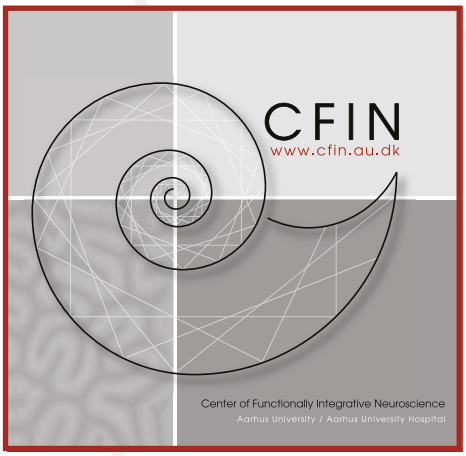


Center of Functionally Integrative Neuroscience
& MIND*Lab*

# ANNUAL REPORT 2018 & 2019

cognition
PET
statistics
data
tensor
dendrite
MR
physics
scanning
music
neuroanatomy

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Preparing to move out of the DNC-house in May 2019 ... and getting installed in CFIN South, Building 1A at Nørrebrogade.
The labels, put on every box and piece of furniture to indicate their destination, can be difficult to read and inaccurate. The dutiful movers may have scratched their heads as they placed this desk ... in the restroom.
Photos: Vibeke Sauer Panyella

# Introduction - 2018 & 2019 in words

by Leif Østergaard

I am pleased to introduce this progress report from CFINs group- and modality-leaders, also featuring a progress summary from our sister-center, the Danish National Research Foundation's (DNRF) Center for Music in the Brain (MIB).

Following years of changing plans and great uncertainty regarding our future office and laboratory space, the decision was made in March 2019 to temporarily move MIB and most CFIN researchers to Building 1A at Nørrebrogade 44, while moving our experimental infrastructure to its intended location at Aarhus University Hospital (AUH) in Skejby, along with key personnel and laboratory researchers. We owe special thanks to Henriette Vuust for coordinating the Nørrebrogade move and working tirelessly to turn the building into our new home, to Torben Lund for developing solutions that could accommodate our needs at the AUH facility, and to the entire infrastructure staff for thinking outside the box to save resources during the expensive move. To this end, we thank our host institutions, Aarhus University and AUH, for their critical support to secure our future in times where their resources were already stretched to the limit.

Building 1A served as CFINs first 'official' home after our inauguration as a DNRF center-of-excellence in 2001. The beautiful old building, which opened in 1893 and comprised *the* Nørrebrogade hospital for decades, holds fond memories, and crucially, much needed office and meeting space after we outgrew the former Danish Neuroscience Center (DNC) building. Nevertheless, we hope for a new DNC building at AUH to reunite CFIN, MIB, our equipment, and all of our scientific and clinical collaborators there, in one place. At AUH, our molecular biology laboratory, MEG system, EEG and TMS facilities are now installed in wing J115, while our two 3.0 Tesla human MR systems, 9.4 Tesla animal MR system, optical imaging lab, and animal facilities found a new home in wing J117, separated from J115 by the indoor University Square near AUHs emergency room.

The separation between CFIN equipment, researchers, and technical staff at AUH, and the CFIN and MIB researchers and administrative staff at Nørrebrogade, is now a tangible 5 kilometers. This is challenging for a center founded upon collaborations across disciplines and easy, immediate access to collaborating physicians and experts within neuroscience and neuroscience methods. I am grateful for all the initiatives CFIN and MIB researchers have already taken to stay in touch, using social media, flexible working and meeting-places, and social gatherings to maintain strong cohesion across geographies.

Moves aside, the ingenuity and productivity of CFIN researchers has been unwavering throughout the past two years, as you will read inside our report. We were proud and delighted to welcome Associate Professor Micah Allen to CFIN early 2019. Micah received prestigious Fellowships from both the Lundbeck Foundation and the Aarhus Institute for Advanced Studies (AIAS). His research lab, the Embodied Computation Group (ECG), will be based at both Aarhus University and Cambridge Psychiatry, working in a multi-disciplinary effort to understand the computational mechanisms of brain-body interactions in health and disease. Stay tuned for news of another talent scheduled to join CFIN and MIB in 2020 and other major programs starting soon – in the 2020 CFIN annual report!

Until then, we wish everybody good health and thank you for your collaboration, interest and support.

Leif Østergaard
CFIN / MIND*Lab* director

# Moving North

by CFIN Infrastructure Staff

From its humble beginnings as an appendix to two hospital departments and over the course of about 15 years, CFIN expanded to a full-scale neuroimaging facility. At the end of its run at the now-shuttered Aarhus University Hospitals Nørrebrogade campus, CFIN sprawled the basements of buildings 9 and 10, housing equipment and experimental facilities for both clinical and preclinical research. It was truly living up to one of its core foundational goals: to provide the infrastructure in which neuroscientific discoveries can not only be made, but also translated into diagnostics and ultimately treatments in a range of clinical patient populations. But nothing lasts forever.

With the decision to consolidate clinical activities to the Skejby campus, CFIN had to begin the task of planning a move, the scale of which was unprecedented, and which needed to be implemented in a way that caused minimal disruption to the many projects that were grant-bound to deliver results. Let it be said that the authors, who generally speaking gladly accept the admiration of their colleagues for well-functioning lab facilities, have at no point been in doubt as to the value of being located in hospital buildings. Not only does our host provide cooling for our delicate scanners' electronics (most of the time), they also provide crucial clinical-grade logistics services that we rely on, and appreciate.

We live in a world in which demands for "efficiency" and "economising" are imposed on all businesses, including the public sector and thereby also research. We were given the challenge to not only move CFIN infrastructure, but in doing so increase the throughput capacity without increasing the footprint in terms of raw space. After a little soul-searching, we decided to see the move as an opportunity to improve on already battle-tested labs!

