. Recognizing the crucial role of the capillary bed in maintaining tissue oxygenation, it was thus proposed, that cerebral oxygenation is limited not only by CBF, and thus by the vasospasm in the case of DCI, but also by the microscopic distribution of blood, so-called capillary transit time heterogeneity (CTH)[4]. The aim of our project was to examine whether capillaries might play a role in the tissue damage after SAH, and begin to explore some of the underlying causes of capillary dysfunction.

In our first study, we investigated capillary flow pattern alteration four days following experimental SAH and sham-operation in mice. We employed two-photon microscopy (TPM) to characterize hemodynamics characteristics after SAH induction. Our results showed elevated CTH and mean transit time (MTT) in SAH group compared to sham animals. Figure 1 shows the extent to which cerebral metabolic rate of oxygen ($CMRO_2$) and tissue oxygen concentration (P_tO_2) are predicted to drop in the SAH group compared to the sham animals based on our hemodynamic meassurements. This finding could be the result of either primary upstream arteriolar vasospasm or primary capillary flow disturbances. Favoring maldistribution of blood among capillaries, we found some cortical capillaries that were either void of red blood cell (RBCs) or revealed stagnant RBCs, as well as capillaries with increased RBC linear density in the SAH group. TPM showed

$(MTT_{SAH}, CTH_{SAH}) = (2.37\ MTT_{sham}, 2.38\ CTH_{sham})$

MTT (s)		CTH (s)		$CMRO_2$ (mL/100mL/min)		Relative change $CMRO_2$ (%)	P_tO_2 (mmHg)		Relative change P_tO_2 (%)
Sham	SAH	Sham	SAH	Sham	SAH		Sham	SAH	
1.0	2.37	0.77	1.83	4.1	3.5	-14.6%	19.0	10.3	-45.8%
1.5	3.56	1.16	2.76	3.9	3.0	-23.2%	14.7	7.0	-52.4%
2.0	4.74	1.54	3.67	3.7	2.6	-29.7%	11.9	5.1	-57.1%

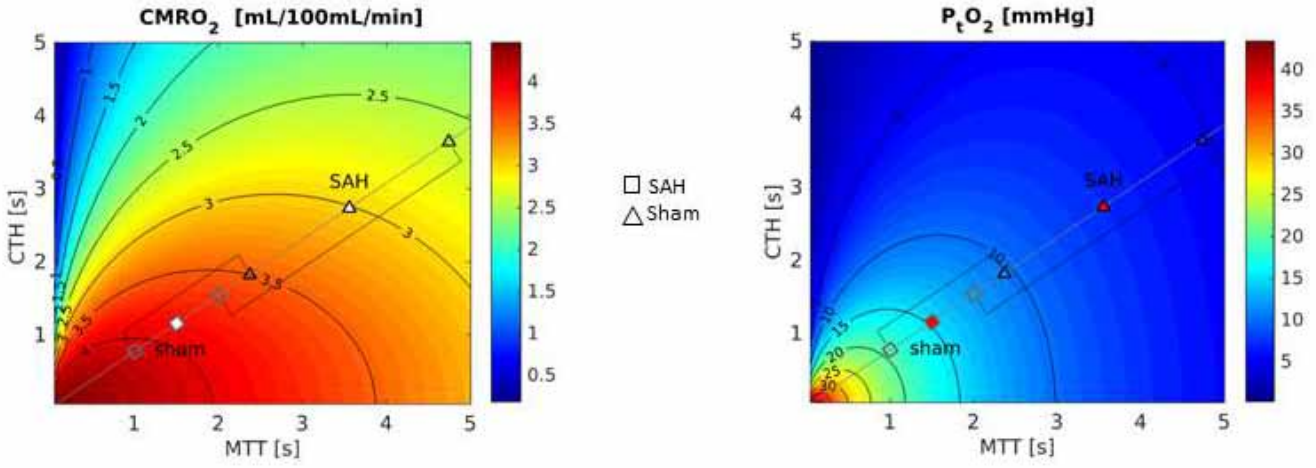


Figure 1
The extent to which cerebral metabolic rate of oxygen (CMRO2) and tissue oxygen concentration (PtO2) are predicted to drop in the SAH group compared to the sham animals based on increased values of capillary transit time heterogeneity (CTH) and mean transit time (MTT) in SAH animals.

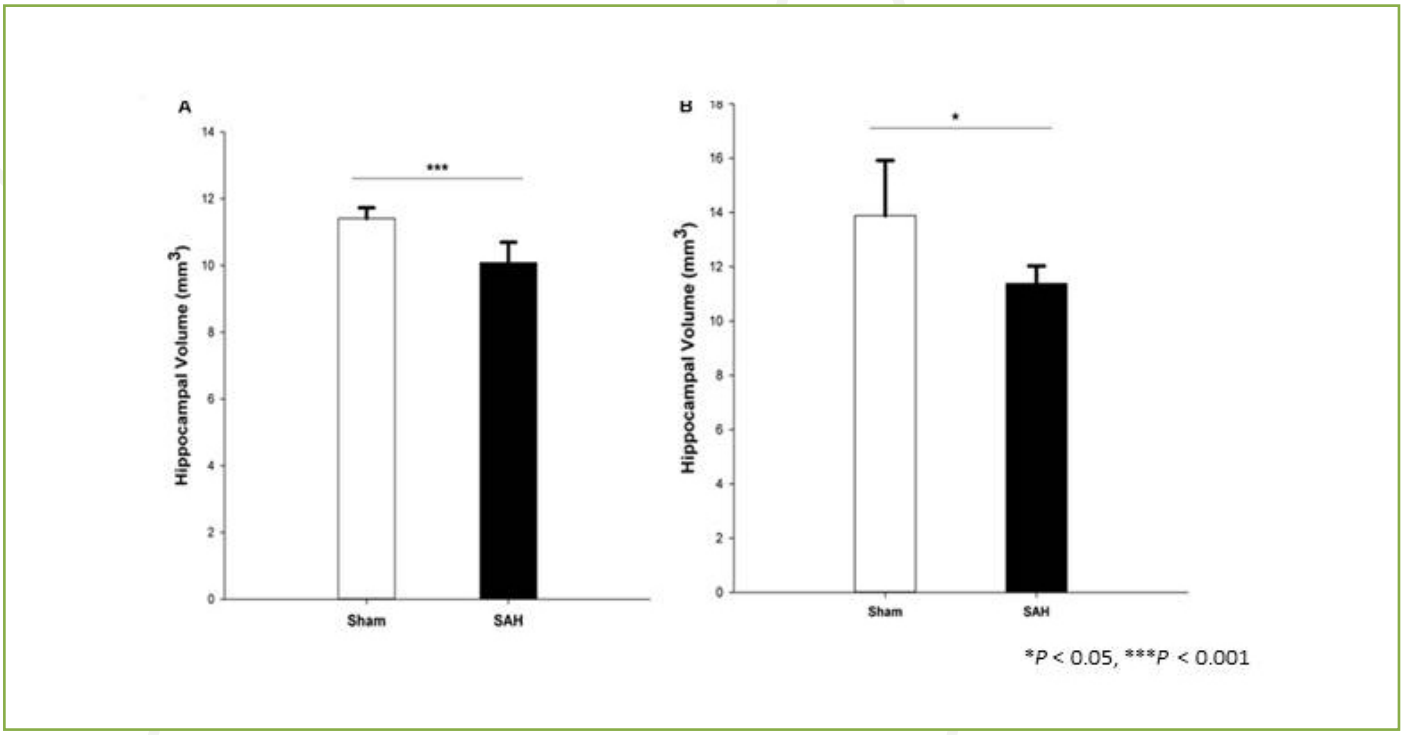


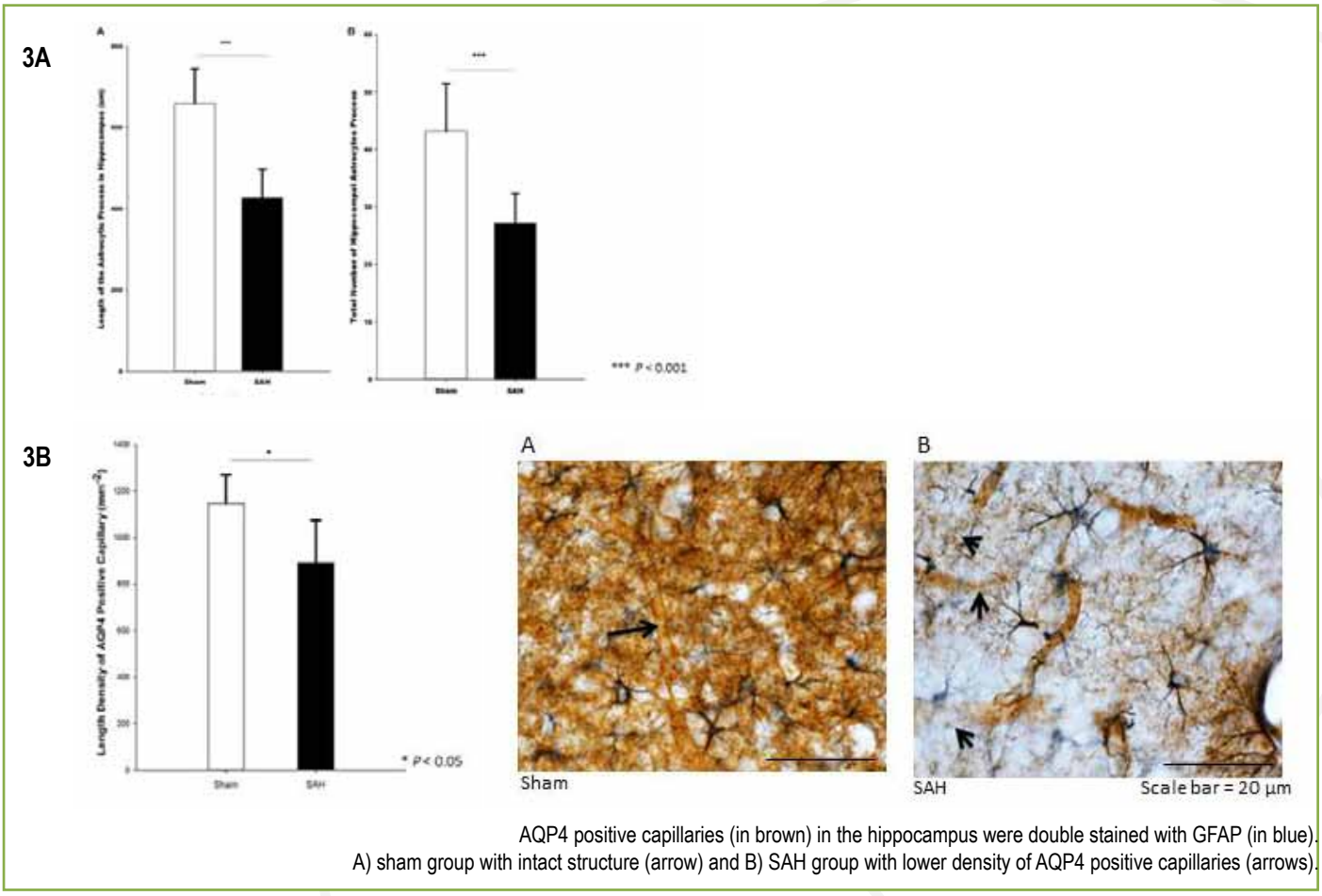
Figure 2
Total volume of the hippocampus in SAH and sham groups 4 days following surgery, obtained from (A). H&E stained sections (Cavalieri estimator method) and (B). MR images segmentation.

no statistically significant difference in arteriolar diameter between groups, but histological examination revealed reduced capillary diameter in the SAH group. The absence of arteriolar constriction in the SAH animals further implied that capillary flow pattern disturbances represent a primary phenomenon in the aftermath of SAH.
Taken together, this study suggests that subacute hypoperfusion and capillary flow disturbances in SAH animals are due to *capillary narrowing*, rather than upstream vasospasm.

Astrocytes are key to several aspects of brain function, including neurovascular coupling mechanisms and functions of the capillary bed, which they ensheath with their endfeet[5]. In particular, Aquaporin-4 (AQP4) water channels on astrocyte endfeet are thought to be key regulators of extracellular space (ECS) volume[6]. Therefore, changes in astrocyte function and AQP4 distribution would be expected to affect neurovascular coupling, capillary function, and tissue volume regulation after SAH.

The hippocampus is critical for cognitive functions, and in SAH survivors, hippocampal atrophy and cellular changes are thought to account for some of the permanent neurological and neurocognitive complications after SAH[7]. In our second study, we therefore characterized morphological changes in hippocampal astrocytes four days following experimental SAH, with special emphasis on gliavascular cross talk and hippocampal atrophy. The hippocampal volumes were determined by both magnetic resonance imaging (MRI) and histological/stereological methods. Stereological techniques were used to detect alterations in astrocyte morphology, and the length density of AQP4 positive capillaries. We found both neuroimaging and stereological evidence of hippocampal atrophy in SAH animals (see Figure 2).

SAH also induced retraction of astrocytes processes (see Figure 3A), accompanied by a significant reduction in the length density of AQP4 positive capillaries (see Figure 3B) as well as a narrowing of hippocampal capillaries. Meanwhile, astrocyte bodies were swollen in SAH mice. We conclude that, in this animal model of SAH, hippocampal atrophy exists already at the time of DCI onset in humans. Meanwhile, changes in astrocyte morphology seemingly disrupt glia-vascular interactions early after SAH and may thereby contribute to hippocampal atrophy[8].

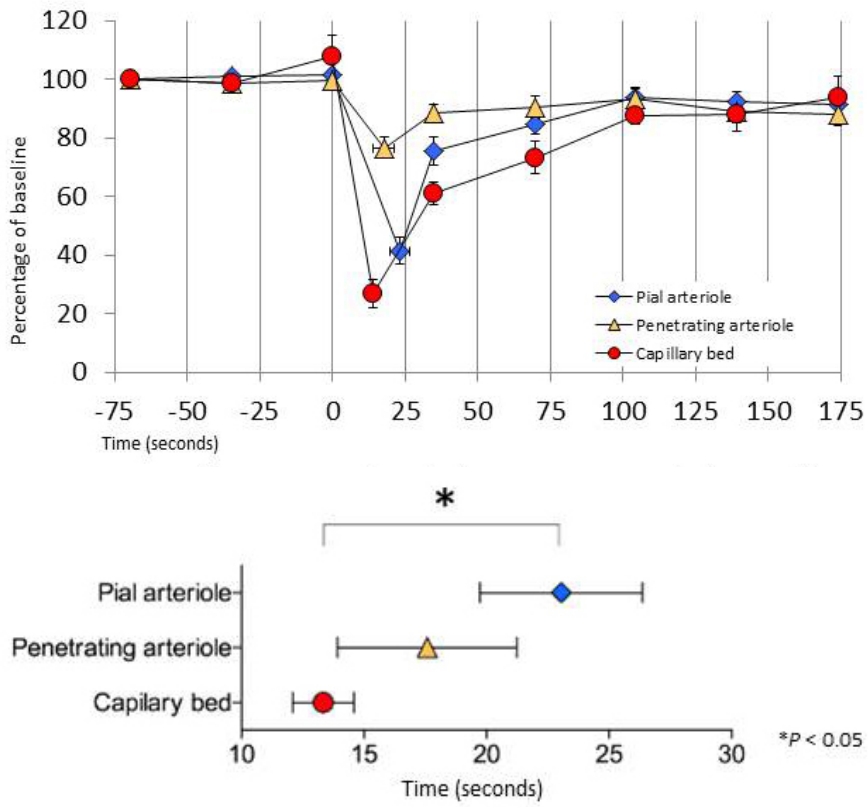


AQP4 positive capillaries (in brown) in the hippocampus were double stained with GFAP (in blue). A) sham group with intact structure (arrow) and B) SAH group with lower density of AQP4 positive capillaries (arrows).

Figure 3A and 3B

While changes in capillary diameter and hemodynamics may represent primary phenomena in the pathophysiology of SAH, microvascular changes and tissue hypoxia may also render brain tissue vulnerable to some of the injuries that are known to occur in the aftermath of SAH. One such injury mechanism, cortical spreading depolarizations (CSDs), imposes extreme metabolic demands on brain tissue and is known to be particularly prevalent in hypoxic brain tissue[9]. CSD is a selfpropagating wave of cerebral depolarization that results in temporary suspension of synaptic activity (spreading depression)[10]. In our third study, we used high-resolution optical coherence tomography (OCT) to determine the temporal dynamics of arteriolar diameter and capillary blood filling in relation to the arrival of the CSD waves. By observing the relative timing of changes in arteriolar diameter and capillary patency to RBCs, we tried to address whether capillaries or arterioles are first affected by CSD-related hemodynamic changes. Following CSD onset, we observed severe and long-term capillary flow disturbances. We also found a prompt and profound diameter constriction in superficial arterioles beside the dropout of the perfused capillaries. Interestingly, the initial drop in erythrocyte-filled capillaries, as well as the subsequent recovery of capillary filling, started prior to parallel changes in upstream vessel diameter (see Figure 4). These findings are consistent with the prediction that during and after CSD, CBF is adjusted according to capillary flow pattern, and thus the oxygen extraction capacity, downstream. We found support that persistent capillary flow disturbances may explain the discordant CBF responses to subsequent CSDs, a well-known observation in mice models of CSD.

Overall, the findings of our three studies support the notion that capillary flow pattern could play a crucial role in the tissue injury after SAH. Indeed, the findings support that capillary flow pattern play a primary role relative to upstream arteriolar constriction.



The initial drop in erythrocyte-filled capillaries started prior to parallel changes in upstream vessel diameter

Figure 4
Time course of changes in mean pial arteriolar diameter, penetrating arteriolar diameter and the density of perfused capillary bed during and after CSD. Measurements are presented relative to their pre-CSD baseline, rather than actual values. Time 0 represents the time point that CSD hits a specific region of interest.

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MCN Lab

CFIN Molecular and Cellular Neuroscience Lab

by Kim Ryun Drasbek

The Molecular and Cellular Neuroscience lab (MCN Lab) at CFIN is focused on understanding ischemic diseases such as stroke and acute myocardial infarction (AMI) and uses molecular tools in animal models to gain insights in how brain activity and cerebral blood flow is linked.

We are a partner in the Novo Nordisk Synergy project, ConBIS, that investigates the molecular response to different interventions in relation to stroke and AMI. In this project, remote ischemic conditioning (RIC), blood-flow restricted exercise, (BFRE), and traditional resistance training (TRT) is studied, as all of them are thought to elicit protective effects on longer ischemic events such as stroke and AMI. RIC is induced by repeated 5-minutes periods of controlled hypoxia in e.g. the arm using an auto-RIC device or simply a blood pressure cuff, while a tourniquet, that stops the venous blood flow to the leg while doing exercise, is used to induce BFRE. In the latter, the training load is only 20% of maximum as the subject performs as many cycles as possible. In contrast, TRT is carried out at 80% of maximum load until exhaustion. For all interventions, we obtain blood samples to look for signaling components that carry a protective effect. In this respect, extracellular vesicles (EVs) found in blood is of special interest, as they are able to protect their cargo of otherwise readily degradable molecules while having molecules on their surface that reflect their origin and the state of the secreting cell. These small nanosize particles have the potential to function as an inter-cellular signaling service that can carry information between organs in the body, as EVs are readily taken up by other cells, thereby being able to have an effect on the recipient cell.

EVs includes all types of small particles released by cells. Historically, they are divided into exosomes (30-150 nm), microvesicles/ectosomes (100-800 nm), and apoptotic bodies (200-5000 nm) based on their secretion mechanism. Here, exosomes are released from multivesicular bodies within the cell while microvesicles are shed from the plasma membrane. Apoptotic bodies are the result of apoptosis (programmed cell death) and these particles differ greatly in size and has completely different content compared to the 2 other subtypes. Many different cell types secrete EVs, including cells in the vasculature such as endothelial cells, pericytes, smooth muscle cells, erythrocytes, and platelets, as well as brain cells such as neurons and glial cells. Curiously, even bacteria, fungi, and plants secrete EVs and could therefore be the mediators of crosstalk between species. EVs change after different stimuli, and current research therefore seeks to use EV characteristics as diagnostic tools. For physical characterization of EVs, we purchased a qNano Gold instrument funded by the Riisfort Foundation. This instrument uses Tunable resistive pulse sensing (TRPS) to determine EV size, concentration, and surface charge on a single particle level (see Figure 1).