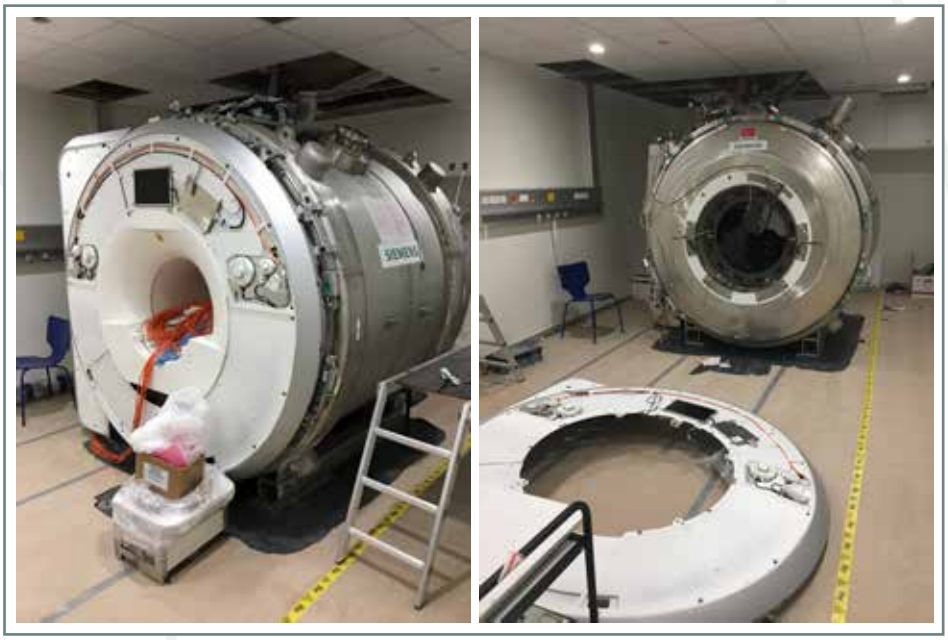
Part of the MEG system being moved out of building 9 at AUH Nørrebrogade.
Photo: Chris Bailey

## Travel plans

Thanks to a dialogue between CFIN staff and the hospital, we managed to keep our labs functional until the very end, even as the hospital was being decommissioned further down the street. We were forced to prioritise the completion of studies rather than initiating new data collections - a task which would not have succeeded without the gracious attitudes of our "customers", despite the fact that we could not give them a definite prediction on when our new facilities would be operational again.

A major hurdle to overcome indeed turned out to be the fact that although space had been allocated in Skejby for CFIN, construction had largely been based on the blueprint of a generic clinical hospital department. We are proud to be associated with a world-class hospital, but generic we are not. So even as we were planning a controlled teardown and relocation, we were still redesigning our future home. We knew and respected that the only economically valid arguments were those founded in functional requirements. Luckily, 15+ years of experience gave us the confidence to request the changes necessary to achieve our goals, despite the organisation-wide budget challenges that have been widely publicised. We believe we were successful in cutting every corner possible, while ensuring facilities that can serve researchers for the next few decades.

Have you ever tried to climb onto a roof using a ladder? Pretty easy, right? But what about coming down again? Not so easy… As it turns out, MR scanners, two-photon laser rigs and magnetically shielded rooms are a lot easier to get into a building than out of one! Particularly when the intention is to re-commission them at another location. We owe big thanks to our partners at Siemens, Bruker, Prairie and Elekta/MEGIN for their flexibility and guidance during the planning and implementation of the move.



MR scanner in parts at the new location at AUH, Skejby
Photo: Chris Bailey

### Making (many) omelets without breaking (too many) eggs

The time period between “home A” and “home B” is notoriously stressful, and usually longer than one would prefer. And our moving boxes were bigger and heavier than most.

Research on the CFIN MR scanners is primarily performed on healthy volunteers or patients. However, the importance of pig models for preclinical research has increased steadily over the years. The layout of the MRI facilities was thus designed to accommodate human and non-human subjects alike, while maintaining hospital hygienic standards. By optimising the all-important ancillary rooms for subject preparation and briefing, and carefully placing our scanners in a non-interfering configuration, we managed to ensure the feasibility of installing a 7T MR research system, once the funds for one have been secured.

There is no move without casualties, as we and our friends at Siemens found out. Despite utmost care taken in the extraction of the Prisma scanner, it was damaged during the last leg of the transport. Investigations revealed that the innermost core of the scanner - the superconducting electromagnet that affords the “M” to “MRI” - would be unable to stably carry the amount of current needed to reach a 3 T field strength. Although CFIN was immune from the direct economic consequences of a move-related damage, we were concerned about the delay that might be incurred. You cannot order a new 3T electromagnet off Amazon - each is built-to-order, and order books were full. Luckily, Siemens managed to locate and upgrade an existing magnet core from a previously cancelled installation, limiting the delay to just a handful of weeks. We were not out of the woods yet, though. Economising on space has limits defined by physics. The terrible truth about Natural Laws is that they could not care less about mortal desires to “fit more angles on the head of a pin”. Society has yet to solve the problem of how our clinical professionals can be afforded the space they require and deserve to keep the rest of us from dying. An MR scanner, on the other hand, will explode its liquid helium guts out if one attempts to pass it on motorised vehicles while it's being ramped up to operation. Twice, to be exact. Through a cool-headed and constructive dialogue with the hospital administration, we are in the process of mitigating the unintended proximity between our MR scanners and a passage where heavy, motorized maintenance vehicles could interfere with their magnetic fields and the beauty of our MRI images.

### The summer heat

Coolness is, in fact, a rather crucial requirement not only of ambitious engineers and administrators, but also of high-power MR gradient systems, ultra-precise optical imaging lasers, and liquid helium recovery plants. As the Spring of 2019 turned into summer, we discovered a critical capacity limitation of the hospital’s centralised cooling system. Throughout the summer, we experienced instabilities and shutdowns due to insufficient coolant flow. This became our introduction to the hospital staff responsible for building operations. Instead of ducking for cover, they took our (at times loud) complaints seriously, and debugged their infrastructure. We hope that these adjustments, and regular cleaning of coolant filters will prevent problems in the future.

The reconstruction of the CFIN human neurophysiology arm began with the sequential tearing down, transport, and

Moving and construction of the new MEG suite at AUH, Skejby
Photos: Chris Bailey

re-assembly of the magnetically shielded room for the MEG system. In a mere 3 weeks the room, consisting of sheets of mu-metal and an aluminium frame with a total weight of over 8 tons, was again standing ready to receive the MEG. Before that, however, we needed to build the surrounding spaces for subject preparation, data acquisition and technical areas. We optimised heavily on space in the latter, managing to squeeze both electronics and the helium recovery system into an extremely small footprint. This allowed the remainder of the MEG lab to retain most of its previous size, and thereby all its critical and well-tested functions and workflows. In Autumn 2019, we welcomed back our clinical colleagues from the Section of Neurophysiology, who could again perform diagnostic measurements on patients suffering from epilepsy.

Due to space constraints, our dual-EEG laboratory needed to await completion of the MEG. We re-designed the stimulus delivery and response monitoring setup to fit into a space-conserving server rack. This, as well as friends at the hospital procurement department, allowed us to mount retractable beds onto to walls of both EEG booths, enabling both traditional ERP studies using psychophysical paradigms, as well as sleep studies. Separate rooms for behavioural testing are shared between MEG, EEG and the yet-to-be-completed TMS facility. The latter was pending the purchase of a second, lighter shielded room that will be installed as soon as the present global travel restrictions are lifted.

## Low-footprint expansion of preclinical capacities

Synergies were not only found within the human imaging modalities but to a high degree also within the preclinical realm. Huge space-saving was achieved by ensuring that both the high-field MR system and the optical systems have access to common surgical benches, a murine stable, and a room for behavioural training and analysis. Such optimisation is only possible due to strong collaboration between the groups, which has also resulted in new research ideas and joint projects.

A donation from the VELUX Foundation provided the funding for a second microscope “head” on the two-photon system that utilises the same laser rig to increase the throughput of microscopic imaging *in vivo*. Even in the modern era of computers, human dexterity and experience are indispensable. This was made evident by an installation delay incurred by staff changes at our commercial partner between the teardown and buildup phases of the optical pathways. The main functional advantage of our tight space economy was that we could allocate a dedicated room for the optical coherence tomography system, which can therefore operate independently form other measurements and provide detailed three-dimensional images of microscopic cortical blood flow dynamics. To complement our palette of imaging modalities for the study of cerebral metabolism, in collaboration with researchers at Boston University, we built a multispectral and laser speckle imaging system that has excellent contrast within the surface vasculature.

The CFIN molecular biology laboratory was the first to be shut down, but faced an uncertain future as no space had been allocated for it in Skejby. Ultimately, our track record of integrating knowledge across neuroscientific disciplines was a convincing argument. A storage room was repurposed as a molecular lab, while redundant animal housing in a nearby wing was allocated as a cell lab. With some thoughtful packing of the existing labs and lots of patience from their users, the “almost homeless” labs could operate even during the interim construction period that ended up stretching over half a year.

## Safe and sound

During CFIN's move, many researchers were asked to be patient regarding new data collection. This would be a brilliant opportunity to get some of those older datasets analysed and published! Provided the CFIN crew of amateur IT-guys could manage to move the storage servers and analysis cluster to safety, that is. We projected confidence outward, while inner alarm bells were ringing. How do you know you're prepared to move almost two decades worth of data collection? Our answer is that you don't know, you just do it. Somewhat to our own surprise, all our services were again running and accessible <48 hours after going down. Team sysadmin@cfin prevailed! We owe special thanks to Peter Skaarup, and the Ophthalmology department for lending his server-savvy mind to us, and to the Central Denmark IT department for accommodating our special network needs and split location. As a testament to our at times admittedly pedantic approach to systems administration, our home-baked Raspberry Pi-based temperature alarm alerted us about a cooling system failure in the hospital server room - this turned out to be news even to the hospital's own staff! A controlled automatic shutdown of the power-hungry servers prevented data loss due to overheating. As unpleasant as such events are, it's good to know that our safeties seem to be well in place.

With an exhaustive move behind us - more or less - we look forward to many fruitful scientific collaborations in state-of-the-art facilities for many years to come!



Two photon equipment in boxes ... and unpacked at the new lab facility at AUH, Skejby
Photo: Chris Bailey and Eugenio Gutiérrez

# High Field MRI Lab

## High Field MRI in new surroundings

by Brian Hansen

Moving the 4.8 ton 9.4T preclinical MRI from the lab in the bunker-like basement at Nørrebrogade was a challenging task (see Figure 1). Ultimately, however, the effort was worth it because now the MRI is housed in a modern, ground-level preclinical facility featuring an abundance of laboratory enhancements and improved opportunities for cross-modality research projects.

Based on our experiences with the laboratory lay-out at Nørrebrogade, we have been able to make ideal use of the space allotted in Skejby Hospital's J117 wing. The result is a modern, preclinical research facility which we believe is quite unique in how it makes use of shared lab-space and allows both for interaction between a diverse group of researchers (see Figure 2). These rooms are central to many projects, and students, staff, and researchers spend a significant amount of time in these rooms doing their utmost to master the intricate

**Figure 1**
The Bruker high field MRI is lifted out of the below-ground labs at Nørrebrogade.

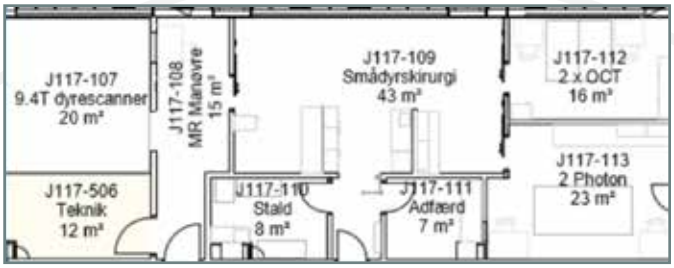



**Figure 2**
Layout of the new preclinical facility including the high field MRI lab (on the left). The MRI control room has direct access to the central lab section where the animal surgery, wet lab, stable, and behavior lab are located. From here there is access to two-photon microscopy and optical coherence tomography labs.

procedures and techniques needed to unravel the wonders of the brain. It is a pleasure to work in these new surroundings and we believe that this will be reflected in the work produced here. It is a great joy to welcome new students into our new preclinical facility.

This chapter will focus on the new research themes the MR-lab is currently pursuing, many of which would not have been feasible in our old facility.

### Scientific perspectives and possibilities

Preclinical research hinges on the use of animal models either to study basic biomedical questions or because an animal model can mimic a specific human disease. The use of animals for research has a long history but the way we use animals in science is changing rapidly. The two most important developments in our research area are 1) more complete, systemic characterization of the animal models and 2) the increased awareness of the effect of anesthetics on measurements. Our new facility is ideally suited to embrace these developments. Here we will describe the MR-lab's involvement in both of these areas.

### Know your animals:

The progress of science has to a great extent revolved around our ability to develop experiments and techniques that allow us to study a phenomenon or mechanism in isolation. In biology, we rarely have this luxury. Rather, our study of a biological phenomenon or a disease almost always has to take place on top of "biological noise" from the animal's complex physiology. Our progress is critically limited by these circumstances. One

strategy to reduce 'noise' in our data is to characterize the animal models more fully. By building data sets composed of measurements from multiple modalities and combining these with assessment of animal behavior, stress levels, grimace scores to mention a few, we gain a more complete picture of the fidelity of the data we obtain from the mouse or rat that is our model system. MRI is ideally suited for this type of work because the same scanner can be used to collect multiple types of data, including brain morphology, chemistry, perfusion and tissue structure. This provides a comprehensive information about brain status in the disease models. Coupled with behavioral scores, this allows us to correlate brain composition to e.g. memory task performance to form robust structure-function relationships. By further combining the MRI measurements with data from other modalities we can carry out extremely detailed investigations of rodent brains. The beauty of our new facility layout is that the MRI lab is situated on one side of the animal surgery and preparation lab, which also has direct access to CFIN's optical labs. Our goal is to perform joint studies where the full suite of MRI, behavior, and *in-vivo* microscopy (i.e. two-photon microscopy and optical coherence tomography) are utilized together for in-depth investigation of our animal models. For these reasons, we are very pleased with our new preclinical site where we are better equipped than ever before to perform exciting neuroscience research.