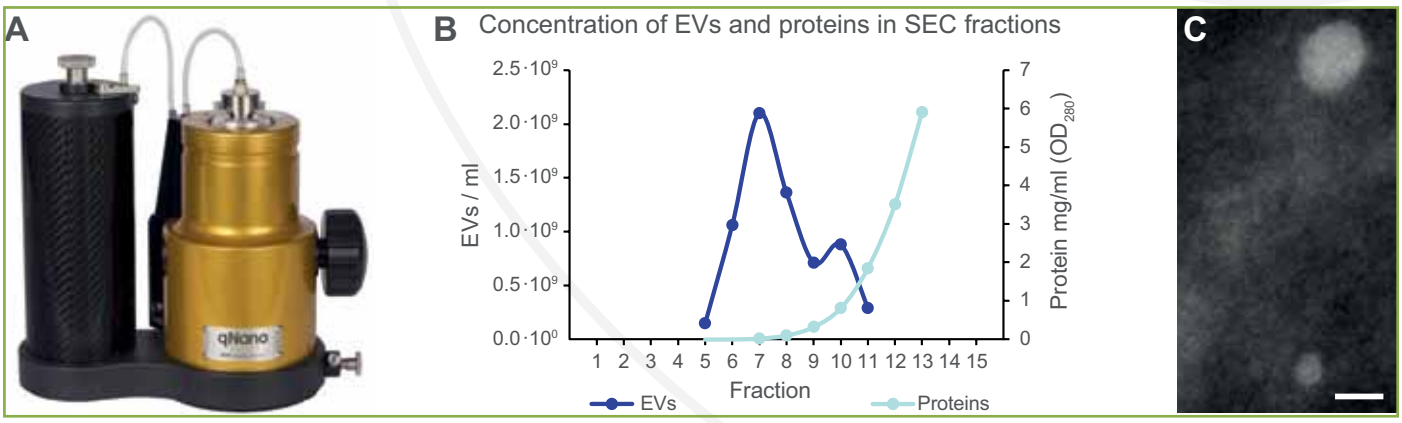


Figure 1
A: The qNano Gold (Izon Science) measures extracellular vesicle concentration, size, and surface charge by measuring small charge changes when individual particles crosses the Nanopore.
B: Using size exclusion chromatography, EVs can be separated from the proteins in plasma samples. C: Electron microscopy of purified EVs. (Data by Jesper Just and Sofie Overgaard Pedersen. EM picture (scale bar 100 nm) is produced with the help of Anete Berg, Section for Stereology and Microscopy)

Interestingly, EVs carries miRNAs that act as post-transcriptional regulators and play a large role in cellular protein expression. As each miRNA targets several proteins, they have the potential of re-programming the recipient cells. Also, the miRNA content of EVs are determined by the secreting cell in a regulated manner and changes according to the state of the cells in the body. This makes them interesting as biomarkers in disease diagnostics and treatment monitoring. Due to their biological impact on the recipient cells, miRNAs present an interesting future treatment strategy.

Next generation sequencing of EV miRNAs is carried out in collaboration with iNANO, AU within the ConBIS consortium. This analysis method detects both known and novel miRNAs and other non-coding small RNAs as well as measures the concentration of each miRNA.

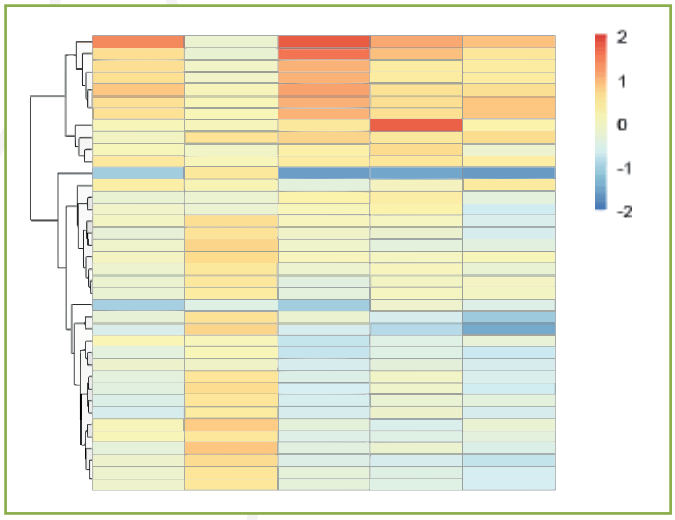
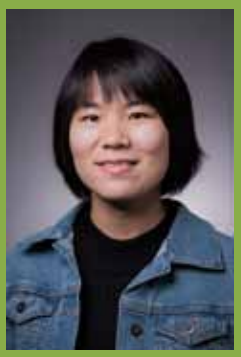


Figure 2
Using bioinformatic pipelines developed for the analysis of miRNA NGS data, we found several miRNAs that are differentially expressed over time following RIC. (Data by Jesper Just with the help of Yan Yan, iNANO, AU).

NEW FACE at CFIN



Tingting Gu, joined CFIN in September 2017 as a PhD student in the Molecular and Cellular Neuroscience Lab, supervised by Kim Ryun Drasbek.

She received her Master's degree in Neuroscience and Neuroimaging from the Neuroscience program at Sino-Danish Center. During her master's degree, she used optogenetics, and behavioral studies to study the underlying neural mechanism of morphine withdrawal at the Institute of Psychology, Chinese Academy of Sciences.

Tingting is now working on the project named "Exploring the protective effects of remote ischemic conditioning in stroke", where she uses stroke mice models, neurological tests and behavioral studies to evaluate the protective effects of Remote Ischemic Conditioning on brain ischemia and the role of extracellular vesicles in the process.

NEW FACE at CFIN

Signe Kirk Fruekilde, MSc. Signe joined CFIN in September 2017 as a PhD student in the Molecular and Cellular Neuroscience Lab, lead by Kim Ryun Drasbek.

She received a Master's degree in Neuroscience and Neuroimaging from the Sino-Danish Center. During her Masters behavioral studies, she worked with a combination of mouse behaviour and chemogenetics as a way to determine the function of a specific neuronal pathways.

For her PhD, Signe will use two-photon microscopy, optical coherence tomography (OCT) and optical intrinsic signal imaging (OISI) to study capillary transit time heterogeneity (CTH) and investigate the effect of inflammation on the neurovascular coupling. She will continue the Danish-Chinese collaboration and will do part of her research at Institute of Neuroscience in Shanghai.

POG

Pre-clinical Optical Group (formerly TPML)

by Nina Kerting Iversen and Eugenio Gutiérrez Jiménez

During the last year, new optical imaging equipment, such as optical coherence tomography (OCT) and Optical Intrinsic Signal Imaging (OISI), has been established in our laboratory. We have decided, therefore, to change the name of the group to Preclinical Optical Group (POG). Our group engages in interdisciplinary preclinical research with the overall goal to understand and quantify capillary dysfunction in various age-related disorders, including ischemic stroke, subarachnoid hemorrhage, Alzheimer's disease, and diabetic neuropathy. We have a strong collaboration with the Optics division at A. A. Martinos Center, Harvard University, USA, Stroke and brain imaging at the Institute of Neuroscience and psychology, University of Glasgow and the Experimental Stroke research unit at the Munich center for neuroscience, Germany, which enables us to combine and develop new methods to conduct brain science of highest quality. The laboratory makes up one of the pillars of the translational scientific preclinical research facility (PIFa) at Aarhus University/ Aarhus University Hospital. By joining forces with the CFIN preclinical MR group, the PET research group and CENSE at the Neurosurgery department at Aarhus University Hospital, we have the opportunity to employ an array of cutting-edge scanning methods that, combined, allow us to shed new light on brain disease mechanisms and hopefully inform the development of future treatments.

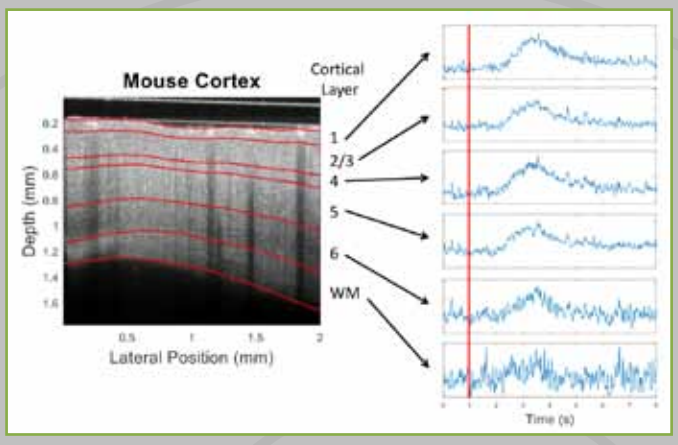


Figure 1
Cortical hemodynamics of the mouse brain using DyC-OCT imaging. Pixel-by-pixel analysis of the DyC-OCT signal following a bolus injection of a contrast agent, reveals functional information about microvascular networks in the mouse cortex. The bolus injection was performed 1 second after the beginning of the scan (red line). The curves represent the dynamic of the bolus injection through the different cortical layers (1-6) and the white matter (WM).

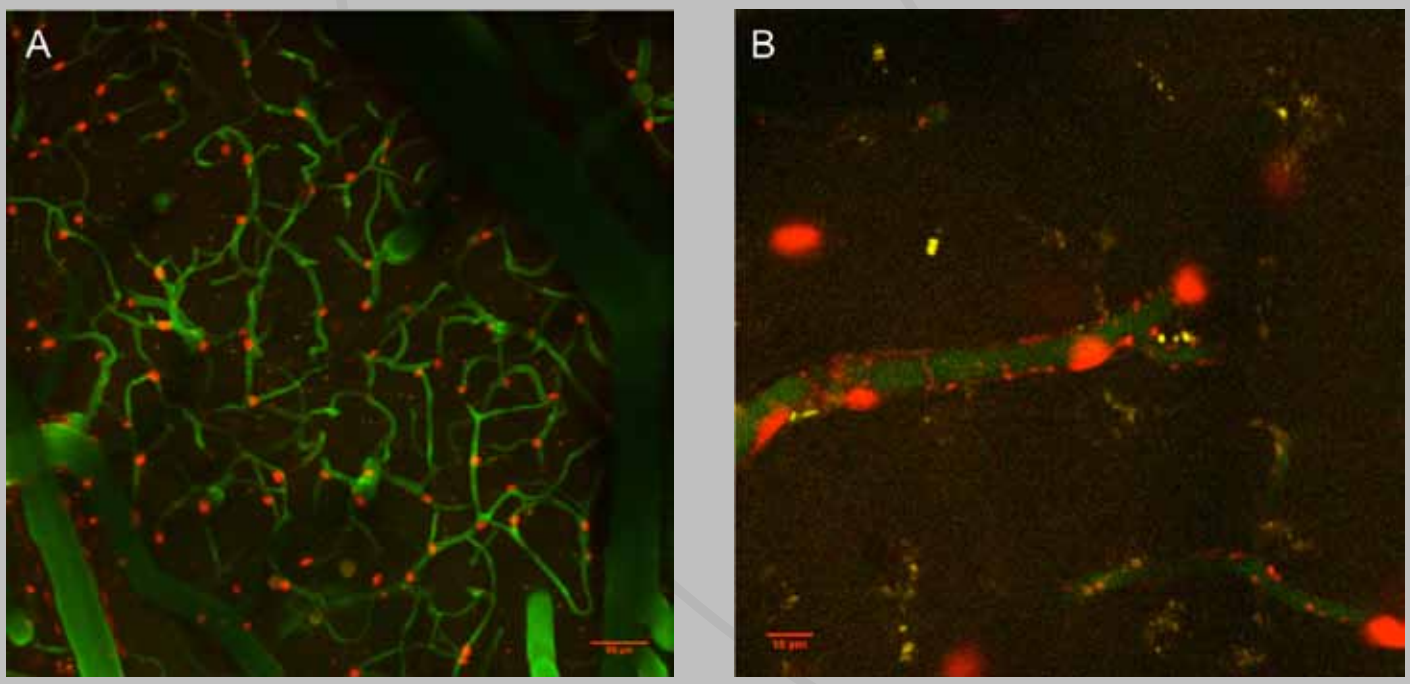


Figure 2
Visualization of the cerebral vasculature (green dye, FITC dextran) in a mouse with Nissl staining displaying the pericytes (red dye) positioned around the capillaries. Angiogram (A), single capillary scan surrounded by pericytes (B), by Eugenio Gutiérrez Jiménez.

The group continues to develop new methods and apply them in preclinical models of brain diseases. In 2017, in collaboration with CFIN/MIND*Lab* and ARCADIA staff, postdoc Eugenio Gutiérrez Jiménez implemented and further developed a two-photon microscope based bolus-tracking method, which enabled us to quantify capillary dysfunction in various disease models. Based on this method, he demonstrated capillary dysfunction in an Alzheimer murine model as well as how the capillary blood flow patterns are affected by the coupling of neuronal activity and blood supply, i.e. the neurovascular coupling mechanism. The project entitled *"Disturbances in the control of capillary flow in an aged APPswe/PS1ΔE9 model of Alzheimer's disease"* was published in the journal Neurobiology of Aging. This technique has also been implemented in a rodent model of acute ischemic stroke and in diabetic neuropathy by Nina K. Iversen and Anete Dudele. In collaboration with the Department of Biomedical Engineering, University of California Davis, USA, we implemented bolus-tracking by OCT, so-called Dynamic Contrast OCT (DyC-OCT). This optical technique will allow us to perform measurement of capillary hemodynamics throughout the whole rodent cortex with high temporal and spatial resolution (Figure 1).

Our laboratory made progress in terms of visualizing pericytes in a murine animal model (Figure 2). Pericytes play an important role in controlling the blood flow in capillaries throughout the body. They are contractile cells that wrap around the endothelial cells that line the capillaries. In the brain, these cells also help sustain the blood-brain barrier as well as other homeostatic and hemostatic functions of the brain. These cells are also a key component of the neurovascular unit and regulate capillary blood flow. They are thought to play an important role in many neurogenerative diseases, stroke, and diabetic retinopathy, and their visualization is therefore of high importance in order to describe the progression of the diseases. Eugenio made progress on this in close collaboration with postdoc Jesper Just and this technique is now used daily in our murine experimental models (Figure 1).

Oxygen is crucial for brain energetics, and tissue oxygenation is one of the most critical parameters with respect to brain physiology and pathology. The ability to measure oxygen partial pressure (pO2) with high temporal and spatial resolution in three dimensions is crucial for characterizing oxygen delivery and consumption in the normal and diseased brain. The developed technique opens up numerous

FACTS

Core and affiliated groups members:

- **Nina Kerting Iversen**
- **Eugenio Gutiérrez Jiménez**

- Anete Dudele
- Jacob Engbjerg
- Katrine Tang Stenz
- Lars Hvass
- Luca Bordoni
- Maryam Anzabi
- Maryam Ardalen
- Sebastian Frische
- Signe Kirk Fruekilde
- Tingting Gu
- Tristan Hollyer

Laboratory technicians
- Susanne Smith Christensen
- Stine Ledet Methmann

possibilities for metabolic studies in neuroscience that will advance our understanding of brain metabolism and function under normal and pathological conditions. In close collaboration with Professor Sava Sakadzic, Optics Division, A. A. Martinos Center, Harvard University, Massachusetts, USA, Eugenio has employed this technique in our Two-Photon microscope (Figure 3).

In stroke, the penumbra surrounds the ischemic core. It is defined as hypoperfused area of tissue that may be salvaged, if blood flow is restored. Therefore, the penumbra makes up the treatment target for clinical- and preclinical stroke research. In the recent year, Assistant Professor Nina K. Iversen has characterized the penumbra area in a rat MCAO stroke model by used of Laser Speckle Contrast Imaging, visualizing the superficial perfusion of the rat cortex. Associate Professor Peter M. Rasmussen has developed software to visualize the penumbra, operationally defined as tissue with perfusion between 25-50 % of the corresponding healthy hemisphere (Figure 4).

In the coming year, we have many new projects evolving and more students communing in the lab.

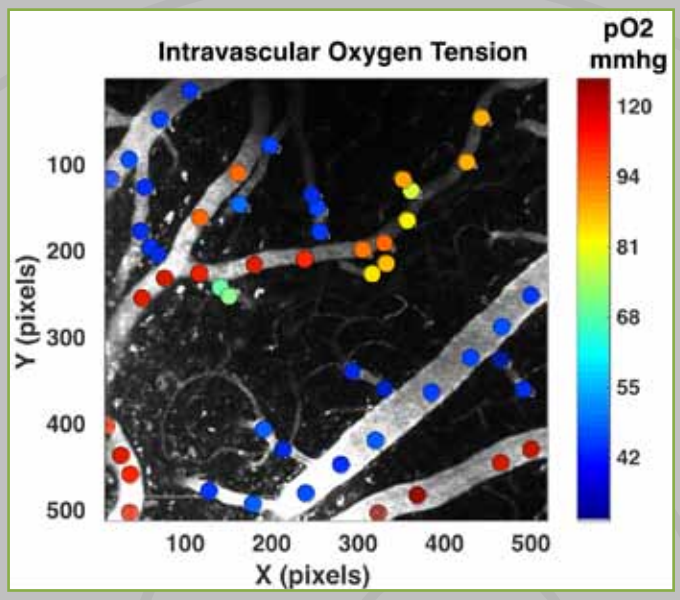


Figure 3
Estimations of intravascular oxygen tension (pO2) of pial vessels on the mouse somatosensory cortex. For these estimations, we performed Phosphorescence Lifetime Imaging (PLIM) with TPM, using a phosphorescence oxygen sensitive dye (PtP-C343). Scale bar = 200 µm.

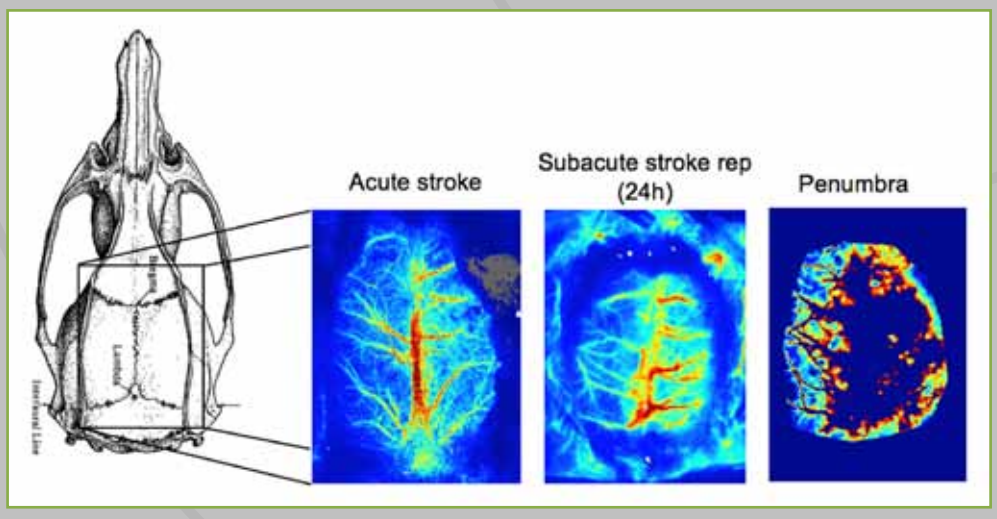


Figure 4
Laser Speckle Contrast Imaging of a rat thinned scull showing the superficial perfusion during acute stroke (4h), and subacute stroke (24h). The penumbra was quantified and visualized an in-house built software and defined as perfusion between 25-50% of the corresponding healthy hemisphere.