## Time to wake up:

For decades, measurements performed in anesthetized animals have formed the experimental foundation for basic neuroimaging research. In recent years however, the fact that even common anesthetics perturb animal physiology has become a concern. This is particularly alarming when the effects or mechanisms we are looking to investigate are very subtle or when our experimental methods become sensitive enough that untoward perturbations of animal physiology - however subtle - become detectable and therefore contaminate measurements. A paradigm shift is therefore underway in preclinical neuroimaging where a growing number of preclinical labs now prefer to perform their investigations in awake animals trained to tolerate the laboratory environment, scanners, and microscopes. The benefit of this approach is two-fold: 1) measurements are not biased by the influence of anesthetics and 2) experiments are being performed without animal stress (another source of physiological disturbance) and discomfort which cannot be entirely avoided e.g. in longitudinal studies where animals are repeatedly anesthetized. The transition from anesthetized animal MRI to awake animal MRI is essential but far from trivial. However, the effort is worth it because awake animal MRI improves our ability to study and understand the brain in its natural, functioning state. In the following section, we introduce a new PhD student and his project involving awake animal MRI.

## Awake animal MRI studies of the glymphatic system

In 2019 we obtained funding to hire Thomas Beck Lindhardt as a PhD-student (Figure 3) working both at the CFIN high field MRI lab and the MR-lab at Institute of Neuroscience in Shanghai, China. The central question of Thomas' research project seems quite simple, namely: Why do we sleep? While old and simple to state, this question remains a mystery in mammalian biology. The physiological importance of sleep, nevertheless, is undeniable. Complete sleep deprivation is known to lead to death in mere days to weeks in rats and dogs. Anecdotal evidence suggests humans to be more resilient to complete lack of sleep (the documented record being 11 days). Nevertheless, in humans, prolonged, partial sleep deprivation due to lifestyle or sleep disturbances has been linked to a number of serious diseases including diabetes, cardiac disease, cognitive impairment, and dementia.

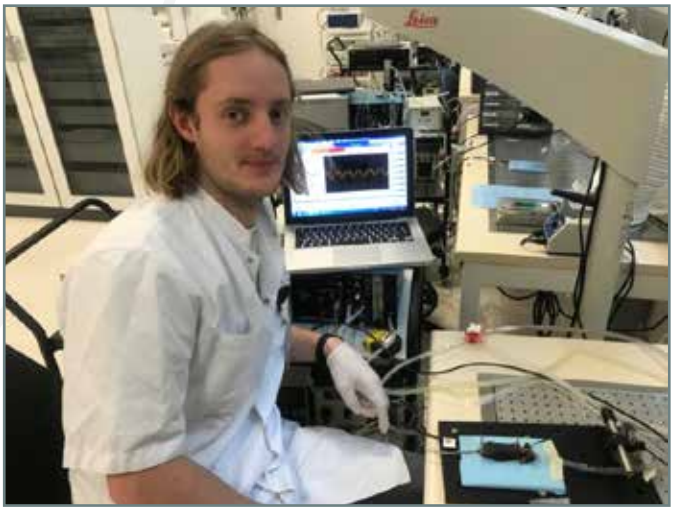


**Figure 3**
Thomas Beck Lindhardt at work at the lab bench.

**Figure 3**
Prototype of the scanner simulation chamber used to habituate mice for awake scanning. The chamber is a dark enclosure similar to the inside of the scanner and is equipped with speakers to also expose the mice to the scanner sounds.

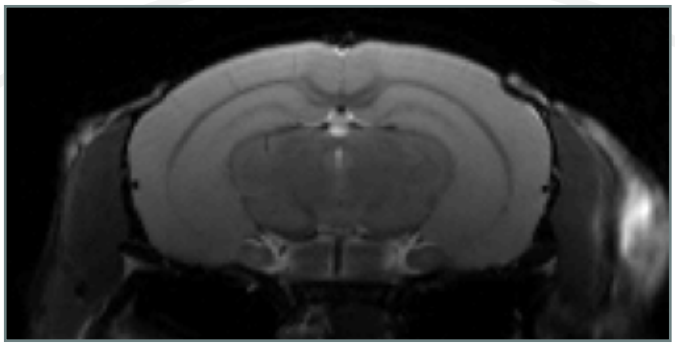


**Figure 4**
This image from our first awake animal MRI experiment shows an axial slice through a mouse brain. The image is crisp, with no signs of animal movement, thanks to the animal's habituation to the scanner environment and gentle head fixation.

While still enigmatic, the function of sleep - especially its basic physiological role - can now be made subject to closer scrutiny due to the development of two-photon microscopy and increasingly sensitive MRI techniques. Such studies may help elucidate the causal relations between sleep and the diverse range of diseases listed above. One intriguing theory stems from two-photon microscopy measurements showing significantly increased diffusivity of extracellular dye in brains of sleeping or anesthetized mice compared to the awake state. The explanation offered for this diffusivity increase is a sleep-induced enlargement of the extra-cellular space brought about by cellular shrinkage. This increase in extracellular water transport pathways points to a sleep-activated macroscopic waste clearance system in the brain termed the glymphatic system. This system may be a prime reason why brain health seems closely linked to sleep. This hypothesis is compelling and calls for closer scrutiny of how such a mechanism would influence and coexist with other fine-tuned physiological systems in the brain. The physiological role of sleep and the glymphatic system are separate but intricately linked fundamental questions. The project will contribute to the understanding of both. Another purpose of the project is to establish experimental methodology which is expected to form the basis for all of our future preclinical MRI studies. At the time of writing this report Thomas has been enrolled in the PhD-programme for little under half a year. In this short time he has designed and built habituation chambers and animal beds (see Figure 3) allowing us to train and image awake mice using the Bruker cryocoil originally built for rat imaging. Our first awake animal MRI is shown in Figure 4. We are very excited about the progress of this project and the interesting research the awake animal methods make possible.


The Bruker high field MRI in its new home at Aarhus University Hospital.
Photo: Tonny Foghmar, AUH Foto

## Funding and selected publications

Brian Hansen received funding for the project "The neurophysiology of sleep: awake animal MRI of the glymphatic system" from two sources:

- 1 mio DKK from the Sino-Danish Center (SDC)
- 590,000 DKK from AUFF NOVA
- Additionally Lippert's Foundation granted DKK 58,500 for hardware and lab equipment.