Part of the POG Group gathered for a one-day seminar in the fall of 2017.
Photo: Maryam Anzabi

FACTS

International Collaborators:

- Assistant Professor Sava Sakadzic
  Optics Division, Athinoula Martinos Center, Massachusetts General Hospital/ Harvard University, USA
- Professor David Boas
  Neurophotonics Center, Boston University
- Assistant Professor Silvia Fossati
  New York University School of Medicine
- Postdoc Conrad Merkle
  Medical University of Vienna, Italy
- Professor Vivek J. Srinivasan
  Biomedical Engineering, UC Davis, USA
- Professor Erlend Nagelhus
  Oslo University - Institute of Basic Medical Science, Norway
- Professor Ninglong Xu
  Institute of Neuroscience, CAS, China
- Dr Chris McCabe
  Institute of Neuroscience and Psychology, University of Glasgow, UK

Neuroscience in China

by Kim Ryun Drasbek & Vibeke Sauer Panyella

Neuroscience and Neuroimaging in China

The Neuroscience and Neuroimaging Master's programme has been running since 2012. In August 2017, we welcomed the sixth batch of new students to the programme. This was the first class to begin their study at the new Yanqihu campus.

Trip to the Great Wall of China during the introduction week 2017.
Photo: Thomas Alrik Sørensen

In September the SDC house at Yanqihu campus was inaugurated, with a grand ceremony where His Royal Highness the Crown Prince of Denmark, the President of Chinese Academy of Sciences and The Danish Minister of Higher Education and Science, amongst others, participated. The house is designed by Danish Architects Lundgaard & Tranberg. It is really quite beautiful on the inside with lecture rooms, group rooms, offices for professors and PhD students,

The SDC building and opening ceremony.
Photo: SDC

SDC secretariat, and small apartments on the top floor for visiting professors.

The 5th annual SDC Neuroscience and Neuroimaging symposium.
Photo: Michael Havgaard Bihlet

A delegation of neuroscientists participated in the inauguration, after which we hosted the 5th annual symposium for Neuroscience and Neuroimaging in the new building. The second year Neuro students presented their thesis projects at the symposium, and this was followed by a scientific session for the attending scientists.

During the summer and fall of 2017, the fourth class of students graduated obtaining their Danish degree. We decided to follow up on our Danish graduates, and we are quite proud to say that as of February 2018, two thirds of all our Danish graduates have continued on to PhD studies within neuroscience and neuroimaging. This fulfils the purpose of the programme of educating the next generation of outstanding neuroscience and neuroimaging researchers.

To continue the scientific education of the graduates, the first SDC Neuroscience and Neuroimaging PhD course was organised by Professor Jianyuan Sun, Institute of Biophysics, Chinese Academy of Sciences (CAS), Beijing, Jens Midtgaard, Copenhagen University, Jens Nyengaard and Kim Ryun Drasbek, AU with administrative support by the SDC office in Yanqihu and Vibeke Sauer Panyella, AU. The Inaugural SDC Neuroscience and Neuroimaging PhD course & Symposium: "The neural basis of brain information processing and behaviour: synapses, cells and circuits" took place in October 2017 where Danish and Chinese PhD students attended exciting talks by 18 renowned experts within the field including Muming Poo, Institute of Neuroscience, CAS, Shanghai, David Kleinfeld, University of California, San Diego, Saskia de Vries, Allen Brain Institute, Seattle, Greg Stuart, Australian National University, Canberra, Kim Krogsgaard, Lundbeck Foundation, and Yury Shtyrov, CFIN, AU. After given their talks, the invited speakers participated in master classes with the students to facilitate in-depth discussions and interaction between professors and students. The course was a great success and included social events to Beijing city center and the Great Wall of China.

List of CFIN / MIND*Lab* researchers involved in SDC Teaching and coordination

Head of Programme: Associate professor Kim Ryun Drasbek
Programme Coordinator: Vibeke Sauer Panyella
Arne Møller
Carsten Gleesborg
Chris Bailey
Dora Grauballe
Jakob Blicher
Jens Kjærgaard Boldsen
Kim Mouridsen
Peter Mondrup Rasmussen
Signe Kirk Fruekilde
Simon Eskildsen
Thomas Alrik Sørensen
Visse Moestrup

FACTS

The Master's program in Neuroscience and Neuroimaging in Beijing, China is part of the Sino-Danish Center for Education and Research (SDC).

CFIN researchers contributed greatly to the design and development of the education, and many remains deeply involved. It is a national initiative that also involves colleagues from the other Danish universities and aims to generate scientific collaboration with Chinese partners.

APPLIED IMAGING AND MODELLING

by Simon Fristed Eskildsen

AIM group

The applied imaging and modelling (AIM) group investigates pathological and developmental brain changes by applying both conventional and novel imaging techniques and analysis methods. Especially within research in Alzheimer's disease (AD), the AIM group invests significant time and resources. In this field, the AIM group collaborates closely with the PET Center on an ambitious project, investigating imaging biomarkers in AD. The project deploys both MRI and PET imaging to understand the pathological processes underlying the disease. A cohort of amnestic mild cognitive impaired (MCI) patients is followed for two years, and in 2017 the baseline data acquisition was completed. Using these baseline data, Dr. Peter Parbo found that neuro-inflammation is an early event in the disease. 85% of the amyloid-positive MCI patients showed increased levels of cortical microglial activation compared with

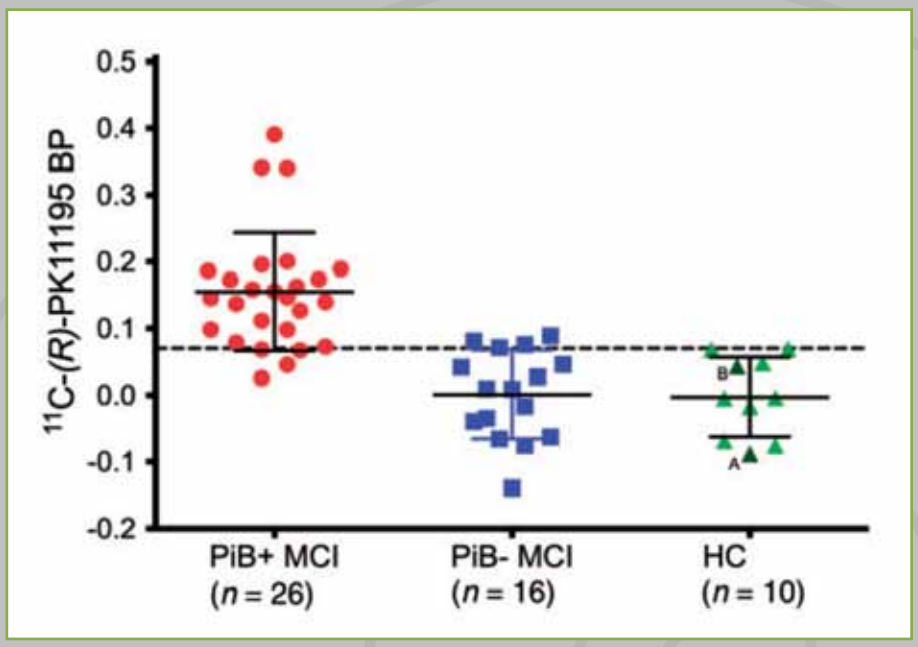


Figure 1
Scatterplot of individual PK11195 binding potential averaged across clusters in the temporal lobe. Twenty-two (85%) of the 26 PiB-positive MCI cases showed PK11195 binding levels above the healthy control range. PK11195 binding levels for individual PiB-negative MCI and healthy control subjects are also shown in the plot. The dashed horizontal line at y = 0.07 marks the upper limit of the healthy control range; short solid lines are group means ± 1 SD. From (Parbo et al., 2017).

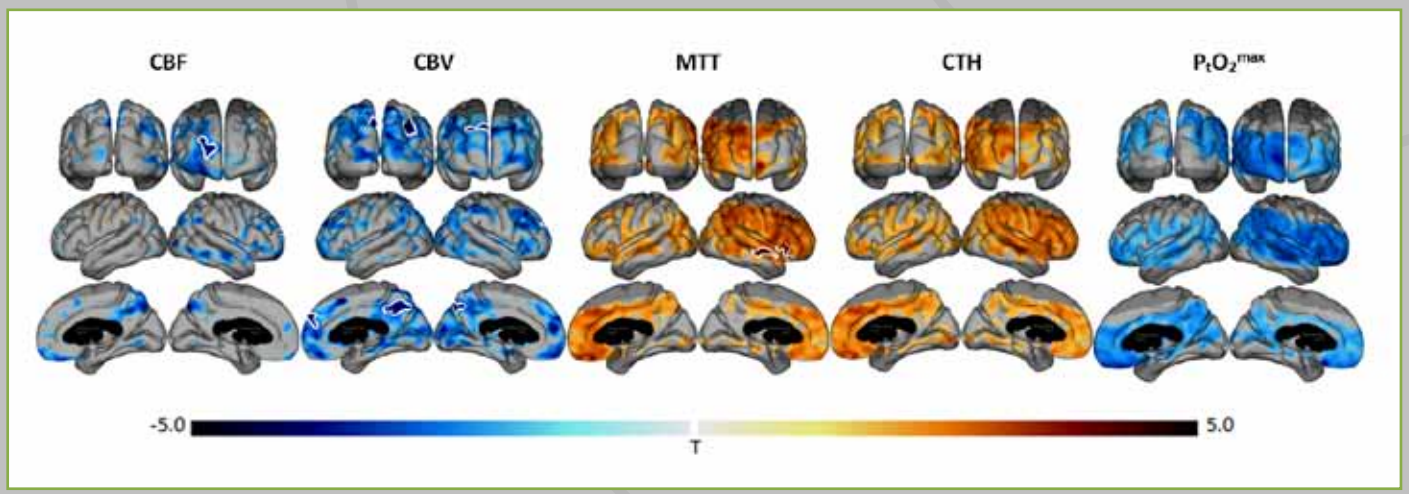


Figure 2
Perfusion differences in 20 amyloid positive patients with amnestic mild cognitive impairment compared with 21 healthy age-matched controls. Statistical T-value maps were adjusted for age and sex using linear regression and thresholded at $p<0.05$. Negative T-values indicate reductions (blue nuances), while positive T-values indicate increases (red nuances). The white outlining denote clusters surviving family-wise error correction for multiple comparisons at $\alpha=0.001$. Subjects were classified as either amyloid positive (Aβ+) or amyloid negative (Aβ-), defined by an atlas based composite regional PiB-SUVr >1.5 and ≤1.5, respectively. CBF: cerebral blood flow, CBV: cerebral blood volume, CTH: capillary transit time heterogeneity, MTT: mean transit time, PtO2max, the tissue oxygen tension required to sustain the minimum metabolic demand of resting brain tissue (2.5mL/100mL/min), given the measured MTT and CTH. From (Nielsen et al., in preparation).

healthy age-matched controls (Figure 1) (Parbo et al., 2017). It is hypothesized that the increase in levels of microglial activation is a protective response to the build-up of neurotoxic β-amyloid.

In the same cohort, Rune Nielsen found reduced cerebral blood flow (CBF) and volume (CBV) with increased capillary mean transit time (MTT) and capillary transit time heterogeneity (CTH) at baseline compared with controls (Figure 2). In addition, modelling the tissue oxygen tension, which may indicate current or imminent tissue hypoxia, we found widespread decreases of PtO2max throughout neocortex compared with controls at baseline (Figure 2, rightmost panel). As these patients demonstrated very little to no cerebral atrophy compared with controls, the observed changes in the cerebral microcirculation cannot be explained by a lower demand for oxygen and nutrients. Thus, these findings indicate an early vascular involvement in the pathophysiology of the disease. The follow-up of the cohort will be completed in 2018, at which time we will be able to study the longitudinal change to the cerebral microcirculation.

FACTS

Core and affiliated group members:

- Simon Fristed Eskildsen
- Rune Bæksager Nielsen
- Mikkel Nygaard
- Lasse Madsen
- Brian Højgaard
- Leif Østergaard
- Torben Ellegaard Lund
- Sune Nørhøj Jespersen
- Brian Hansen
- Kim Mouridsen
- Jesper Frandsen
- Irene Klærke Mikkelsen
- Mikkel Bo Hansen
- Jakob Udby Blicher
- Erhard Næss-Schmidt
- Rikke Dalby

National & International collaborators:

- Professor David Brooks, Positron Emission Tomography Center, Department of Clinical Medicine, Aarhus University, Denmark.
- Professor Louis Collins, McConnell Brain Imaging Center, Montreal Neurological Institute, McGill University, Montreal, Canada.
- Dr. Pierrick Coupé, Laboratoire Bordelais de Recherche en Informatique, Unité Mixte de Recherche CNRS (UMR 5800), Bordeaux, France.
- Professor José Manjon, Instituto de Aplicaciones de las Tecnologías de la Información y de las Comunicaciones Avanzadas (ITACA), Universitat Politècnica de València, Valencia, Spain.
- Dr. Tim Dyrby, Diffusion Imaging Group, Danish Research Centre for Magnetic Resonance, Hvidovre, Denmark.
- Professor Marc Vérin, Institut des Neurosciences Cliniques de Rennes, Université Rennes, France.
- Professor Risto Kauppinen, School of Experimental Psychology, University of Bristol, United Kingdom.
- Associate Professor Ulrik Dalgas, Department of Public Health - Sport Science, Aarhus University, Denmark.
- Professor Vibeke Hjortdal, Department of Thoracic and Cardiovascular Surgery, Aarhus University Hospital, Skejby, Denmark.
- Professor Ludvig Muren, Department of Medical Physics, Aarhus University Hospital, Denmark.
- Dr. Eduardo A. Garza-Villarreal, National Institute of Psychiatry, Mexico.
- Dr. Per Qvist, Department of Biomedicine, Aarhus University, Denmark.

In collaboration with Department of Biomedicine, the AIM group studies brain morphometry in mice with genetic susceptibility and phenotypic relevance to schizophrenia (Brd1+/- mice). Using post-mortem 3D MR imaging coupled with histology and regional mRNA marker analysis, we found that Brd1+/- mice displayed subcortical abnormalities, including volumetric reductions of amygdala and striatum (Figure 3). We demonstrated that structural alteration in striatum correlated with a general loss of striatal neurons, differentially affecting subpopulations of medium-sized spiny neurons and thus striatal output. Similar to parvalbumin interneuron dysfunction found in patients, a decline in parvalbumin expression was found in the developing cortex, mainly driven by neuronal loss within or near cortical layer V, thus potentially affecting cortical projections to striatum in Brd1+/- mice. Collectively, our findings highlights the translational value of the Brd1+/- mouse as a pre-clinical tool for schizophrenia research and

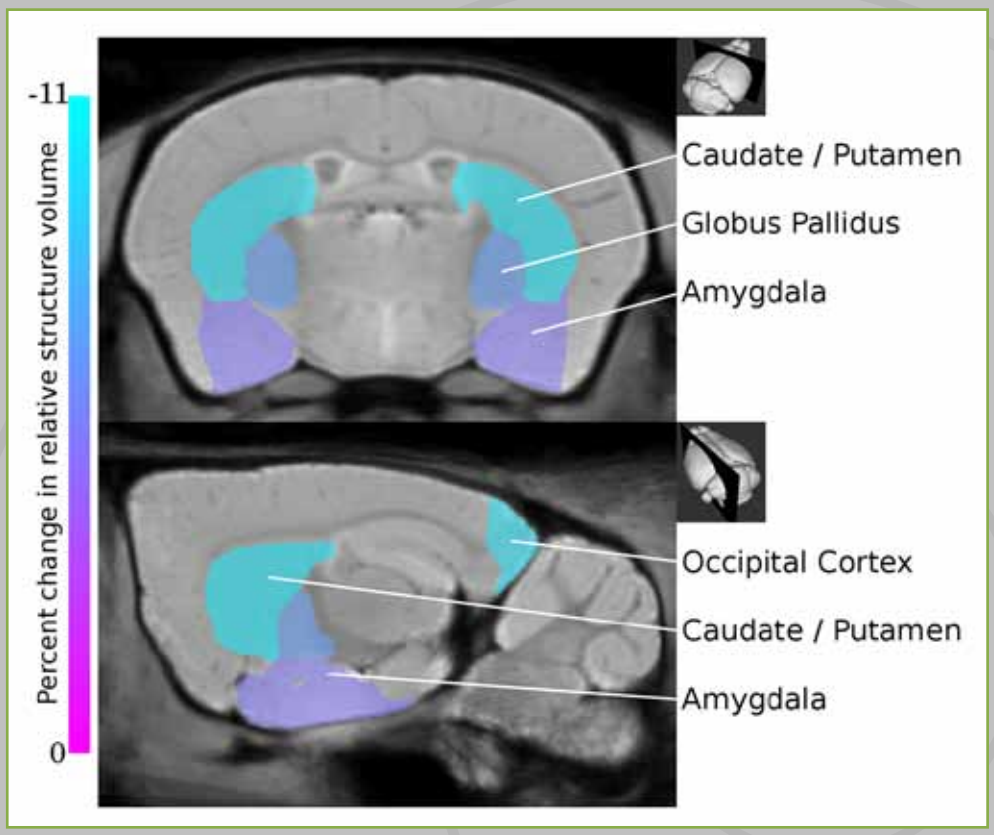


Figure 3
Subcortical volumetric changes in 15 weeks old Brd1+/- mice. The colours indicate smaller subcortical volumes in 10 Brd1+/- mice compared with 9 age-matched wild type mice. From (Qvist et al., in review).

NEW FACES at CFIN

In the fall 2017, the AIM group was extended with three members: Mikkel Nygaard, Lasse Madsen and Brian Højgaard. They are all employed as student assistants within the project investigating imaging biomarkers of Alzheimer's disease.

Mikkel Nygaard,
Master student in Engineering

Lasse Madsen,
Master student in Engineering

Brian Højgaard,
MSc in Engineering

provides novel insight into the developmental, structural, and cellular pathology of the disorder (Qvist et al., in review). Our collaborative efforts continue and further studies will deepen our understanding of this potential model of schizophrenia.

During 2017, two Master's students enrolled in the Neuroscience and Neuroimaging programme at the Sino-Danish Center for Education and Research and co-supervised by the AIM group defended their theses. Fróði Gregersen successfully defended his thesis entitled "Quantitative Sodium Magnetic Resonance Imaging at Ultra High Field Strength" and Zhengzheng Deng graduated with the thesis "Encoding mental states in natural-viewing: A functional network approach".

In the fall 2017, the AIM group was extended with three members: Mikkel Nygaard, Lasse Madsen and Brian Højgaard. They are all employed as student assistants within the project investigating imaging biomarkers of Alzheimer's disease, thereby strengthening our efforts in pursuit of understanding this devastating disease.

References

1. Parbo, P., Ismail, R., Hansen, K.V., Amidi, A., Marup, F.H., Gottrup, H., Braendgaard, H., Eriksson, B.O., Eskildsen, S.F., Lund, T.E., Tietze, A., Edison, P., Pavese, N., Stokholm, M.G., Borghammer, P., Hinz, R., Aanerud, J., Brooks, D.J., 2017. Brain inflammation accompanies amyloid in the majority of mild cognitive impairment cases due to Alzheimer's disease. Brain, 140, 2002-2011.
2. Nielsen et al., Reduced Cerebral Blood Flow and Blood Volume in Mild Cognitive Impairment: Relation to Capillary Function and Amyloidosis. In preparation.
3. Per Qvist, Simon Eskildsen, Brian Hansen, Mohammad Baragji, Steffen Ringgard, Jolien Roovers, Veerle Paternoster, Simon Mølgaard, Thomas Corydon, Hans Stødkilde-Jørgensen, Simon Glerup, Ole Mors, Gregers Wegener, Jens Randel Nyengaard, Anders Børglum, and Jane Christensen. Brain volumetric alterations accompanied with loss of striatal medium-sized spiny neurons and cortical parvalbumin expressing interneurons in Brd1+/- mice. In review.

FACTS

Selected research projects:

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

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

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

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

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

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

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

Per Qvist, Steffen Ringgaard, Simon F. Eskildsen, Jens R. Nyengaard, Gregers Wegener, Jane H. Christensen, Anders Børglum: The implication of the schizophrenia-associated gene, BRD1, in behavior, cognition and brain development in genetically modified mice.

Eduardo A Garza-Villarreal, Mallar Chakravarty, Brian Hansen, Sune Jespersen, Simon Eskildsen: Brain morphology and connectivity in cocaine addiction.

Martin Langeskov Christensen, Simon Eskildsen, Ulrik Dalgas: Effects of aerobic exercise on brain health in multiple sclerosis.

Mette Høj Lauridsen, Steffen Ringgaard, Simon Eskildsen, Vibeke Hjortdal: Brain Matters in Heart Matters – from early fetal development.

Events:

PhD Day 2017 – Rune Nielsen (poster) and Simon Eskildsen (chairman).

Neuroscience Day 2017 – Rune Nielsen (poster) and Simon Eskildsen.

Two months visit by Zhengzheng Deng, SDC student, Institute of Psychology, Chinese Academy of Sciences, Beijing, China.

Simon Eskildsen: Chairman of the PhD defense: "Automated detection and prognostic value of the regional distribution of early diabetic retinopathy lesions" by Giovanni Ometto.

DISEASE AND PLASTICITY

by Jakob Udby Blicher

The disease and plasticity group at CFIN engages in translational and clinical neuroscience within areas as amyotrophic lateral sclerosis, stroke rehabilitation, and traumatic brain injury. The group was founded in 2017 and is led by Associate Professor Jakob Udby Blicher.

Stroke

More than 10 years of research on the role of inhibitory cortical activity in post-stroke by CFIN researchers reached a momentary highpoint in early 2017. Earlier studies by Jakob Blicher showed that decreasing inhibitory cortical activity could be beneficial in post-stroke recovery. During his PhD CFIN researcher Krystian Figlewski investigated the effect of transcranial direct current stimulation (tDCS) as an add-on treatment during so-called constraint-induced movement therapy (CIMT) for patients recovering from stroke at Hammel Neurorehabilitation and Research Center, the results were published in Stroke, and showed that tDCS leads to a 50% increase in the effect of motor training[1]. Further studies on the effect of tDCS together with collaborators from the Danish Research Center for Magnetic Resonance indicate that the effect likely is very dependent on the lesion location and size (see Figure 1)[2], and thus further studies are still needed to fully understand the effect and possible role for tDCS in post-stroke recovery.

Amyotrophic Lateral Sclerosis and Brain Computer Interface

In 2017 the project "Restore motor function through robotic arm exoskeleton and brain computer interface" (REMAP) was started in collaboration with Department of Neurology, Aarhus University Hospital, Center for Sensory-Motor Interaction, Aalborg University, Aalborg U Robotics, Aalborg University, The Danish National Rehabilitation Center for Neuromuscular Diseases and the Swedish company BioServo Technologies. The REMAP project is funded by Innovation Fond Denmark and led by Associate Professor Jakob Udby Blicher from the Disease and Plasticity group. The aim of REMAP is to develop and implement a robotic exoskeleton and a brain computer interface (BCI) to assist patients with the progressive neurodegenerative disease ALS. Via recordings of the patient's brain activity by electroencephalography (EEG), the BCI can potentially control the robotic exoskeleton allowing the patients to perform arm and hand movements such as eating and handling various objects. During 2017, 19 patients suffering from ALS were enrolled in the REMAP project and tested at the hospital or in their own home. Thus, REMAP is already one of the largest studies on movement related EEG-changes in patients with ALS. Preliminary results, presented at the 28th International Symposium on ALS/MND (Aliakbaryhosseinabadi S et al. 2017), showed that EEG signature of movement intention, i.e. movement related cortical potentials (MRCPs), can be recorded in all stages of ALS. The next challenge in the REMAP project is to use the recorded brain signals to control external robotic devices as the SEM-glove from BioServo.

In April 2017 REMAP researchers met with children and their parents at "Forskningens Døgn" at Aalborg University Hospital (see Figure 2 and 3), demonstrating both EEG-equipment and control of robotic devices. Children wearing EEG- and EMG electrodes were remote-controlling their parents, wearing an exoskeleton-glove, and this was fun experiences for parents, children and researchers alike.

References

1. Figlewski K, Blicher JU, Mortensen J, Severinsen KE, Nielsen JF, Andersen H. Transcranial Direct Current Stimulation Potentiates Improvements in Functional Ability in Patients With Chronic Stroke Receiving Constraint-Induced Movement Therapy. Stroke 2017 Jan;48(1):229-32.
2. Minjoli S, Saturnino GB, Blicher JU, Stagg CJ, Siebner HR, Antunes A, et al. The impact of large structural brain changes in chronic stroke patients on the electric field caused by transcranial brain stimulation. Neuroimage Clin 2017;15:106-17.
3. Aliakbaryhosseinabadi S, Blicher JU, Dremstrup K, Jiang N, Farina D, Mrachacz-Kersting N. Detection of hand movement from EEG in ALS-patients and healthy individuals. Abstract presented at the 28th International Symposium on ALS/MND, Boston 2017

Figure 2
Researchers from CFIN and Center for Sensory-Motor Interaction at Aalborg University together at "Forskningens Døgn" at Aalborg University Hospital.

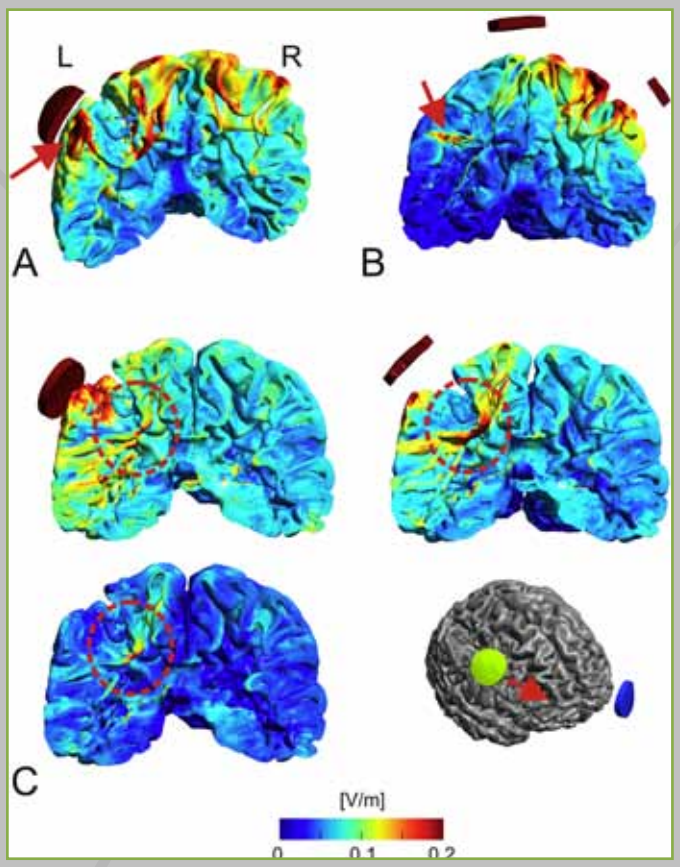


Figure 1
Example of simulations of tDCS stimulation. Notice the areas of unexpected high current intensity due to current passing through the CSF in the cavity of the lesion after the stroke.

Figure 3
Poster for the event at "Forskningens Døgn".

FACTS

Core and affiliated group members:

- Jakob Udby Blicher
- Erhard Næss-Schmidt
- Krystian Figlewski
- Tobias Glaston Stærmose
- Christina Shen-Zhuang Nielsen
- Camilla Lund Pedersen

Current projects:

Restore motor function through robotic arm exoskeleton and brain computer interface.
Participating partners: CFIN, Aarhus University; SMI Aalborg University; Aalborg U Robotics, Aalborg University; Department of Neurology, Aarhus University Hospital; BioServo Technologies, Sweden; Rehabiliteringscenter for Muskelsvind.

Kortikal GABA/Glutamat aktivitet ved ALS; et MR-spektroskopi studie.
Participating partners: CFIN, Aarhus University; Department of Neurology, Aarhus University Hospital.

Perceptual distortion - a new approach to better understand chronic facial pain.
Participating partners: CFIN, Aarhus University; Danish Pain Research Center, Aarhus University Hospital.

Assessing motor neuron disease pathophysiology by two novel methods –Threshold Tracking and MR Spectroscopy.
Participating partners: CFIN, Aarhus University; Department of Clinical Neurophysiology, Aarhus University Hospital.

MEG

MEG research at CFIN keeps on growing

by Yury Shtyrov

Among the most active users of the MEG facility are AUH Neurology Department clinicians (who use MEG for presurgical epilepsy mapping), Centre for Music in the Brain, NeuroDynamics of Human Communication (NeDComm) group, Neuroelectromagnetic Oscillations (NEMO) Laboratory, Parkinson's Disease Research Group, Hedonia TrygFonden Research Group, Danish Pain Research Centre, Perception and Neuroarchitectural Mapping Group, etc. Together, they cover a wide range of fundamental, applied biomedical and technological aspects of MEG research.

Among other MEG developments at CFIN during 2017 is a range of new projects and initiatives that were started during that year. A major new project aimed at understanding the nature of cognitive pathologies in Parkinson's disease (PD) received a ~2.5 million kroner support from the Danish Foundation for Independent Research (DFF). PD is a neurodegenerative disorder primarily characterised by severe motor deficits, but also known to affect cognitive abilities including language. Deep brain stimulation (DBS) is an established therapy for advanced PD, which ameliorates cardinal motor symptoms but may negatively affect the language function. The newly started project will use EEG/MEG to explore the effects of DBS on neurolinguistic processes in PD. A novel language paradigm has already been developed to assess different levels of linguistic processing in the brain. The project will advance our understanding of PD and DBS and offer clinical benefits to patients undergoing DBS therapy.

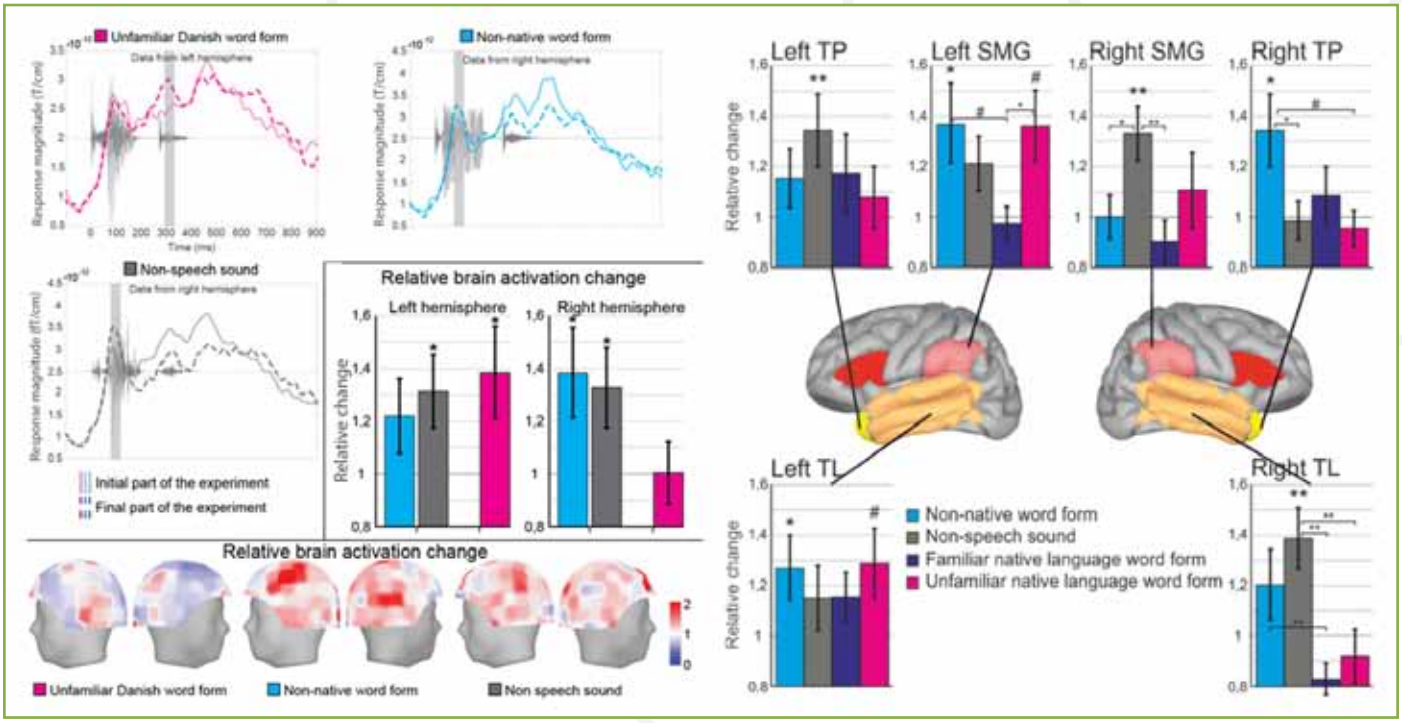
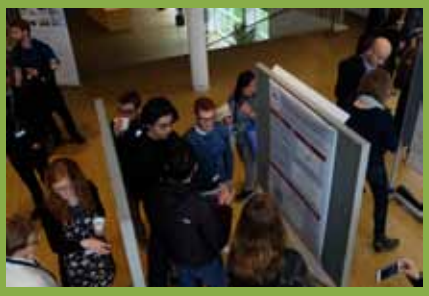


Figure
A new MEG study by NeuroDynamics of Human Communication group at CFIN investigated activity in children's brain during rapid acquisition of new words. It showed that neural mechanisms that underlie novel word acquisition in children operate on a much faster scale than known for adults, demonstrating rapid functional changes over just a couple of minutes of listening to them. Moreover, unlike what we know about adults, this rapid and automatic brain plasticity operates for all kinds of new acoustic information that children encounter, be that new words of the native language, foreign speech or even non-speech sounds. (Flexible, rapid and automatic neocortical word form acquisition mechanism in children as revealed by neuromagnetic brain response dynamics. Partanen E, Leminen A, de Paoli S, Bundgaard A, Kingo OS, Krøjgaard P, Shtyrov Y. Neuroimage. 2017 Jul 15;155:450-459. doi: 10.1016/j.neuroimage.2017.03.066.)

Aarhus at the centre of MEG research in Northern Europe: The inaugural MEG Nord meeting



by Christopher Bailey, Sarang Dalal and Yury Shtyrov

In May, we hosted the inaugural Nordic MEG conference (MEG Nord 2017) – the first international meeting dedicated to development of magnetoencephalographic science and technology in Northern Europe and Scandinavia. The aim of the conference was to forge stronger ties between a growing number of MEG groups in Northern Europe. CFIN scientists organised this meeting to promote the exchange ideas and techniques, initiate collaborative projects, create and document common standards, and jointly apply for funding. The intent to start such and international initiative was long-standing; it took a resolute move by the CFIN MEG/EEG-group to make it happen!

MEG Nord started with a data analysis workshop at CFIN on 8 May, and continued on 9-10 May 2017 at the picturesque AU Lakeside Auditorium, where over 100 registrants, representing 8 labs in 4 countries as well as guest participants from other MEG labs across the world, took part in a programme designed to showcase the work being done at the different Nordic sites. Thanks to co-financing from the AU Department of Clinical Medicine and generous donations by the major MEG manufacturers, participation in the meeting was free of charge which stimulated high attendance, particularly from more junior researchers including many students and postdocs. In addition to oral and poster presentation sessions, a selection of 3-minute "lightning talks" was well-received by the captive audience. The conference Keynote entitled *"Decoding rhythmic and arrhythmic brain dynamics: New adventures in MEG"* by Professor Karim Jerbi, University of Montreal, introduced novel modeling and analysis frameworks that elevate the potential of MEG-based neurophysiological inquiry into healthy and pathological brain function. After a final special interest session on Nordic and European joint funding schemes (prepared by CFIN's own Simon Jeppe Bjerg), a business meeting was held amongst the participants; with great enthusiasm it was decided that the meeting would be annual, rotating across the different sites. The next conference, MEG Nord 2018, will be hosted by Karolinska Institutet, in Stockholm. The meeting has already led to a formation of a large cross-Nordic consortium and large-scale research initiatives and grant applications. The 2017 conference abstract booklet can be accessed via the CFIN website (under Events Archive). See www.megnord.org for more on our Nordic MEG community.

All photos by Sarang S. Dalal

NeDComm Lab

Laboratory of NeuroDynamics of Human Communication

by Yury Shtyrov

The Laboratory of NeuroDynamics of Human Communication (NeDComm Lab) is an international research group at CFIN, headed by Professor Yury Shtyrov; its major research focus is on understanding the neurobiological foundations of the language function. Language is a uniquely human neurocognitive function which plays a defining role in our lives. In spite of the obvious importance of language and the high cost of its deficits, it remains one of the least understood functions of our brain. One reason for this is that, as a communication system, human language is unparalleled in its complexity and has no suitable animal models. In our work, we explore the dynamic processes of storage and access of linguistic representations in the brain. We combine neuroscientific, linguistic, behavioural and clinical approaches, and our team includes scientists of diverse cross-disciplinary backgrounds. State-of-the-art neuroimaging techniques are combined with psycholinguistic and neuropsychological experimentation in order to address a range of questions related to the language function, from phonological processes to lexical semantics, syntax and pragmatics.

During 2017, we continued to explore various aspects of the language function in the brain. One major line of this research is focussed on language learning. We strive to understand the rapid plastic processes that underpin brain's ability for rapid formation of linguistic memory traces. For instance, in one of our MEG studies, Eino Partanen with his colleagues at CFIN and collaborators at AU Psychology Department investigated activity in children's brain during acquisition of new wordforms. It showed that neural mechanisms that underlie novel word acquisition in children operate on a much faster scale than known for adults, demonstrating rapid functional changes over just a couple of minutes of listening to them. Moreover, in children - unlike adults - this rapid and automatic brain plasticity operates for all kinds of new acoustic information that they encounter, be that new words of the native language, foreign speech or even non-speech sound.

Another important direction is the role of modality specific structures in language comprehension. In one such study, Nikola Vukovic and Yury Shtyrov investigated integration of spatial cognition and neural language systems using multi-channel EEG. When we read or hear stories about characters, we have to represent the inherently different perspectives people have on objects and events, or even "put ourselves in their shoes". This study has shown that we mentally simulate these sentence perspectives by involving non-linguistic brain areas typically in charge of visuo-spatial thought. Remarkably,

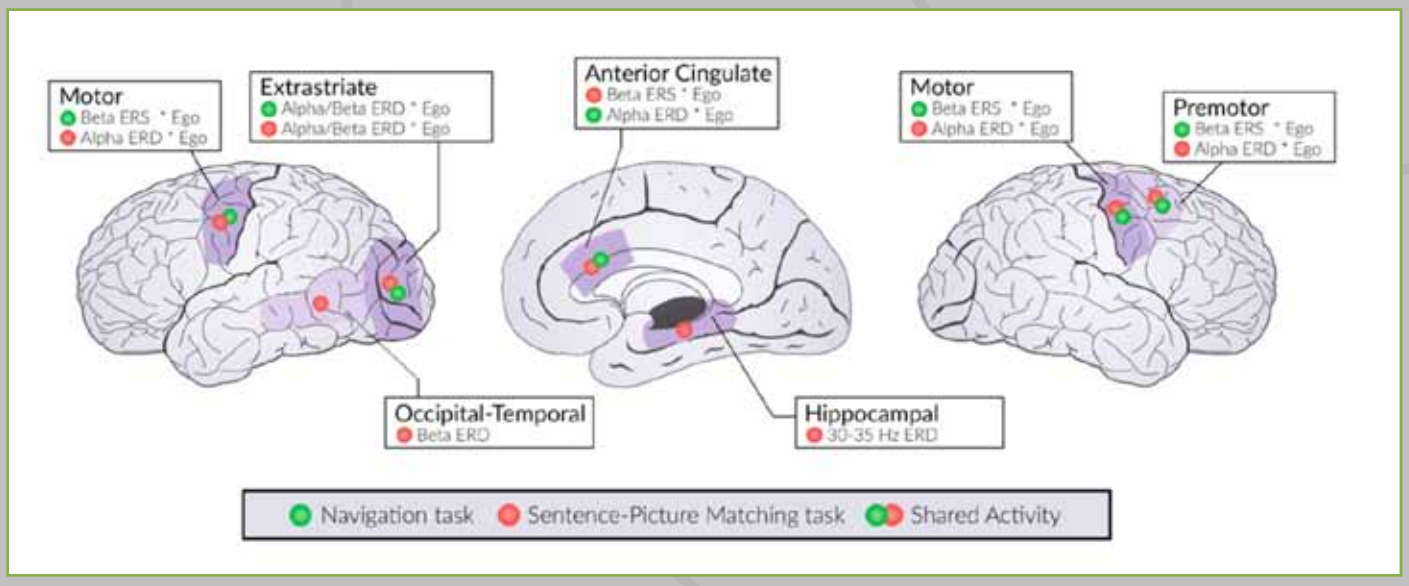


Figure
Brain areas in which shared or separate activity (ERSP, event-related spectral perturbation) was observed in the navigation task and the sentence-picture matching task. Boxes mark event-related power changes (desynchronisation: ERD, or synchronisation: ERS) and presence of association with individuals' navigation preferences (egocentricity ratings).
Cortical networks for reference-frame processing are shared by language and spatial navigation systems, Nikola Vukovic & YuryShtyrov, NeuroImage, 161, 1 November 2017: 120-133

we find individual co-variability across these very different tasks: people's strategies in spatial navigation are reflected in their construction of sentential perspective. Furthermore, a distributed network of cortical generators of such strategy-dependent activity responded not only in navigation, but in sentence comprehension. Thus we reported, for the first time, evidence for shared brain mechanisms across these two domains - advancing our understanding of language's interaction with other cognitive systems, and the individual differences shaping comprehension.