1. B. Hansen: Diffusion kurtosis imaging as a tool in neurotoxicology. Neurotoxicity Research, 37, 2020, p. 41-47.
2. B. Hansen: An Introduction to Kurtosis Fractional Anisotropy. American Journal of Neuroradiology, 40, 2019, p. 1638-1641.
3. TB Lindhardt and B. Hansen: "Det er tid at vågne op!", Aktuel Naturvidenskab, 2, 2020.

Opposite page: Moving North
Photos: Brin Hansen, Torben E. Lund, Chris Bailey, Eugenio Gutiérrez


Moving North
BATTERY LOW
SMART

# POG

## Preclinical optics group

by Eugenio Gutiérrez, Anete Dudele and Nina K. Iversen

The laboratory of the preclinical optics group engages in interdisciplinary research to understand the physiological role of capillary blood flow patterns and to quantify capillary dysfunction in various disease models. We do this by employing mathematical models and by analysing data obtained by Two-Photon Microscopy (TPM), Optical Coherence Tomography (OCT), Laser Speckle (LSC), and Intrinsic Optical Signal Imaging (IOS).

Our TPM was recently updated thanks to a grant from the VELUX foundation (ARCADIA II) to add a second scanning head (Ultima Investigator) for improving work efficiency and allowing more projects to run at the same time. This new microscope is a modified version of our current Ultima-IV microscope with the capabilities of high-resolution, high-speed and high-sensitivity deep *in vivo* imaging. We also improved the detection capabilities of both systems, adding GaAsP photomultipliers. In particular, the detectors of our Ultima-IV TPM are fitted with a lens shutter that keeps the detectors closed in case of high light excitation. This update will allow us to perform future experiments with optogenetics.

We also updated our Ultima-IV with a liquid-fiber guide to reduce background noise, which is essential for our oxygen measurements. In addition, our other optical systems were further expanded by building a microscope for multispectral and laser-speckle contrast imaging system (MSLS) into the system. This was designed by our collaborators at the Neurophotonics Center at Boston University and was funded by the Velux Foundation (ARCADIA I). With this system, we can examine the spatial and temporal relationship between hemodynamics and metabolic responses which is essential when studying neurovascular coupling in the brain.

In our new facilities at Aarhus University Hospital, we have the opportunity to employ an array of cutting-edge scanning methods by combining optical scanning methods with high-field MR in the same laboratory. With this capability, we hope to shed new light on brain disease mechanisms and hopefully inform the development of future treatments. Having access to these methods in the same facility has

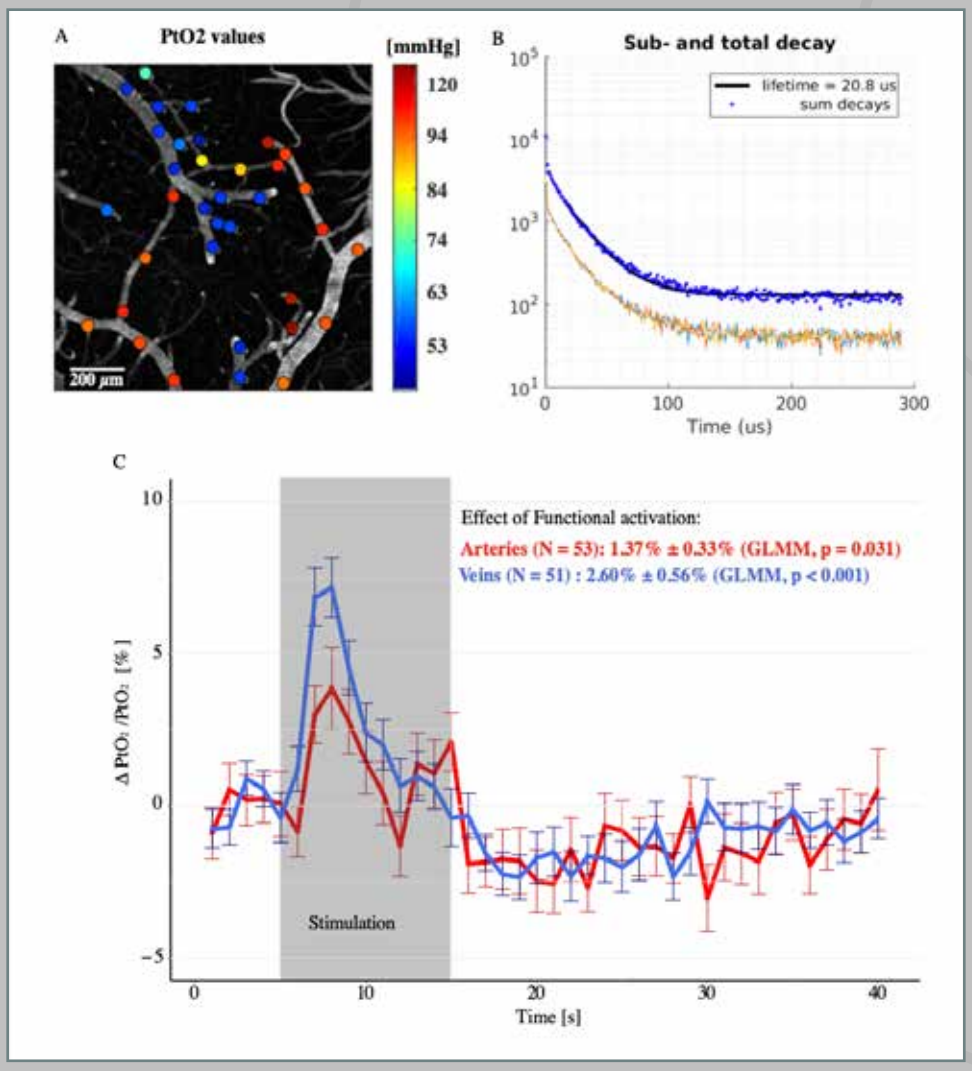



**Figure 1**
For estimation of oxygen tension ($PO_2$), we used phosphorescence life-time imaging by TPM and an oxygen sensitive dye (PtP-C343). The estimation of oxygen tension during functional activation was calculated in 35 points along the pial vasculature of brain cortex of C5Bl/6 mice (7 months old male mice) (A). Experimental measurement (B) of phosphorescence decays (blue dots) and corresponding single exponential fit (black fitting line) from a single point scanned. (C) Estimated relative changes in oxygen dynamics of the pial vasculature during functional activation. Error bars = S.E.M.

POG Lab leader Nina Kerting Iversen in the lab.
Photo: Tonny Foghmar, AUH Foto

also created a unique foundation for attracting new scientific collaborators, more grants, and talented young researchers and students interested in neuroscience and physiology. It is our ambition to form strong international collaborations and conduct cutting edge neuroscientific research.

### Oxygenation

Oxygen is crucial for brain energetics, and tissue oxygenation is hence one of the most critical parameters with respect to brain physiology and pathology. The ability to measure oxygen partial pressure ($PO_2$) with high temporal and spatial resolution in three dimensions is central for characterizing oxygen delivery and consumption in normal and diseased brain. Such techniques open up numerous possibilities for metabolic studies in neuroscience that will advance our understanding of brain metabolism and function. In close collaboration with Professor Sava Sakadzic, Optics Division, A. A. Martinos Center, Harvard University, Massachusetts, USA, Dr. Eugenio Gutiérrez has employed this new technique in our Ultima-IV TPM using the PtP-C343 fluorescence dye produced by Sergei Vinogradov, University of Pennsylvania, USA. We have recently used this technique to evaluate the effect of functional activation on brain oxygen extraction fraction (OEF) in healthy mice (see Figure 1). The extraction of oxygen to the tissue not only depends on the changes of cerebral blood flow (CBF) during functional activation, but also on the mean transit-time (MTT) and the distribution of blood flow capillary transit-time heterogeneity (CTH) through the capillary bed.

# FACTS

## Group members, students and collaborators

- Nina K. Iversen
- Eugenio Gutiérrez
- Anders Dyhr Sandgaard
- Anete Dudele
- Brian Hansen
- Christian Damsgaard
- Donato Sardella
- Halvor Østerby Guldbrandsen
- Ina Maria Schiessl
- Katrine Tang Stenz
- Kim Ryun Drasbek
- Lisa Ann Hald
- Luca Bordoni
- Mia Skjødt Viuff
- Sebastian Frische
- Signe Kirk Fruekilde
- Susanne Smith Christensen
- Thomas Beck Lindhardt
- Tingting Gu
- Vladimir Matchkov

## Main research strands

The group is focusing on understanding the role of microcirculatory dysfunction in the hemodynamics in health and disease, e.g.:

1. Layer-wise changes on CTH on the mouse brain cortex during functional activation.
2. Effect of carbonic anhydrase inhibitors in Alzheimer's disease.
3. The role of the microcirculation for tissue survival in the penumbral tissue after ischemic stroke
4. Microcirculatory dysfunction in diabetic neuropathy
5. Delayed cerebral ischemia after subarachnoidal haemorrhage

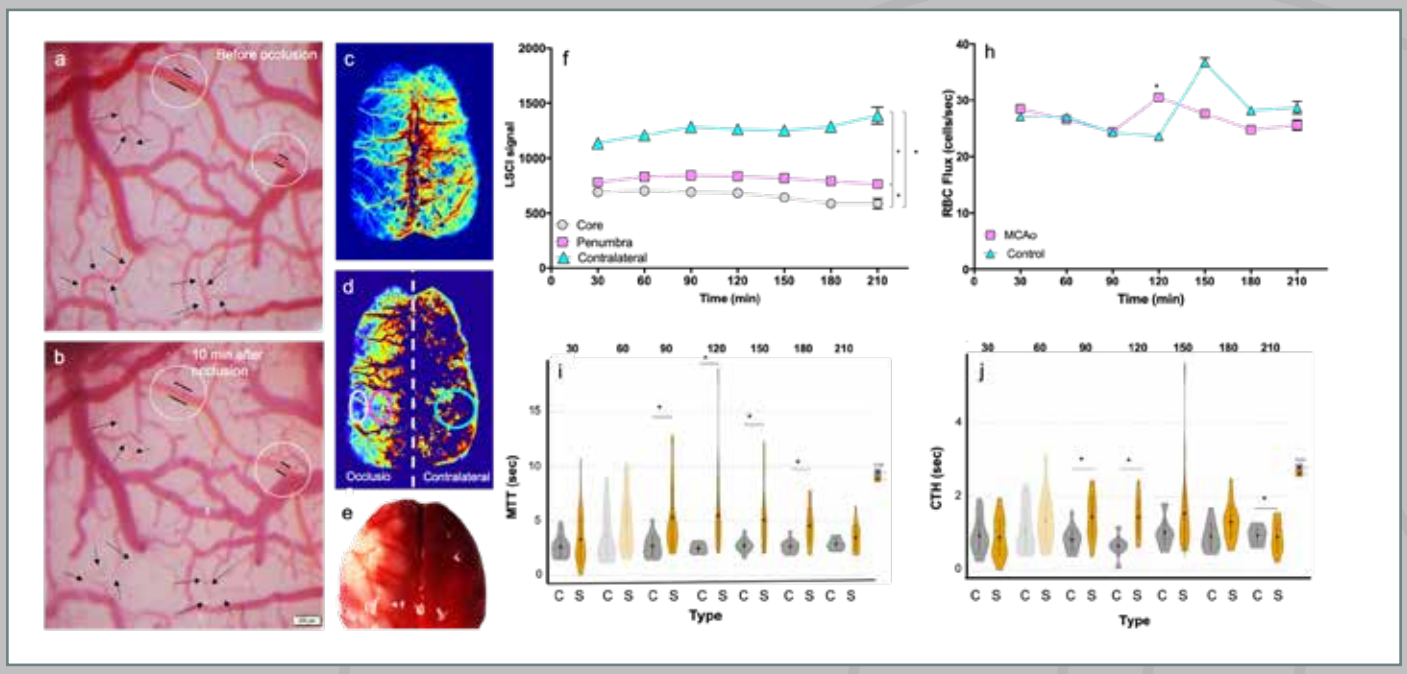



**Figure 2**
Typical light microscope images of the rat cortical vasculature (a) before and (b) 10 minutes after middle cerebral occlusion (MCAO) in a rat. Black arrows indicate small arterial branches and cortical rterioles whose diameter decrease dramatically 10 minutes after occlusion. Within the white circles, the black lines indicate the outer arterial circumference before occlusion to visualize the diameter change. The scale bar indicates 200 µm. (c) Laser speckle contrast (LSC) image after 30 min of filament occlusion. Red colors correspond to high image intensity and high blood flow, whereas blue colors represents low LSC image intensity and low perfusion. (d) The same image thresholded so only tissue with image intensity between 25-50% of the contralateral hemisphere average is shown (the white dotted line indicates midline). Penumbral tissue was identified as tissue with LSC image intensity between 25 and 50% of contralateral tissue (pink) and infarct core (grey) as tissue with image intensity less than 25% LSC image intensity compared to a contralateral tissue. The core area was further verified by 2,3,5-Triphenyltetrazolium chloride (TTC) staining of the intact brain (e), where the white tissue shows the core 4h following MCA occlusion. The contralateral region of interest (turquoise) encircles the mirror-regions of the two, relative to the mid line (dotted while line). (f) LSC image intensity signal as a function of time for the core, penumbra, and contralateral mirror region. Asterisk indicates statistical significance between the three areas. (g) Red blood cell (RBC) kinetics measured by two photon microscopy (TPM) line scanning of 530 individual penumbral capillaries (270 in control animals, 260 in MCAo, n= 8 for each group) every 30 min after filament occlusion provided estimates of capillary diameter, (h) RBC flux, and (i) RBC velocity (i). Asterisk indicates statistical significance ($p < 0.0001$) by two-way ANOVA test and Tukey multiple pairwise comparisons test.