A further major direction in our work is development of clinical application of this research for understanding disorders of language. For instance, one of our newly started projects is aimed at exploring the nature of cognitive pathologies in Parkinson's disease. The work received a ~2.5mln DKK support from the Danish Foundation for Independent Research (DFF) to use E/MEG to explore the effects of DBS on neurolinguistic processes in PD. A novel language paradigm has been developed by the group's scientists (PhD students Christelle Gansonre and Rasha Hyder and postdoctoral researcher Mads Jensen) in collaboration with the PD research group at CFIN/AUH (Andreas Højlund, Karen Østergaard) to assess different levels of linguistic processing in the brain.

FACTS

NeDComm present members and alumni:

- Yury Shtyrov
- Nikola Vukovic
- Mads Jensen
- Rasha Hyder
- Christopher Bailey
- Alina Leminen
- Miika Matias Leminen
- Eino Partanen
- Christelle Gansonre
- Malte Henningsen
- Jana Krutwig
- Maria Lenzen

Main research strands:

The group is focussing on assessing the linguistic function in health and disease, e.g.:

- Architecture of brain circuits for linguistic representations
- Neural time course of linguistic processes in the brain
- Language learning and word acquisition
- Language-attention interactions
- Language deficits and their assessment

Visit the NeDComm pages at the CFIN website for more information on ongoing research projects:
cfin.au.dk/NeDComm

NEMO

Neuroelectromagnetic Oscillations (NEMO) Group

by Sarang S. Dalal

The speed of light – and darkness – in the human visual system

The speed at which visual information propagates down the visual pathway remains surprisingly unclear. We aimed to characterize the timing of impulses down the visual pathway with a combination of ERG (electroretinography) and MEG while participants viewed a sequence of very brief (1 ms) light flashes.

ERG responses were examined with respect to the corresponding responses of thalamus and visual cortex, as reconstructed with MEG. We implemented a novel neuroimaging strategy, combining beamforming with the Hilbert transform to examine high-frequency response in bands ranging from 55 Hz to 145 Hz. The first cortical responses appear at 27 ms at ~115 Hz, lagging the corresponding retinal oscillatory potential by 8 ms (Figure 1).

Some studies suggest that the processing of dark stimuli may occur more quickly by taking advantage of greater neural resources in the visual system. In a second experiment led by Britta Westner, longer light pulses of about half a second were employed. In the cortex but not in the retina, high frequency responses occurred more quickly with transitions from light

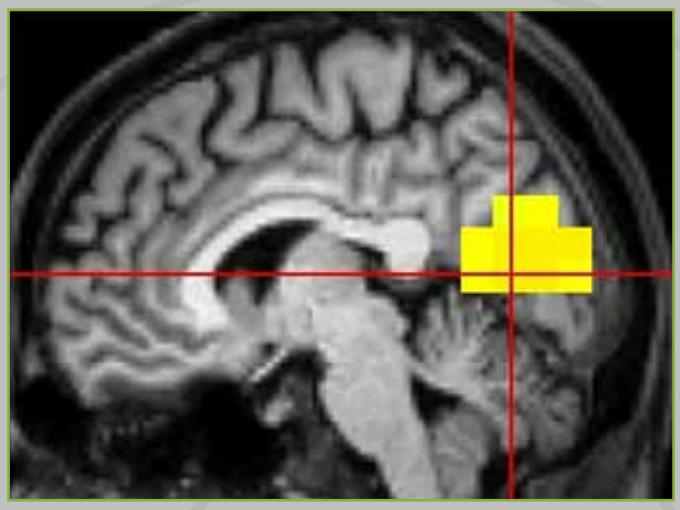


Figure 1
We found that high-frequency brain activity in visual cortex begins only ~27 ms after a light flash, only 8 ms after corresponding activity in the retina, and much earlier than is reported in textbooks on human vision.

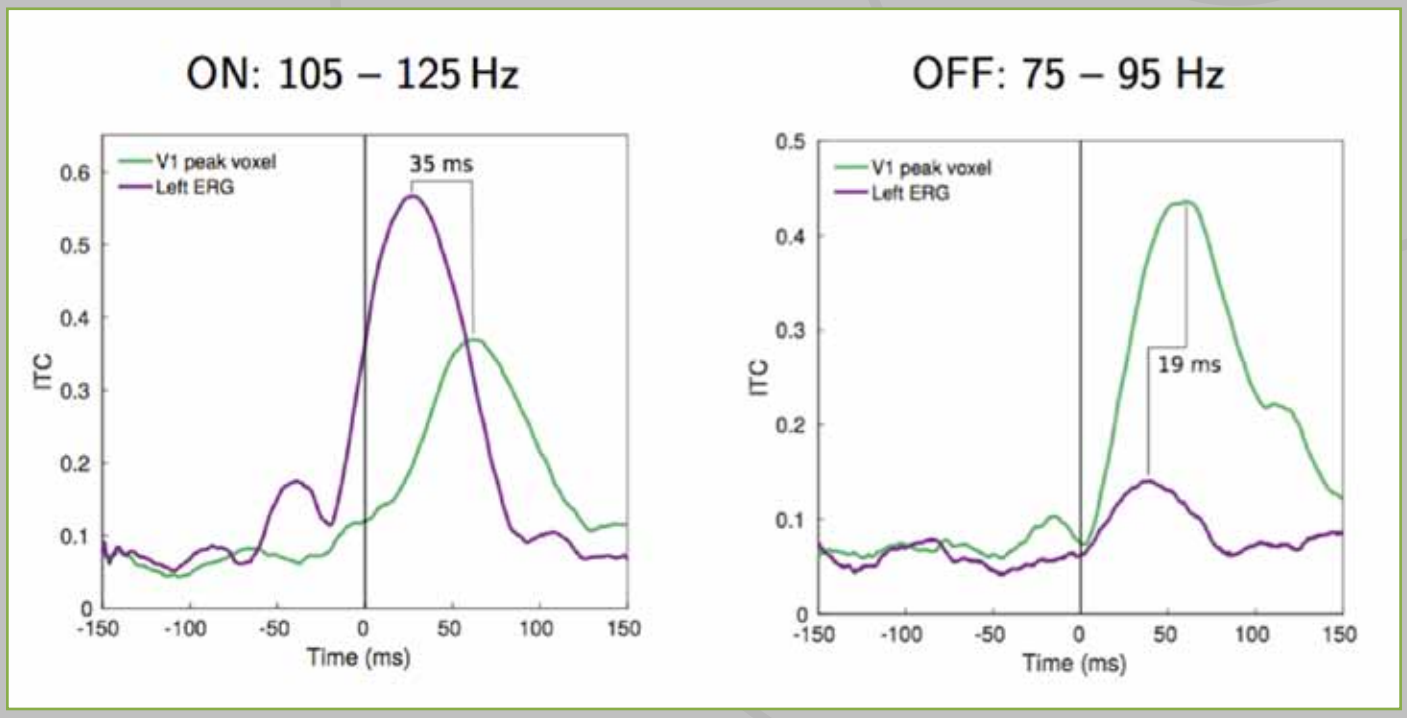


Figure 2
Group member Britta Westner discovered that the retina responds with similar timing to transitions from dark-to-light as light-to-dark, but the first responses in visual cortex actually arrive earlier for the latter. Additionally, light-to-dark responses in both retina and cortex was restricted to 75-95 Hz, while dark-to-light responses are broadband.

to dark compared to transitions from dark to light (Figure 2). Interestingly, while dark-to-light transitions involved a wide range of frequencies (55-195 Hz in the retina, and 55-145 Hz in the cortex), light-to-dark transitions were restricted to the 75-95 Hz frequency band in both retina and cortex.

The rapid timing of these responses across various conditions together with their sequential appearance first in the retina and then the cortex support the view that such high-frequency modulations reflect the precise timing of information handling throughout the human nervous system. These responses occurred much earlier than classic visual evoked responses arising from the retina or the cortex.

Measuring ERG together with MEG thereby provides a more informative measure of information processing at each stage of the visual pathway. It may furthermore constitute a potential strategy to uncover disturbances of the visual pathway in disease, not only in disorders of vision but also as a diagnostic of systemic abnormalities relevant to many neurological and psychiatric disorders.

FACTS

NEMO group members:

- Sarang S. Dalal
- Alexandra Vossen
- Britta Ulrike Westner
- Sabine Leske
- Martin Dietz
- Jordan Nicolas Alves
- Tommy Clausner

NEW FACES at CFIN

2017 brought two new faces to the NEMO group and CFIN:

Alexandra Vossen joined CFIN as postdoc in October 2017. She has a broad interest in the meaning and function of electromagnetic brain activity and has worked on diverse projects involving behavioural methods, EEG, and non-invasive brain stimulation (tACS, TMS). She holds a BSc in Liberal Arts and Sciences from University College Maastricht, and a Research Master degree in Cognitive Neuroimaging awarded by Maastricht University. For her PhD, which she recently completed at the School of Psychology at the University of Glasgow, she studied the effects of transcranial electrical stimulation on neural oscillations. Alexandra now works with Sarang Dalal in the NEMO lab using ERG and EEG to investigate how sleep affects retinal activity and how such changes are linked to cortical activity.

Britta Westner completed her PhD in Sarang S. Dalal's group at the University of Konstanz, and transitioned to a postdoc position while moving to CFIN. She led some of the groups first studies investigating the interaction of retina and cortex, and will now investigate the role of alpha waves in mediating this coupling. Furthermore, she is interested in the use of machine learning techniques for MEG data and is working on combining source reconstruction with machine learning algorithms to decode from signals with low signal-to-noise ratio like MEG high frequency activity.

Parkinson's disease, freezing of gait, and bicycling

In 2011, a dramatic video and follow-up study from a group in the Netherlands showed that, surprisingly, most Parkinson's disease patients can bicycle even when they can barely walk. That such related movements, involving similar muscles moving at a similar pace, could be preserved in bicycling yet severely impacted in walking simply did not line up with what we know about how the brain works to control movement. In order to understand how this can happen, we formed a partnership with the Movement Disorders Clinic at the University Hospital Düsseldorf and a computer science lab at the University of Konstanz to adapt a lab bicycle originally designed for training competitive cyclists (Figure 3; Gratkowski et al., 2017).

The basal ganglia is the primary brain structure implicated in Parkinson's disease. We found that the basal ganglia of patients with severe problems walking ("freezing of gait") generate an apparently abnormal signal of a specific frequency (~18 Hz) that is not there in other Parkinson's patients who do not have that symptom (Figure 4, right).

We showed that bicycling suppresses the broader beta band in general, including this abnormal 18 Hz oscillation (Figure 4, left). Meanwhile, walking appears to intensify the abnormal oscillation in patients with freezing of gait. Exactly why walking should strengthen this oscillation in these specific patients remains an open question, but our results suggest that this is indeed the signal that blocks movement, while these same patients are able to easily bicycle since it causes suppression of this blocking signal.

Figure 3
The BrainCycles team, pictured with the laboratory bicycle we constructed for Parkinson's patients. From left to right, Maciej Gratkowski (University of Konstanz), Lena Storzer and Markus Butz (University of Düsseldorf), and Sarang Dalal.

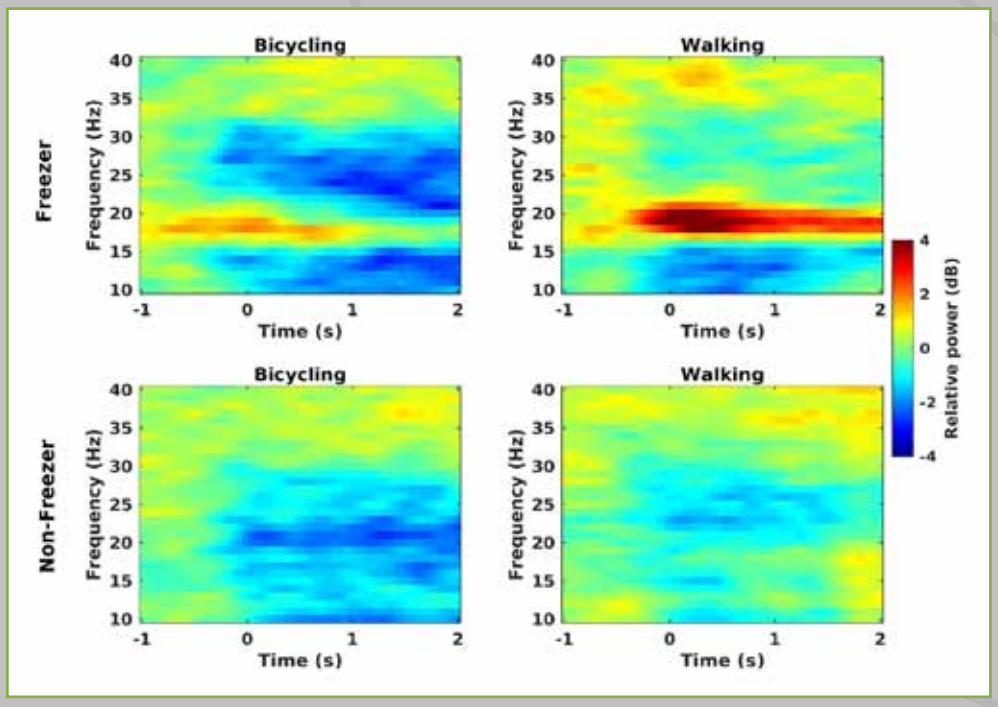


Figure 4
The basal ganglia of Parkinson's patients responds differently to bicycling and walking. Notably, we discovered that patients who are prone to episodes of freezing of gait (severe difficulties with walking) exhibited an 18 Hz oscillation that intensified when attempting to walk. Bicycling instead alleviates this apparently abnormal oscillation.

MEG/EEG methods development and open source software contributions

We have also made significant strides in contributing to open source software for MEG/EEG analysis. Through a project funded by Google's Summer of Code program, group member Britta Westner ported MEG/EEG source reconstruction methods to MNE-Python, a rapidly growing open source toolbox. This included the several beamformer variants, including the Hilbert beamformer method developed in our group to reconstruct amplitude and phase information across frequency bands. We have found it is particularly well-suited to high gamma band responses (75-150 Hz) that have been notoriously difficult to track down with other techniques.

Group member Sabine Leske furthermore developed a new method for removing electrical interference from our MEG/EEG recordings. The noise originating from electrical cables and equipment has been a nuisance since the early days of neurophysiological recordings, and techniques for managing it are about as old. AC power is ubiquitous and couples strong sinusoidal interference into sensitive electrophysiological recordings. Increasingly, MEG and EEG are reaching into higher frequencies that traverse the fundamental power line frequency (50 Hz in most of the world and 60 Hz in North America) and its harmonics (multiples of the fundamental frequency). As a first line of defense, modern laboratories aim to simply shield the recording environment as much as possible from such interference, but with varying degrees of success depending on the setting (e.g., an urban hospital) and whether electrical equipment needs to be in the recording room for stimulus presentation. Furthermore, there is growing interest in "field" recordings (including sleep studies, brain-computer interfaces, and neural prosthetics), where effective shielding is simply not feasible. Sabine's method is now included in a leading open source toolbox, FieldTrip, for the immediate benefit of the MEG/EEG community, and a manuscript describing the technique is in review.

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Visit the NEMO pages at the CFIN website for more information on the groups research:
cfin.au.dk/nemo

CNRU

Cognitive Neuroscience Research Unit

by Morten Overgaard

Human consciousness can be defined as the inner subjective experience of mental states such as perceptions, judgments, thoughts, intentions to act, feelings or desires – all of which are observable from a first person perspective only. Cognitive neuroscience is, however, classically conceived as a science of behaviour and brain – i.e. what can be observed from a third person perspective. Although this fundamental difference in perspective makes a scientific approach to consciousness highly methodologically challenging, CNRU researchers attempt to approach the question from different angles. The approach is fundamentally integrational – i.e. different classical disciplines as psychology, neurology, neurophysiology, and philosophy are synthesized during all phases of a study – and it is translational – i.e. ideas from basic research are brought into clinical domains or different basic research domains.

Over the last years, most work has focussed on exploring the neural correlates of conscious perception and how this relation should be generally conceived and how individual differences can be explored, the understanding volition and agency, and clinical applications in psychiatry and neurology.

The challenge

Consciousness is a challenge to science for one reason above all other – that its very existence seems mysterious based on our most popular scientific conceptions of physical reality. If consciousness is defined as an experience, i.e. not in physical or objective terms, and if all aspects of the brain's activities, including its processing of information, can be described completely in physical terms, then how can we say anything about the relation between consciousness and the brain? This problem is in fact vast, because much research in neuroscience is fundamentally motivated by the attempt to understand how some conscious experience (e.g. how pain, perception, hunger, psychiatric conditions, etc) relates to the physical structure and function of the brain.

Access and phenomenal consciousness

One approach to the problem takes as its point of departure that we must distinguish between so-called access consciousness (information we can act on or speak about) and phenomenal consciousness (subjective experience). The highly recognized philosopher Ned Block has repeatedly argued that access consciousness and phenomenal consciousness are not just conceptually but also empirically different, and that we experience more than we can access. If this were true, it would greatly impact how we should do experiments about consciousness, because what we think could be a neural correlate of phenomenal consciousness might in fact be a correlate of acces consciousness

Peter Fazekas (CNRU and University of Antwerp) and Morten Overgaard hosted an international conference at CFIN February 2017 about this exact idea with participation of some of the most recognized consciousness researchers, including Ned Block and Victor Lamme. Papers from the conference will be published in Philosophical Transactions of the Royal Society of London.

Figure 1
Ned Block (left) and Peter Fazekas at the "Phenomenal consciousness and Cognitive access" conference, 18-19 February 2017 at Aarhus Institute of Advanced Studies (AIAS), Aarhus University.

Theoretical modelling

CNRU attempts to approach these challenges in different theoretical models. Although much experimental work was produced in 2017, no less than three different and rather advanced theoretical models were published from CNRU. The most ambitious is the REF, REF-CON, and in 2017 the REF-GEN models developed by Morten Overgaard and Jesper Mogensen (University of Copenhagen) that fundamentally rethink brain function.

The REF model essentially describes a connectionist network in which, however, the "unit" is not a neutral and functionally "indifferent" "neuron" – but information processing modules called elementary functions (EFs). The EF does not have any functional specificity beyond its basic information processing.