Combining measurements of intra-vascular $PO_2$ and measurements of MTT and CTH with an indicator-dilution technique (Gutiérrez-Jiménez et al., 2016), we are currently working to examine the role of CTH on oxygen extraction in the brain as modeled by our colleagues Sune Jespersen and Leif Østergaard (Jespersen & Østergaard, 2012).

## Stroke

The estimations of $PO_2$ can also be performed on brain tissue. This technique is currently being employed in characterizing the effect of an altered capillary blood flow pattern during acute ischemic stroke (AIS), which is a frequent cause of death and adult disability. The acute management of AIS patients targets the ischemic penumbra, which is characterized as hypoperfused, electrically silent brain tissue, which can be salvaged by restoring blood flow during the first, critical hours after symptom onset. Neuroimaging studies in AIS patients suggest that penumbral tissue is characterized not only by hypoperfusion, but also by microvascular flow disturbances that strongly affect tissue outcome, independent of blood flow (Thorbjørn Engedal, JCBFM, 2019). Nina K. Iversen has recently demonstrated that microvascular flows grow increasingly chaotic in the ischemic penumbra in the hours after middle cerebral artery occlusion in a rat model of AIS (see Figure 2 and 3). Biophysical models suggest that these disturbances are accompanied by increasing hypoxia. Understanding this mechanism is crucial for discovering future treatment targets to improve the outcome for acute stroke patients.

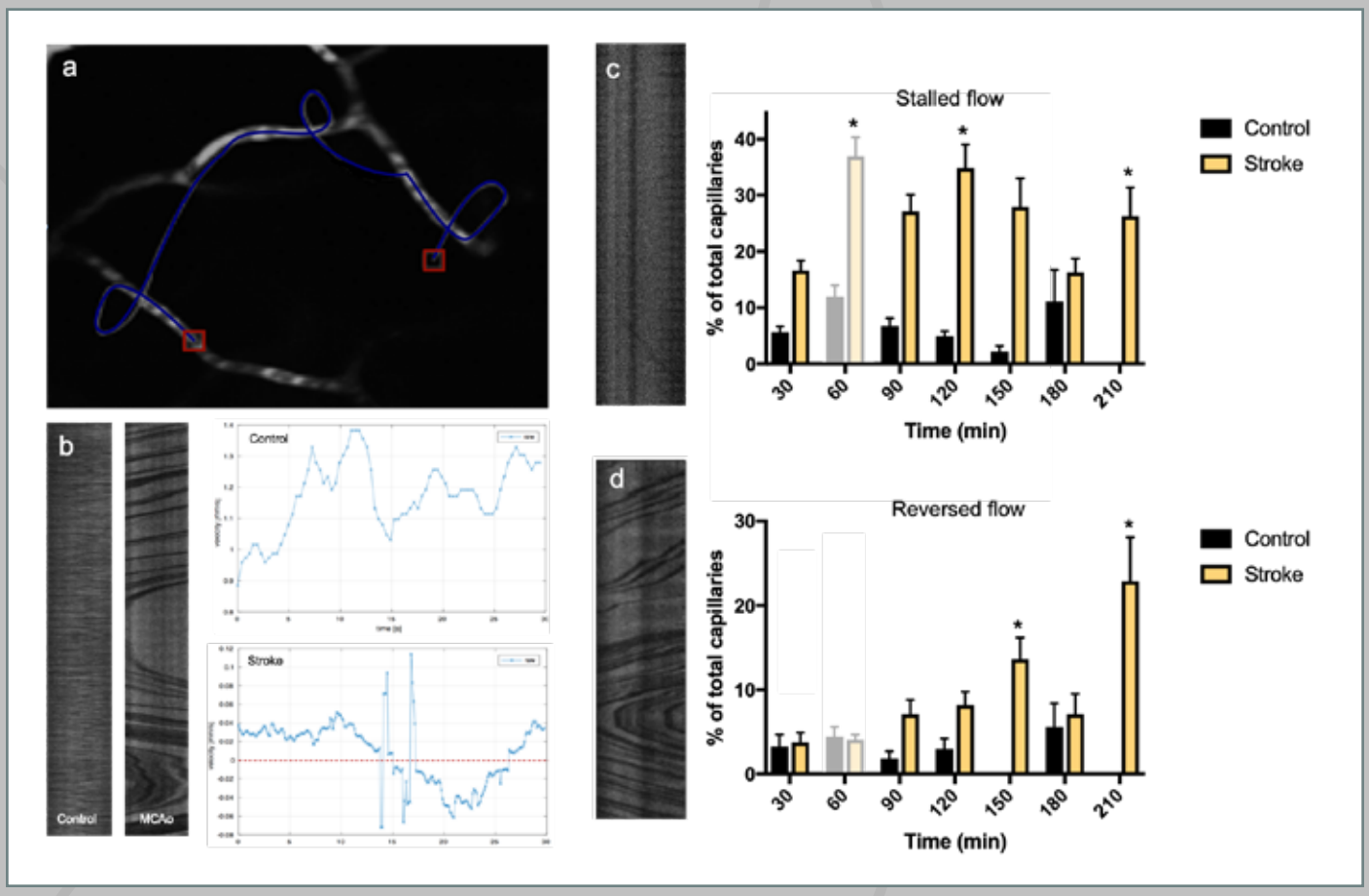



**Figure 3**

Using two-photon line scanning, 530 capillaries were scanned (270 in control animals, 260 in penumbral tissue of MCAO in the depth range between 100-250 m. Twenty-five capillaries were excluded from further analysis as the analysis yielded unrealistic cell densities (in excess of 300 cells/mm. (a) Typical line scanning trajectory. Injected FITC makes plasma appear bright while individual red blood cells (RBCs) can be observed as dark shadows within the vessel lumen. Two scan paths were prescribed for each capillary; one along the axis for RBC velocity estimation, and one transversal scan for RBC flux and capillary diameter assessment. (b) Typical line scan data for cortical capillaries in control animal and penumbral tissue of an MCAO animal, respectively. The corresponding, 30-second velocity profiles are shown for the control animal capillary (top) and a capillary within penumbral tissue (bottom). Note that RBC flow direction changes during the 30 second observation period (red dotted line indicates zero velocity). (c) shows the percentage of penumbral capillaries with such 'chaotic' behaviour as a function of the duration of ischemia. Note how the percentage of capillaries with reversing flows remains constant in normal tissue but increases dramatically in penumbral capillaries. (d) shows (left) the line scan of a capillary with stalled flow (flux=0) and (right) the percentage such capillaries represented of the total number of scanned capillaries for control and penumbral tissue over time. Asterisk denotes statistically significant difference ($p<0.05$).