This model is able to account for both the localization and posttraumatic recovery of functions. According to the original version of the REF model, the surface level of task solution – be it in the form of overt behavior or mental representation – is achieved via two underlying levels: the lower level of the EFs and the level of the Algorithmic Strategies (ASs). EFs perform basic information processing and are localized within restricted subdivisions of neural structures. In contrast, ASs consist of numerous interacting EFs and are distributed in the sense that the neural substrate of an AS includes both the neural substrates of the individual EFs and the neural connections mediating the complicated interaction between these EFs. Thus, an AS is the totality of a given set of EFs and their interactions. A given surface phenomenon (e.g., behavioral pattern/task solution) may be achieved via different ASs. Focal brain injury will deprive the individual of a substantial number of EFs and thereby all ASs including those EFs. Thus, injury will lead to behavioral impairments of tasks previously achieved via activation of those ASs. However, the model suggests that a different organization of underlying strategies, using different EFs, may realize "the same" surface phenomenon.

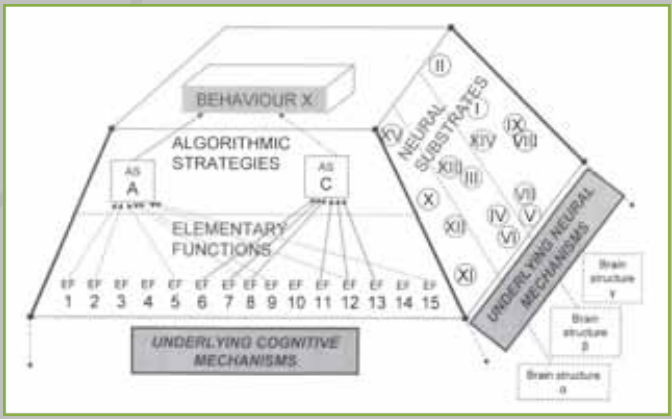

Figure 2
The original REF model (Mogensen & Mala, 2009)

In the REF-CON model, consciousness is fundamentally seen as related to a particular kind of AS, that is, the Situational Algorithmic Strategy, or SAS, representing the "current now". As elaborated in the REF-GEN model, this "current now" is constantly compared with a representation of the expected future, and SAS is thus constantly updated. Consciousness is here considered as "fundamentally related" to information that is available to action (or access) by a kind of "natural law" that does not have an independent further cause or explanation.

FACTS

CNRU group members:

- Morten Overgaard
- Peter Fazekas
- Martin Dietz
- Mia Y. Dong
- Michael Lohse
- Timo Lehmann Kvamme
- Thomas Alrik Sørensen

Peter Fazekas and Morten Overgaard published a multidimensional model to account for the increasing evidence that mental states are gradual in at least three dimensions: Intensity, precision, and stability. An analysis of mental states with these terms will lead to a much more precise understanding of them. CNRU research has repeatedly shown that a dichotomous measure of consciousness will lead to highly imprecise results that are dramatically different from gradual measures. This is not just the case in consciousness research, but generally in neuroscience and neuropsychology. For instance, brain injured patients often demonstrate a reduced rather than absent manifestation of the impaired cognitive domain. Working memory is reduced but not absent and patients with prosopagnosia do not experience "nothing" where a face should have been but rather "something unfamiliar". It has also been established that, even in intact individuals, the performance on neuropsychological tests represent a spectrum rather than a fixed "normal" level of performance. Consequently, under normal as well as pathological conditions the level of cognitive proficiency is best evaluated as a given position within a broad spectrum. The multifactor model is easily integrated into the REF framework, as it can explain how different strategies are gradually integrated into the SAS.

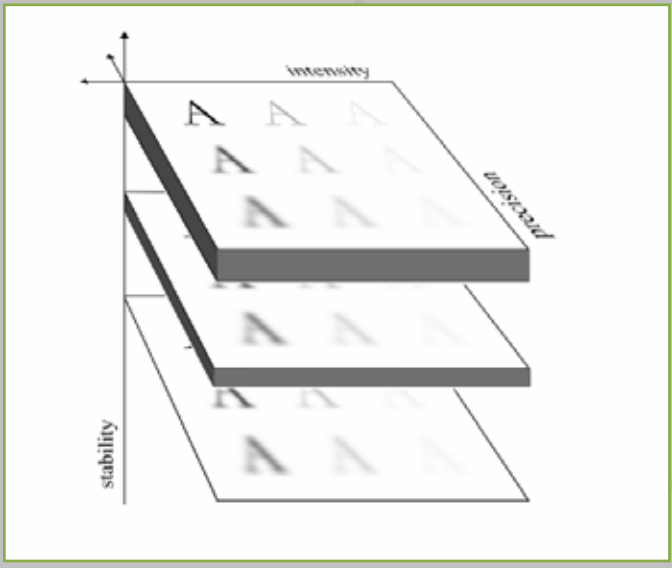

Figure 3
The Multidimensional Model (Fazekas & Overgaard, in press)

Morten Overgaard and Jesper Mogensen further developed another model – The Integrative Model - to account for the relation between metacognitive states (i.e. mental states that have another mental state as its content) and first order cognitive states. The distinction is methodologically important as experimental participants need to report about their cognitive states in experiments somehow, and the experimenter must know how to distinguish neural activations related to metacognition from first order states in order to pinpoint which activations that actually relate to the phenomenon under investigation. Based on reviews on existing metacognition research, Overgaard and Mogensen suggest a "parallel" model, the first of its kind, which does not suggest that metacognition actually "follows" first order states, but work in parallel.

Model application

In 2017, two clinically oriented studies were published from the CNRU group, both of which have been long underway.

We have repeatedly shown that subjective experience and objective correctness are well correlated, so that the more vividly you experience a particular content, the more correct you will be about this content (as explained by the multidimensional model above). We show that, in a systematic way, this is not the case for patients suffering from schizophrenia. Notably, the Integrative Model above provides an analytic framework to better understand schizophrenia and psychotic hallucination based on these results.

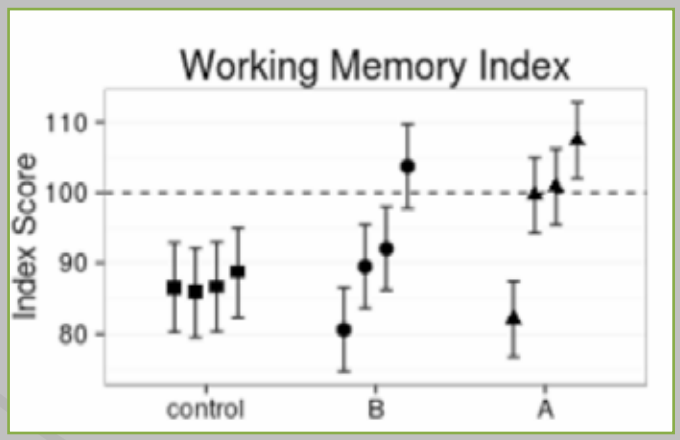

Figure 4
Change in working memory in the two active groups and control (Lindeløv, Overgaard & Overgaard, 2017)

Furthermore, we published a study in Brain showing the rather controversial result that a hypnosis protocol developed by Rikke Storm Overgaard dramatically improve working memory function in brain injured individuals in a highly consistent – and long-lasting – way. The study involved 68 patients and it represents the most positive result in rehabilitation of attention and working memory until date. The protocol directly targeted "strategies" for remembering, and can be analyzed in the REF framework, according to which there is a high potential for recovery after brain injury given a proper strategy selection is possible. Said differently, according to REF, it is possible to establish novel ASs (utilizing preserved EFs). And potentially, the novel ASs will allow a task solution with a similar proficiency to what was seen before the patients' trauma. Comparing the task performance of such recovered individuals to non-injured controls, one may draw the faulty conclusion that the task solutions in question are not only of similar proficiency but also identical. Only in detailed experimental analysis, it will become clear that apparently similar surface phenomena are achievable via significantly different neural and cognitive mechanisms – "strategies." Needless to say, these results hold considerable promise for future rehabilitation strategies.

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PNM

Perception and Neuroarchitectural Mapping Group

by Kristian Sandberg

The Perception and Neuroarchitectural mapping group is a new research group focusing on basic as well as clinical research. A main line of research within the group focuses on human perception, particularly conscious vision. Within this line of research, we use magnetic resonance imaging (MRI), magnetoencephalography (MEG), and transcranial magnetic stimulation (TMS) to examine the link between perception and brain structure/function. Our long term aim is to build MRI based neuroarchitectural models that give exhaustive explanations for a range of perceptual and cognitive phenomena. In another line of research, we examine how individual neuroarchitectural models of patients with different types of brain disorders differ from that of healthy individuals and how these individual models predict patient outcome. We pursue both aims through local and international collaboration.

In 2017, we published the last in a series of articles mapping the relationship between cortical GABA (measured using magnetic resonance spectroscopy, MRS) and various cognitive phenomena. In this article (Song, Sandberg, Andersen, Blicher, & Rees, 2017), we examined the role of GABA in the magnitude of two visual illusions; a size illusion (the Ebbinghaus illusion) and an orientation illusion (the Tilt illusion). Both these illusions have been related to surround modulation, a fundamental property of the visual system causing neuronal responses to stimuli within their classic receptive field to be modulated by stimuli presented outside this receptive field (in the near or far surround). Modulation of activity through presentation in the near surround is believed to be modulated through lateral inhibitory connections. As GABA is the main cortical inhibitory neurotransmitter, we hypothesised that the size illusion would be related to GABA in the areas of the parietal cortex containing organised maps of size preference whereas the orientation illusion would be related to GABA in the areas of the occipital cortex containing organised maps of orientation preference. The results presented in Figures 1-2 support these hypotheses, thus revealing a region- and feature-dependent influence of GABA level on human visual perception.

In another ongoing visual perception study, Justyna Hobot use Transcranial Magnetic Stimulation (TMS) to investigate the neural underpinnings of subjective visual experience and metacognition. Within the field, it is currently debated which cortical areas are related to perceptual metacognition, and doubt has been cast on earlier key findings. Justyna's first experiment consisted of different TMS protocols applied to a specific prefrontal cortical area indicated to be involved in metacognition, and her second experiment focuses on TMS applied to the primary visual cortex (V1). The goal of these experiments is to examine the effects of TMS influence on task accuracy, visibility and metacognition, and whether they depend on the parameters used in individual studies. The third experiment focuses on consequences of congruence of TMS-induced motor responses and aims to assess the involvement of an additional evidence accumulation in judgments about visual experience. The study is expected to be of significant basic scientific value in relation to understanding the neural mechanisms underlying conscious perception.

In the near future, the group will focus on optimisation of statistical modelling of subjective reports and metacognition within the perceptual domain, on computational and statistical modelling of the relationship between neural architecture and perception within the neuroscientific domain, and on predictive modelling (using machine learning incl. deep learning) of patient outcome after anoxic brain injury within the clinical domain.

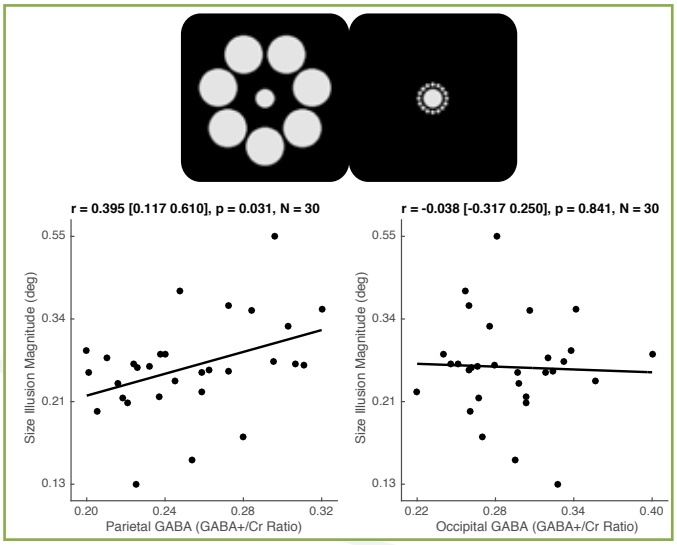


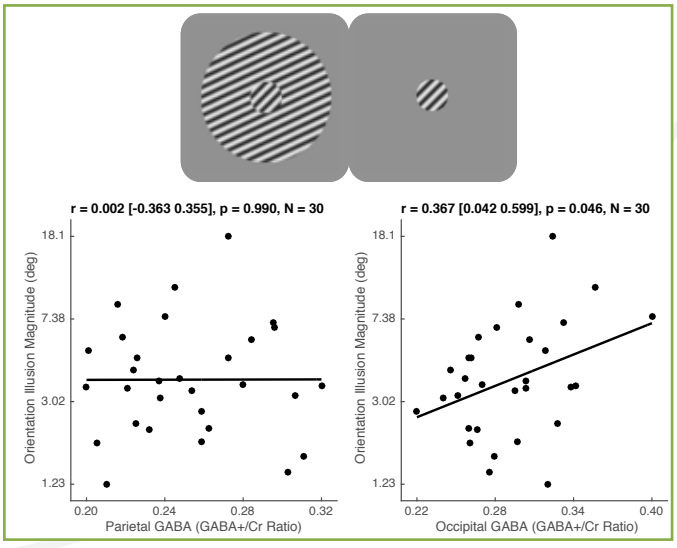
Figure 1
GABA and size illusion. In the Ebbinghaus illusion, two physically identical central circles appear to have different perceived size as a result of the surrounding context of either smaller or larger circles. The magnitude of Ebbinghaus illusion for each participant was plotted against their parietal or occipital GABA level, illustrating a positive correlation between size illusion magnitude and parietal GABA level, as well as a lack of significant correlation between size illusion magnitude and occipital GABA level. Each data point represents a participant. Statistics are Pearson's correlation and bootstrap results.

NEW FACE at CFIN

Simon Bang Kristensen, MSc (Statistics)

Simon obtained his masters in statistics from the Department of Mathematics, Aarhus University, in 2015 with a thesis on estimation in stochastic processes. After graduating, he was employed as a statistical consultant at the Department of Public Health, Aarhus University.

From mid-2017 Simon began a PhD project titled *"Statistical models for consciousness experiments"* supervised by Associate Professor Bo Martin Bibby, Section for Biostatistics, Department of Public Health, AU, and co-supervised by Associate Professor Kristian Sandberg, Danish Neuroscience Center, AU. The project focuses on statistical methods for experiments of metacognition and how the results of such analyses can be connected to MRI brain images. In broader terms, Simon is interested in hierarchical and mixed models, copulae and other techniques for modelling multivariate and longitudinal observations of binary or ordinal outcomes, another topic of interest being general methodology of regression including regularisation. Simon is housed by the Section for Biostatistics, but will be visiting CFIN on a regular basis.



NEW FACE at CFIN

Justyna Hobot, MSc, MA. Justyna holds a Bachelor's degree and a Master's degree in Neurobiology from Jagiellonian University and a Master's degree in Philosophy from Pontifical University of John Paul II in Cracow, Poland.

During her master studies, she investigated neuronal mechanisms responsible for antidepressant effects of serotonin agonists and the validity of objective measures of consciousness in clinical diagnosis. After completing the master studies, in October 2015 Justyna has started PhD studies in Psychology at Jagiellonian University and since then she has been working under co-supervision of Dr Kristian Sandberg. Justyna's research interests include methodology of non-invasive brain stimulation techniques, while her main focus is on their employment in visual perception research. She has been working on a project entitled *"Cognitive and neuronal mechanism of metacognitive awareness"* focusing on how the brain processes and assesses visual perceptual content. Justyna uses TMS combined with behavioural measures to identify areas involved in visual perception and investigates how manipulation of activity in certain brain areas influences participants' performance in perceptual tasks.

At CFIN, Justyna has been working on healthy participants and her stay has been financed by a grant for international collaboration, received from Polish National Science Centre and a travel grant for a research stay at Health Faculty received from Aarhus University.

Figure 2
GABA and orientation illusion. In the tilt illusion, two physically identical central gratings appear to have different perceived orientation as a result of their immediate surroundings. The magnitude of tilt illusion for each participant was plotted against their parietal or occipital GABA level, illustrating a positive correlation between orientation illusion magnitude and occipital GABA level, as well as a lack of significant correlation between orientation illusion magnitude and parietal GABA level. Each data point represents a participant.

Neurotransmission and gambling

PhD project: Impulsivity and compulsivity

by Casper Schmidt

Impulsivity and compulsivity: the roles of dopamine and serotonin in rewards

Within the neuroscience of addiction, there is a knowledge gap both in terms of assessing its mechanisms and in terms of optimally treating its different forms. This Cambridge-Aarhus PhD project seeks to disentangle the roles of dopamine and serotonin in rewards, and their roles in the neuropsychological measurements of impulsivity and compulsivity. Although a lot is known about their separate roles, no research has been devoted to the neurochemical mechanisms underlying the combined exposure to serotonin and dopamine in humans.

The experiments were carried out during 2017, in a between-subjects double blinded design involving testing of 127 subjects. The study includs four arms of appr. 25 healthy volunteers (HV) in each and a fifth arm of 25 subjects with pathological gambling disorder (PG), a psychiatric patient group with profound deficits in impulsivity and compulsivity. This was done in order to isolate the neural and behavioural correlates of both increasing dopamine and decreasing serotonin levels.

The study examines how such dopamine and serotonin levels affect

1. Neural activity in a task-based fMRI experiment with different forms of rewards
2. Cognitive components of impulsivity and compulsivity as determined by behavioural testing (in HV and relative to a placebo PG group)
3. Functional connectivity of neural networks in HV

So far, we have found preliminary evidence that HV can be primed towards PG, suggesting that such priming may in fact also be reversible. We hope such insights may help us reduce addictive symptomatology in affected subjects in the future.

We expect to assess a subset of the current subjects for further examination using PET scanning. In conclusion, this project holds great promise to unravel neural and behavioural processes associated with dopamine and serotonin in combination, thus providing a novel foundation for future treatment options within the neuroscience of addiction.

Supervisors:
Arne Møller (Main supervisor at Aarhus University)
Valerie Voon (Co-supervisor at the University of Cambridge)

NEW FACE at CFIN

Casper Schmidt, Cand. Psych.

Most of us are aware of behaviours that we repeat despite their negative impact on our lives - but why does this occur when clearly, our cost-benefit analyses tell us that it shouldn't?

Casper's research focuses on self-control and on devising new strategies to assess and treat different forms of addiction, with focus on neural and behavioural mechanisms underlying impulsive and compulsive disorders within behavioural addictions in the general population. Casper uses methods of cognitive neuroscience, neuroimaging, cognitive-behavioural testing and pharmacological modulation.

Casper is a psychologist with a MSc degree in Neuropsychology from Aalborg University. Since, he has been active in research at Aarhus University in the Arne Møller group, whom he met in 2013 during his BA studies. He is currently a PhD fellow in clinical neuroscience at Aarhus University, supervised by Arne Møller in Aarhus and co-supervised by Valerie Voon in Cambridge.

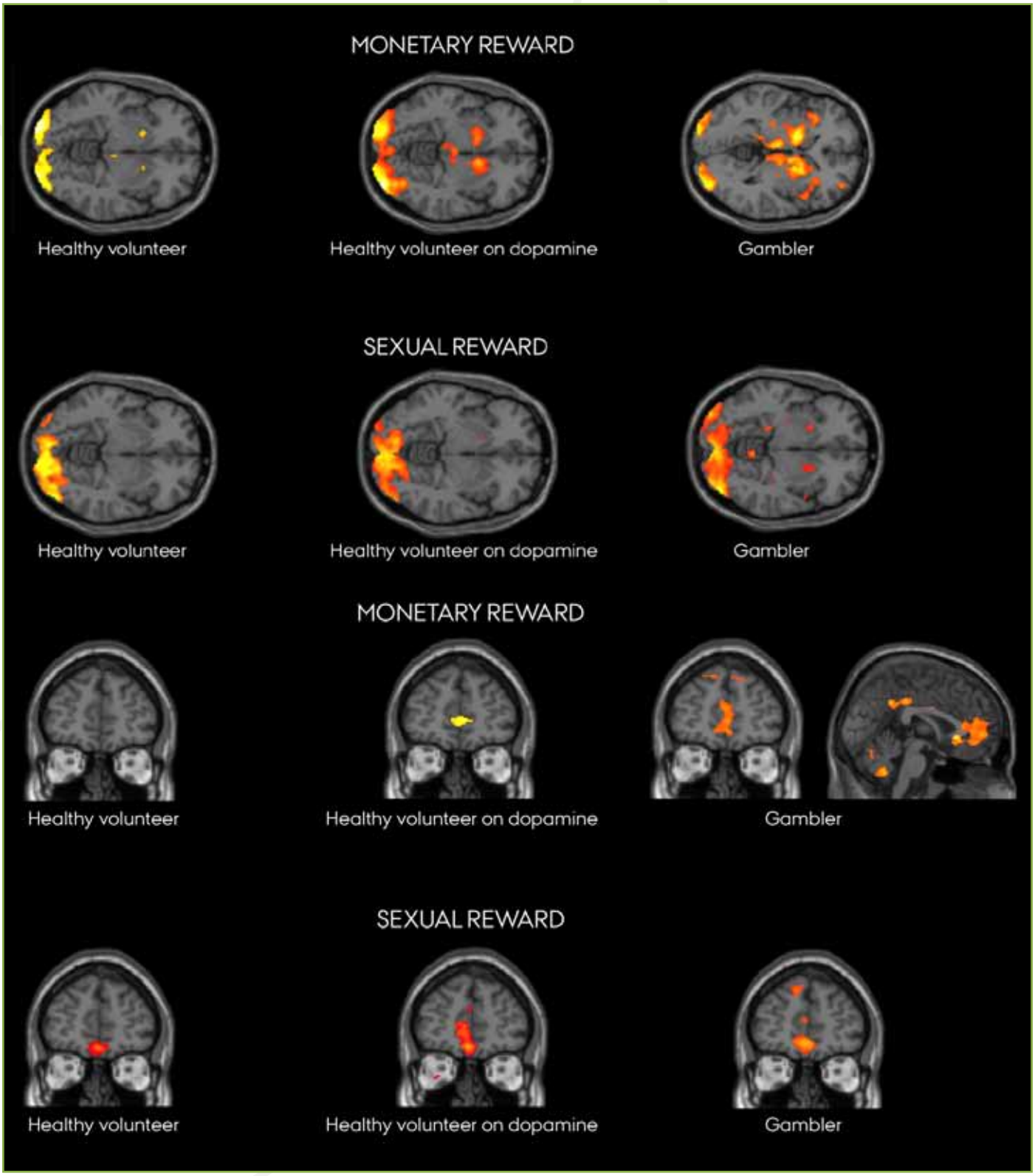


Figure
The figures show descriptive priming with L-dopa administered to HV (middle) compared with placebo HV (left) and PG (right) to reward anticipation (top) and outcome (bottom).

CENTER FOR MUSIC IN THE BRAIN

by Peter Vuust

2017 – the third year of The Danish National Research Foundation's Center for Music in the Brain (MIB) – has been a year of consolidation, cooperation, and growth. Thanks to the hard work of the center's now more than 30 researchers, we made a number of significant discoveries, resulting in a growing number of publications in high ranking peer reviewed journals in 2017. The growing international recognition is testified by the forthcoming conference "Neurosciences and Music VII" in Aarhus in 2020. Notable papers by Alluri, Toiviainen, Burunat, Kliuchko, Brattico and Vuust published in Human Brain Mapping showed the involvement of more action-based neural networks during naturalistic listening in musicians than in non-musicians, and the paper by Atasoy, Roseman, Kaelen, Kringelbach, Deco and Carhart-Harris published in Scientific Reports compared brain states in participants experiencing LSD and music using a connectome-harmony decomposition.

A particular highlight in 2017, was the participation of 15 MIB researchers at the Neurosciences and Music VI conference in Boston, sponsored by the Mariani Foundation. MIB presented 14 posters, and Peter Vuust and Stefan Koelsch's symposium on predictive coding of music, with speakers Marcus Pearce, and Uta Noppeney and moderated by Robert Zatorre, was chosen among a highly competitive field of proposals for this conference, which is considered the most prestigious within the field of neuroscience and music. At the final day of the conference, during the closing ceremony, it was announced that Center for Music in the Brain will be hosting the next Neurosciences and Music conference in 2020 in Aarhus. This is a great international acknowledgement of our centre and we look very much forward to hosting scientists from all over the world.

On the agenda this year has also been a number of outreach activities. We consider the task of communicating our results to both fellow scientists and laypersons an important and natural task for our centre. This is evident in the number of invited talks at international conferences and the media attention that our research generates. Already at the beginning of the year, when the results of the Mass Experiment were published, MIB found itself in the middle of the limelight receiving an enormous amount of media attention in both local and national news media. The results from more than 20,000 children from schools all over Denmark, demonstrated a correlation between music practice and working memory in children. Later in the spring, this was followed by the center leader's book "Musik på Hjernen", in which he, in layman terms, tries to answer the million dollar question: Why do we have music? The critics liked it and the book received 5 stars in Gaffa, making its way into the evening news on national TV.

Combining outreach and science, MIB ran a live-experiment during a concert with the power-trio Randolph Cricket at the annual SPOT festival in Aarhus in May 2017. Equiped with a simple motion capture device, the movements of each person in the audience were followed while they listened to music of various rhythmic complexity. The results extend Witek et al.s laboratory findings showing an inverted U-shaped relationship between rhythmic complexity and wanting to move, into a real world setting.

MIB received acknowledgement throughout the year: PhD student Patricia Alves da Mota won the prize for Best Poster at the Annual PhD day at Aarhus University, PhD student Signe Derdau Sørensen won the clinical research Flash Presentation prize for her 3 minutes' talk about the Mass Experiment at the annual Neuroscience Day 2017 at Aarhus University, and finally, center leader, Peter Vuust was awarded Dansk Lydpris 2017 in Struer.

In 2017, we hired postdocs Massimo Lumaca, Marina Kliucho and Angus Stevner and started up no less than seven PhD students: Mette Kaasgaard (financed by Trygfonden, Danmarks Lungeforenings Fond, Region Sjællland, Region Midtjylland, Aase og Ejnar Danielsens Fond and Fonden til Lægevidenskabens Fremme) Rasmine Mogensen (fully financed by the Graduate School of Health, AU), Signe Hagner (1/3 financed by the Graduate School of Arts, AU), Nadia Høgholt, Leonardo Bonetti, Pauline Cantou and Marie Dahlstrøm (fully financed mobility stipend from the Graduate School of Health, AU). In June, Manon Grube agreed to join MIB in 2018 as Assistant Professor, and in December, Christine Ahrends arrived to start preparing her PhD studies that will commence in early 2018.

This year was also a sad goodbye to two highly treasured long-time members of MIB. Assistant Professor Maria Witek accepted a Senior Birmingham Fellow Position, but fortunately, Maria remains a close collaborator to MIB. Associate Professor, Line Gebauer left us to finish her certification approval as a clinical psychologist, but thankfully, she will still maintain supervising tasks at MIB. We thank both of them for a number of years of excellent research and strong commitment to the center and wish them the best of luck.

International collaborations are highly prioritized at MIB. Funded by Aarhus University Research Foundation (AUFF) Senior Lecturer Marcus Pearce from Queen Mary University of London spent five months at MIB, and Professor Maria Dolores Roldan Tapian from University of Almeria, Spain visited for six months. Furthermore, during 2017 we hosted many prominent guest speakers, including Brain Prize winner Wolfram Schultz, Professor Isabelle Peretz, Professor Luisa Lopez, Professor Sonja A. Kotz and Professor Maria Chait. Furthemore, ten international pre- and postgraduate students stayed at MIB for shorter and longer periods of time. Finally, we signed cooperation agreements with Virginia Penhune at Concordia University, Canada, among others.

We wish to thank MIB and CFIN scientists and collaborators, the Danish National Research Foundation, the Central Denmark Region, the Department of Clinical Medicine at Aarhus University, The Royal Academy of Music Aarhus/ Aalborg, Aarhus University, and our other generous funding sources for their continued support.

Center for Music in the Brain publishes their own annual report. This may be downloaded or a printed copy may be provided by contacting the MIB center administration.
See more at: http://musicinthebrain.au.dk/

MIB researchers in Boston during the Neuroscience in Music VI Conference, 15-18 June 2017.
Photo: Music in the Brain

FACTS

MIB Center members and collaborators:

- Peter Vuust

- Elvira Brattico
- Lauren Stewart
- Morten Kringelbach

- Angus Stevner
- Bjørn Petersen
- Boris Alexander Kleber
- Henrique Fernandes
- Joana Cabral
- Kira Vibe Jespersen
- Line Gebauer
- Manon Grube
- Maria Witek
- Marina Kliuchko
- Massimo Lumaca
- Tim van Hartevelt

- Cecilie Møller
- Christine Ahrends
- David Ricardo Quiroga Martinez
- Davide Ligato
- Leonardo Bonetti
- Maria Celeste Fasano
- Marie Dahlstrøm
- Mette Kaasgaard
- Nadia Flensted Høgholt
- Ole Adrian Heggli
- Patricia Alves da Mota
- Pauline Cantou
- Rasmine Louise Holm Mogensen
- Rebeka Bodak
- Signe Nybo Hagner
- Stine Derdau Sørensen
- Suzi Ross
- Titta Marianne Tiihonen
- Victor Manuel Pando Naude

- Niels Trusbak Haumann
- Pauli Brattico

- Hella Kastbjerg
- Laura Vestergaard Pedersen
- Tina Bach Aaen

- Alexander Fjælstad
- Ana M. Zamorano
- Christine Parsons
- Eduardo A. Garza Villarreal
- Eus Van Sommeren
- Iris Mencke
- Ivana Konvalinka
- Marcus Pierce
- Petri Toiviainen
- Risto Näätänen
- Vinoo Alluri

CENTER FOR MUSIC IN THE BRAIN

Predictive Coding

by Peter Vuust

Prediction is increasingly viewed as a fundamental principle of brain processing that determines perception, action, and learning. Emerging predictive coding theories[1] have offered novel explanations for how specialized brain networks can identify and categorize causes of its sensory inputs, integrate information with other networks, and adapt to new stimuli. Briefly, predictive coding, as recently formulated by Friston and colleagues[2], proposes that perception, action and learning is a recursive Bayesian process by which the brain attempts to minimize the prediction error between lower-level sensory input and the brain's top-down predictions.

The Predictive Coding of Rhythmic Incongruity (PCRI) model for how the brain processes rhythmic incongruity is a special case of the general predictive coding theory. Under a Bayesian formulation of predictive coding in the brain, perception corresponds to inverting a generative model of the things in the world that cause our sensations.

Computationally, this model inversion could be achieved in continuous time by minimizing a free-energy bound on the surprise $\mathcal{F} > -\ln p(\tilde{s} \mid m)$ about sensory input $\tilde{s}$ given the brain's model *m* of the world. In predictive coding, top-down connections provide lower levels with predictions in the form of prior expectations about states of the world, whereas bottom-up connections carry prediction errors that update posterior expectations in higher levels to provide better predictions. This leads to the following hierarchical equations for how top-down predictions $g(\mu^{(i)})$ given by posterior expectations $\mu^{(i)}$ at higher levels and bottom-up prediction errors $\epsilon^{(i)} = \mu^{(i-1)} - g(\mu^{(i)})$ from lower levels evolve when exposed to changes in stimuli $\tilde{s}$.

Predictions

$$\dot{\mu}^{(i)} = \frac{\partial g(\mu^{(i)})}{\partial \mu^{(i)}} \cdot \xi^{(i)} - \xi^{(i+1)}$$

Precision-weighted prediction errors

$$\xi^{(i)} = \pi^{(i)}(\mu^{(i-1)} - g(\mu^{(i)}))$$

where the dot notation (·) denotes the time derivative and π is the precision assigned to the prediction errors. The index-i is

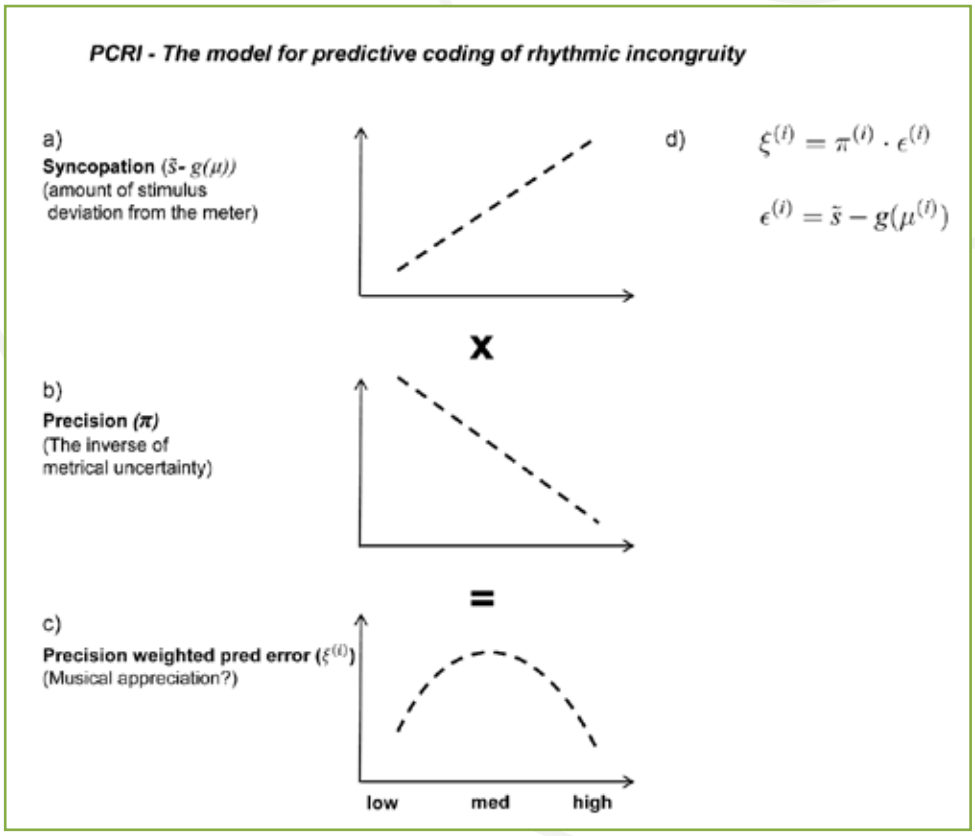


Figure 1
Proposed model of the PCRI. The figure provides a schematic illustration of the variables related to increasing syncopation of musical grooves (dotted lines).
A) Under predictive coding, the precision-weighted prediction error is given by the difference between the sensory stream $\tilde{s}$ and the brain's predictions g(μ) timed with the precision π. The index-i is used to refer to a relative hierarchical level in the brain. For grooves, the syncopations result in a prediction error ε = $\tilde{s}$ - g(μ), which can be calculated directly from the score by using e.g. Witek et al's modification[3] of Longuet-Higgens & Lee's formulation.
B) By assigning more or less precision or confidence to the ensuing prediction errors, the brain perceives the grooves as more or less groovy.
C) We propose that the observed U-shaped relationship between syncopation and grooviness[4] can be explained by the PCRI model as a function of the level of syncopation and precision or confidence assigned to the ensuing prediction errors.
D) The formulas for describing the relationship.

used to refer to a relative hierarchical level. Both higher-level predictions and lower-level prediction errors are weighted by their precision. The precision is the inverse of the variance and encodes the confidence about sensory inputs in lower areas, relative to the confidence with which states in the world that cause sensory inputs can be predicted in higher areas.
The PCRI model proposes that the precision weighted prediction error caused by a given rhythm's syncopation (the occasional appearance of a surprising beat followed by a surprising rest) is at the heart of how the brain models rhythm and meter based on priors, the metrical uncertainty (precision) and the stimulus deviation (see Figure 1).

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MIB Annual Retreat 2017 - Grenå
Make Time to Think

MIB center leader Peter Vuust introducing the *Make Time to Think* concept.

Group work ... making time to think.

MIB researchers gathered for a group photo during the retreat in Grenå, August 2017.
Photos: Hella Kastbjerg and Ole A. Heggli

MUSIC IN THE BRAIN RESEARCH

Hedonia research

by Morten L. Kringelbach

Emotion is most powerfully evoked by music and we continue to explore how this can give rise not only to hedonia (*hedone*, the ancient Greek word for pleasure derived from the sweet taste of honey, *hedus*) but also to eudaimonia (a life well-lived)[1,2]. This distinction was already proposed by Aristotle but music has proven a powerful empirical tool for investigating the underlying brain states constituting and underlying emotion[3-7].

The research is supported by the strong collaborative links between MIB, Oxford and Barcelona, where we are developing new groundbreaking whole-brain computational models with Professor Gustavo Deco[8-13]. As such, this enables us to study music with methods from many disciplines, including psychology, neuroscience, physics, engineering, and computer science to create groundbreaking science. An excellent example is the feature written by Kira Vibe Jespersen and Angus Stevner on *Music, sleep and state transitions in the brain*. Another example is the project conducted by doctoral student Patricia Alves da Mota using neuroimaging to explore the underlying neural mechanisms of spontaneous musical composition in jazz musicians. Yet another example comes from the research of doctoral student Ole Heggli on describing the intricacies of interpersonal tapping through coupled Kuramoto oscillators.

Music and psychedelics expands the brain's repertoire

Here we highlight one example of recent published findings of how the effects of music can be powerfully synergised with psychedelics to expand the repertoire and criticality of the human brain[14,15]. Working with Dr Selen Atasoy, Professor Gustavo Deco, and Dr Robin Carhart-Harris, we investigated the effects of music and LSD (lysergic acid diethylamide).

LSD was initially synthetized by Albert Hofmann in 1938 to stimulate the respiratory and circulatory systems. Yet, it was 5 years later that he accidentally discovered the profound effects of LSD on perception and consciousness, which led to its extensive use as a research and therapeutic tool in psychiatry in the 1950s. Today, LSD and related psychedelics are considered by some to be 'microscopes' or 'telescopes' for the psyche, because they reveal more of the mind than is normally accessible. However, the brain mechanisms underlying LSD's profound effects have remained largely elusive.

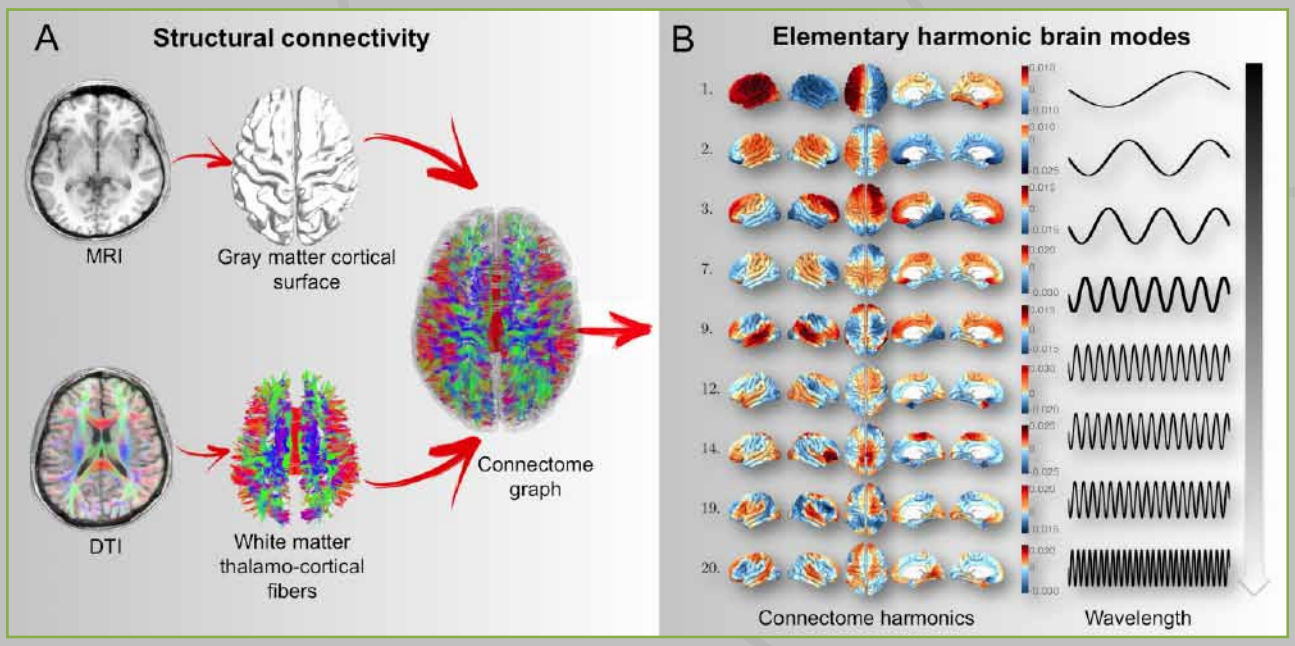

Figure 1
Connectome Harmonics Framework. (A) Structural connectivity of the human brain defined as the combination of local cortical, gray matter connections. (B) Elementary harmonic brain modes defined as fully synchronous patterns of neural activity are estimated as the harmonic modes of structural connectivity; that is, connectome harmonics.

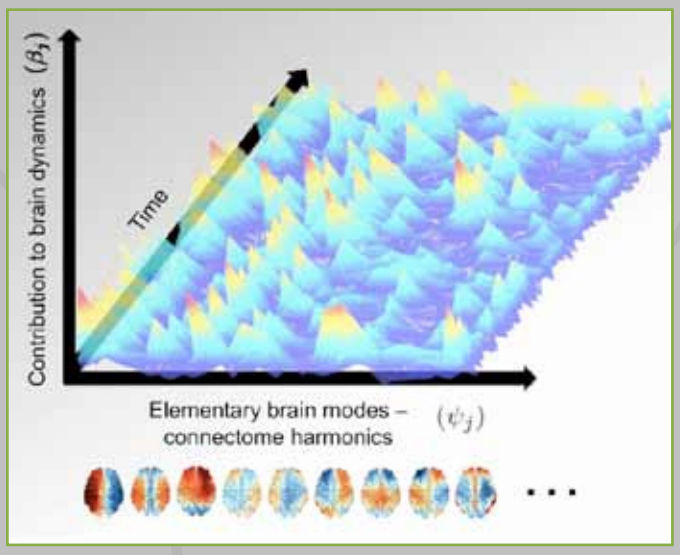

Figure 2
Connectome Harmonics. Projection of spatiotemporal patterns of neural activity reveals the contribution (βj) of each connectome harmonic (ψj) - elementary harmonic brain mode - to brain dynamics.

To decode the effects of music and LSD in the brain, we used a novel harmonic language of brain activity, which was first introduced in a Nature Communications publication in January 2016[16]. This harmonic decoding of fMRI data showed that LSD increases the total energy and enriches the repertoire of connectome harmonics - the basic elements of this harmonic language. The research also revealed that LSD selectively activated high-frequency connectome harmonics, which remarkably caused the brain activity to self-organize, right at the edge of chaos. This effect was enhanced when listening to music.

The connectome harmonics that we used to decode brain activity are universal harmonic waves, such as sound waves emerging within a musical instrument, but adapted to the anatomy of the brain. Translating fMRI data into this harmonic language is actually not different than decomposing a complex musical piece into its musical notes. What LSD does to the brain seems in many ways similar to jazz improvisation: where the brain combines many more of these harmonic waves (connectome harmonics) spontaneously, yet in a structured way, the improvising jazz musicians play musical notes in a spontaneous, non-random fashion.

FACTS

Group members, students and collaborators:

Postdocs:

- Dr Joana Cabral
- Dr Selen Atasoy
- Dr Henrique Fernandes
- Dr Angus Stevner
- Dr Alexander Fjældstad
- Dr Kira Vibe Jespersen
- Dr Diego Vidaurre
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- Carsten Gleesborg
- Ole Heggli
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- Nadia Høgholt
- Josephina Cruzat
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Collaborators:

- Peter Vuust, Aarhus University (music, prediction)
- Gustavo Deco, ICREA, Barcelona (modelling)
- Yair Bar-Haim, Tel Aviv (PTSD)
- Peter Whybrow, UCLA (neuropsychiatry)
- Alan Stein, University of Oxford (caregiving)
- Kent Berridge, University of Michigan (hedonia)
- Nuno Sousa, University of Minho (neuropsychiatry)
- Tipu Aziz, University of Oxford (DBS)
- Alex Green, University of Oxford (DBS)
- Mark Woolrich, University of Oxford (modelling)
- Robin Carhart-Harris, Imperial College (psychedelics)
- Tony James, University of Oxford (neuropsychiatry)
- Roger Crisp, University of Oxford (philosophy)
- Arne Møller, Aarhus University (Olfaction Research Center Aarhus)
- Therese Ovesen, Aarhus University (Olfaction Research Center Aarhus)
- Nikos Logothetis, Stanford (neuromodulation)
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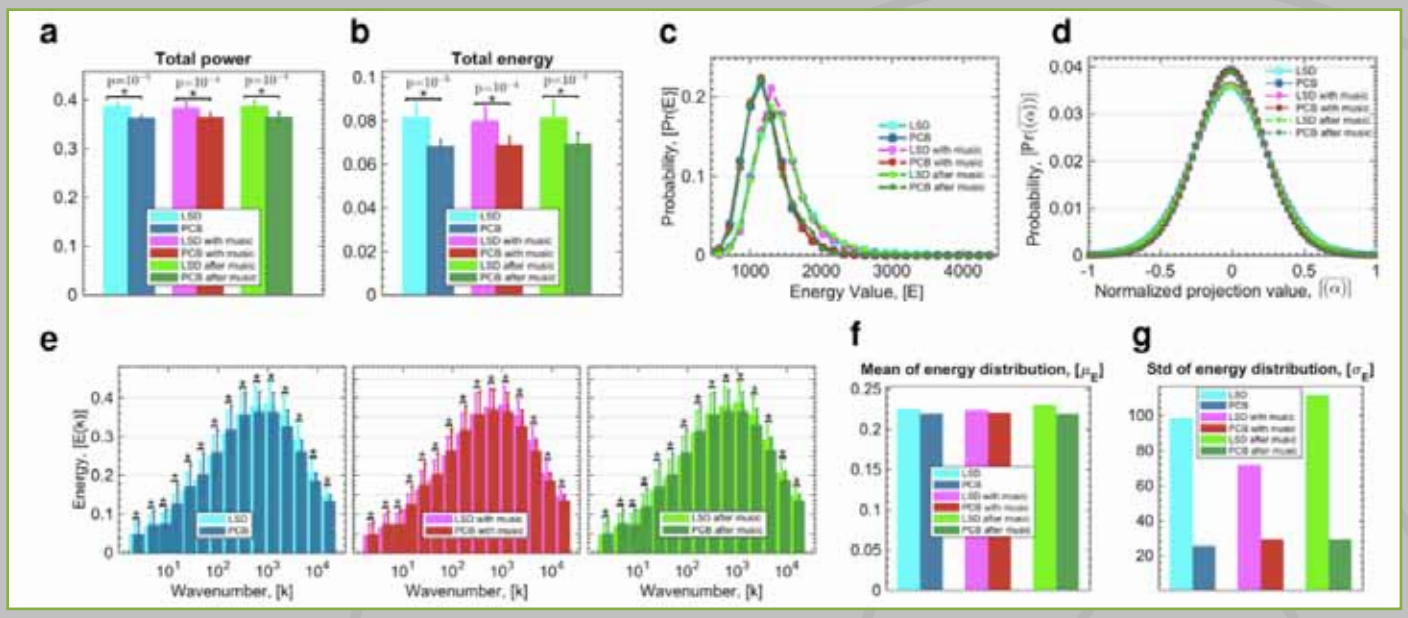

Figure 3

Changes in power and energy of brain states under LSD and music. Total power (**a**) and total energy (**b**) of all harmonic brain states for all 6 conditions, where stars indicate signicant differences ($p < 10^{-4}$, two-sample t-test) between each pair of LSD vs. PCB conditions with indicated *p*-values. (**c**) Probability distribution of total energy values (sum over all harmonics) for all 6 conditions. (**d**) Probability distribution of the occurrence of projection values (the amount of contribution) of connectome harmonics after normalization of each harmonic's contribution by the maximum value of the baseline (PCB) condition, shown for all 6 conditions; LSD, PCB, LSD with-music, PCB with-music, LSD after-music, PCB after-music. (**e**) Energy of connectome harmonics quantized into 15 levels of wavenumbers *k* (in the log-scale) for conditions (le) LSD vs. PCB, (middle) LSD with-music vs. PCB with-music, (right) LSD after-music vs. PCB after-music. Stars indicate significant di erences ($p < 0.01$, Monte-Carlo simulations after Bonferroni correction). (**f**) and (**g**) show the mean (μ) and standard deviation (σ) of the fit of the energy distribution of frequencies shown in (**e**) to normal distribution for all conditions, respectively.

The method introduces a new paradigm to study brain function that links space and time in brain activity via the universal principle of harmonic waves. It also shows that this spatio-temporal relation in brain dynamics resides at the transition between order and chaos.

Our findings reveal the first experimental evidence that LSD tunes brain dynamics closer to criticality, a state that is maximally diverse and flexible while retaining properties of order. This may explain the unusual richness of consciousness experienced under psychedelic drugs and the notion that they 'expand consciousness'.

By revealing the characteristic differences between LSD and normal awake state, the applied harmonic wave decomposition opens-up the possibility of extracting the signatures of various mental states, including sleep, anesthesia, and disorders of consciousness as well as psychiatric and neurological disorders.

Continued development of novel methods

As shown, we are continuing to develop new methods to study the dynamic effects of music on emotion. In particular we have developed whole-brain computational modelling for revealing the underlying causal brain mechanisms[17]. These developments will help us identify how music evokes emotion and how music can best help emotion regulation. One pertinent finding is the role of music in controlling sleep which can contribute to regulate overall mood in neuropsychiatric disorders.

Overall, careful experimental methods combined with novel analysis methods including connectome-harmonics and causal whole-brain modelling are helping to reveal the brain mechanisms of music and emotion, potentially opening up for new treatments; perhaps even eudaimonia and better lives - especially if coupled with early interventions.

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FACTS

Selected ongoing research projects:

- Figueroa C.A., Cabral J., Mocking R.J.T., Rapuano K., van Hartevelt T., Deco G., Schene A.H., Kringelbach M.L. & Ruhe H.G. (2018) Decreased ability to access a clinically relevant control network in patients remitted from Major Depressive Disorder
- Witek M. A. G., Gilson M., Clarke E., Wallentin M., Hansen M., Deco G., Kringelbach M.L. & Vuust P. (2018) The brain dynamics of musical groove: whole-brain modelling of effective connectivity reveals increased metastability of reward and motor networks.
- Stevner A.B.A., Vidaurre D., Cabral J., Rapuano K., Nielsen S.F.V., Tagliazucchi E., Laufs H., Vuust P., Deco G. Woolrich M.W., Van Someren E. & Kringelbach M.L. (2018) Discovery of key whole-brain transitions underlying the healthy human sleep cycle
- Deco G., Cruzat J., Cabral J., Knudsen G.M., Carhart-Harris R.L., Whybrow P.C., Logothetis N.K. & Kringelbach M.L. (2018) Whole-brain multimodal neuroimaging model links human anatomy, function and neuromodulation: serotonin receptor maps explain non-linear functional effects of LSD
- Fernandes H.M., Cabral J., Lord LD., Gleesborg C., Møller A., Deco G., Whybrow P.C., Petrovic P., James A.C. & Kringelbach M.L. (2018) Disrupted brain structural connectivity in Pediatric Bipolar Disorder
- Kringelbach M.L., Cabral J., Laufs H., Tagliazucchi E. & Deco G. (2018) Awakening: Stimulation-driven transitions between wakefulness and sleep in a novel probabilistic state-space framework

Highlights in 2017

New IRB at CFIN and MIB

Most of the research at CFIN and MIB relies on the participation of volunteers, who give their time to help us understand the brain and its many functions. The safety and comfort of these volunteers, and the protection of their privacy and anonymity, is therefore at the heart of all our activities. Legally, the "Act on Ethical Approval of Clinical Research" and the "Privacy Act" ensure those vital rights. Observing these laws, we seek approval by the Regional Ethics Committee and written informed consent from volunteers before we conduct any biomedical research projects, just as we follow certain guidelines, as we safe-keep our volunteers' personal information during any research project.

Some of our research projects, however, study basic brain functions and behavior in ways that fall outside the term 'biomedical' research. In 2017, a dedicated group of researchers and staff members from CFIN and MIB set out to describe the ethical guidelines and safety procedures we wish to follow as we involve volunteers in these types of research. Helped by guidelines from various organizations, the thoughts of laypersons who might participate in our studies, and insights from professionals with a deep understanding of the examinations we use, the group has now produced the framework for an Institutional Review Board (IRB), which can approve projects, which our Regional Ethics Committee finds to fall outside the area of biomedical research. The group has produced rules of procedure for the IRBs work, standardized subject information material, and check-sheets to help researchers address potential ethical, safety, or privacy considerations while they plan their studies.

Starting January 2018, the IRB meets on a monthly basis and future annual reports will report on the IRB's work. Meanwhile, CFIN staff, and especially computer scientist Jesper Frandsen, have worked hard to implement technical solutions and procedures to ensure that all data we acquire are stored and handled according to new EU data protection rules – GDPR. These rules are intended to protect our privacy and personal data – also as we volunteer to take part in research projects. Understanding the minds of lawyers, researchers excited to analyze data in new ways, and hackers, as one adapts the functionality of databases and computer systems for modern neuroimaging and computational modeling, is not a task for the faint-hearted, but one that Jesper manages admirably, and we wish to thank all of our researchers for their cooperation during this important process.

The current IRB members are:

- Leif Østergaard (Chairman)
  Scientific and medical representative
- Christopher Bailey (Vice chairman)
  CFIN Project Initiation Group member, MEG expert
- Tina Bach Aaen (Secretary)
  Layperson representative
- Elvira Brattico
  Senior scientific representative
- Torben E. Lund
  CFIN Project Initiation Group member, MRI expert
- Dora Grauballe (Project Initiation Group at CFIN)
  CFIN Project Initiation Group member, represents patients' perspective
- Jesper Frandsen
  IT specialist, data protection expert
- Kristian Sandberg
  Early-career scientific representative
- Suzi Ross
  Junior scientific representative
- Hella Kastbjerg
  Layperson representative
- Henriette Blæsild Vuust
  Layperson representative
- Lone Taulborg (Substitute)
  Layperson representative

NEW FACE at CFIN

Lone Taulborg, Project Economist

Lone joined CFIN in the beginning of 2016 after working for many years in the administration of the Department of Physics and Astronomy and Finance Center Science & Technology, Aarhus University.

Lone is CFINs Project Economist and handles all CFIN researchers' financial businesses with great care and precision. She is a key person in the joined CFIN and MIB administration group and collaborates closely with AU administrative functions - especially HR and Economy - to ensure that all CFIN projects are followed and guided in all stages.

DHL Relay race 2017

Pouring rain is what we will all probably remember most from the annual DHL Relay race, along with the high spirits. As usual CFIN and MIB participated with several running and walking teams and despite the extremely bad weather we all had a fun evening in Mindeparken on 17 August 2017. Our CFIN - Running Brains 1 team finished in the impressive total time of 1 hour, 45 minutes and 14 seconds.

CFIN and MIB mobilized 5 running teams and 2 walking teams and we were (as usual) supported by CFIN and MIB 'hangarounds' (children and friends) who stepped in on short notice to fill in for injured runners. This way, we hopefully also encourage the next generation of brain researchers ... and get fresh physical strength as a very nice bonus.

The pouring rain ruined many running shoes ...

Fathers and sons ... Gorm Wallentin, Peter Vuust, Mikkel Vuust, and Mikkel Wallentin

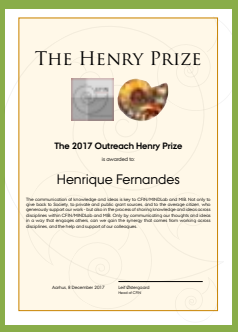
Two of the fast CFIN runners ... Ryan Sangill, who actually ran two rounds in the Relay race, and Erhard Næss-Schmidt

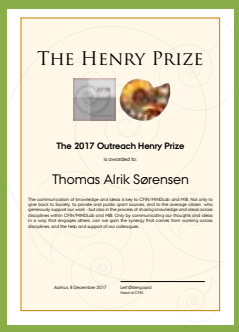
All is well that ends well ... Chris Bailey and Sarang S. Dalal

The Henry Prize

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

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





In 2017 The Henry Prize was split between MIB researcher Henrique Fernandes and CFIN researcher Thomas Alrik Sørensen. They were both nominated for the prize by their fellow researchers as worthy of the 2017 prize for their research contributions, initiative, helpfullness and overall admirable efforts to promote the research of MIB and CFIN to a broader audience.

CFIN / MIND*Lab* staff

CFIN Coordination

Group and modality leaders, from CFIN and closely collaborating centers, who meet to discuss and coordinate scientific activities and practical matters.

Arne Møller (PET)
Brian Hansen
David Brooks (PET)
Elvira Brattico (MIB)
Eugenio Gutiérrez Jiménez
Jakob Udby Blicher
Kim Mouridsen
Kim Ryun Drasbek
Kristian Sandberg
Leif Østergaard
Morten L. Kringelbach (MIB)
Morten Overgaard
Nina Kerting Iversen
Per Borghammer (PET)
Peter Vuust (MIB)
Sarang S. Dalal
Simon Fristed Eskildsen
Sune Nørhøj Jespersen
Torben Ellegaard Lund
Yury Shtyrov

Neurophysics

Group leader: Sune Nørhøj Jespersen

Ahmad Khan
Andrey Chuhutin
Brian Hansen
Hugo Angleys

Neuroinformatics

Group leader: Kim Mouridsen

Anne Nielsen
Irene Klærke Mikkelsen
Jens Kjærgaard Boldsen
Mikkel Bo Hansen
Thorbjørn Ø. B. Grønbæk

Functional Hemodynamics

Group leader: Leif Østergaard

Anete Dudele
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Hugo Angleys
Maryam Anzabi
Peter Mondrup Rasmussen
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Casper Schmidt
Cindy Jørgensen
David Brooks
Jørgen Scheel-Krüger
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Nicola Pavese

Molecular and Cellular Neuroscience Lab

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Sun Sha
Tingting Gu

Pre-clinical Optical Group (POG)

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Optical lab coordinator: Eugenio Gutiérrez Jiménez

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Katrine Tang Stenz
Lars Hvass
Luca Bordoni
Maryam Anzabi
Maryam Ardalan
Sebastian Frische
Signe Kirk Fruekilde
Stine Ledet Methmann, Laboratory technician
Susanne Smith Christensen, Laboratory technician
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Applied Imaging and Modelling

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Christine Ahrends
David Ricardo Quiroga Martinez
Davide Ligato
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Henrique Fernandes
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Joana Cabral
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Louis-David Lord
Maria-Celeste Fasano
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Selen Atasoy

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Michael Lohse
Peter Fazekas
Thomas Alrik Sørensen
Timo Lehmann Kvamme

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Daniel Gramm Kristensen
Justyna Hobot
Simon Bang Kristensen
Simon Hviid Del Pin

NeDComm Group

Group leader: Yury Shtyrov
Alina Leminen
Christopher Bailey
Eino Partanen
Mads Jensen
Miika Matias Leminen
Nikola Vukovic
Rasha Hyder

NEMO Group

Group leader: Sarang S. Dalal
Alexandra Vossen
Britta Westner
Jordan Alves
Martin Dietz
Tommy Clausner

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Erhard Trillingsgaard Næss-Schmidt
Krystian Figlewski
Marie Krøll Knudsen
Tobias Glaston Stærmose

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Dora Grauballe, Research Radiographer
Irene Klærke Mikkelsen, Data manager
Jesper Frandsen, Software Developer
Martin Snejbjerg Jensen, Engineer
Michael Geneser, Radiographer
Mikkel Bo Hansen, Software Engineer
Ryan Sangill, MR Physicist

Administrative Staff

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Henriette Blæsild Vuust, Communications Coordinator
Kim Ryun Drasbek, Scientific Coordinator
Lone K. Taulborg, Project Economist
Mai Drustrup, CFIN Secretary & PA to Leif Østergaard
Laura Vestergaard Pedersen, PA to Peter Vuust / MIB
Simon Jeppe Bjerg, Scientific Coordinator
Tina Bach Aaen, MIB Center Administrator
Vibeke Sauer Panyella, SDC Educations Coordinator

2017 Publications

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