## Alzheimer's Disease

During 2018, Eugenio Gutiérrez received a grant from Alzheimer's Foundation (~175,000 USD) for a project to examine the effect of a novel treatment on an animal model of Alzheimer's disease (AD). AD is the most common cause of dementia, and it has a projected incidence of 100,000 people by 2015 (Scheltens et al., 2016). It is characterized by the accumulation of the misfolded protein Amyloid-beta (Aβ) and the axonal protein Tau, and by the presence of microvascular impartment (Østergaard et al., 2015; Scheltens et al., 2016).

Currently there is no long-term treatment to prevent or revert the symptoms in AD patients. In search of new therapies, carbonic anhydrase inhibitors (CAIs) are considered a potential treatment since *in vitro* experiments have shown them to reduce cellular death caused by the accumulation of the fore-mentioned proteins (Fossati et al., 2016).

This group of drugs has well-known vascular effects (Aamand et al., 2009), thus we designed a set of experiments to evaluate the possible improvement that the CAIs may induce on brain hemodynamics and oxygenation of a transgenic

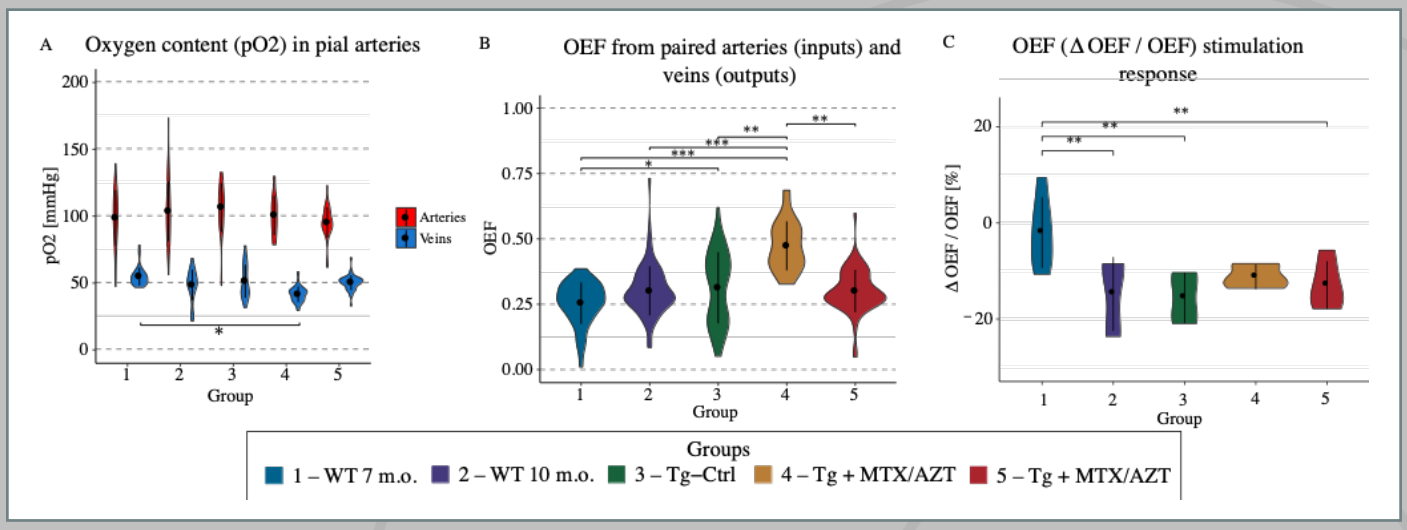



**Figure 4**
OEF in Alzheimer's disease anima model Tg-SwDI treated with carbonic anhydrase inhibitors. We assume the arterial network supplies oxygenated blood and oxygen to the deeper layers of the area scanned, whereas veins collect the deoxygenated blood coming from those layers. (B) No significant differences between groups were observed on neither of the vessel networks. (C) Pairing arteries and veins, we estimated the OEF of each mouse. We observed that during steady-state, all transgenic groups, except for G4, showed an increased OEF, which is a sign of reduced tissue oxygen tension. When testing for equality of G4 with G1 and G2, we observed that G4 as a similar response as observed in G2. (D) During functional activation, the expected reduction in OEF was observed in all groups; however, the decrease was significantly larger in G2, G3, and G5 as compared to G1. Error bars: Mean ± S.E.M. P-values: * = $p \leq 0.05$; ** = $p \leq 0.01$; *** = $p \leq 0.001$.

model of AD. The optical imaging techniques were all performed on awake mice. After the first two batches of experiments, we performed a preliminary statistical analysis on the male mice group which comprise five different subgroups. This analysis was presented at the Alzheimer's Association International Conference 2019, in Los Angeles, CA, USA. In this analysis, we observed that the treated groups (G5 - MTZ/AZT) showed a similar oxygenation response to functional activation as the young and middle age WT mice. We also observed that the OEF was significantly higher in non-treated Tg-SwDI mice and in one treated group as compared with the young WT mice (see Figure 4).

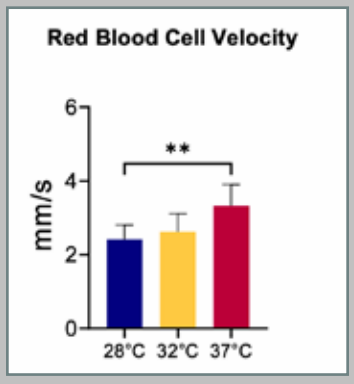



**Figure 5**
Red Blood Cell Velocity.

An increased OEF in steady-state conditions suggest a decreased absolute CBF. These observations indicate that one of the treatments might recover the vascular impairment observed in the disease, improving oxygen diffusion and metabolism in brain tissue. The project also involves estimations of CTH and MTT by indicator-dilution techniques, OCT angiograms of estimation of capillary density and capillary stalls, proteomic analysis from brain tissue, plasma, and cerebrospinal fluid. We estimate to have the full set analysis ready by the end of 2020.

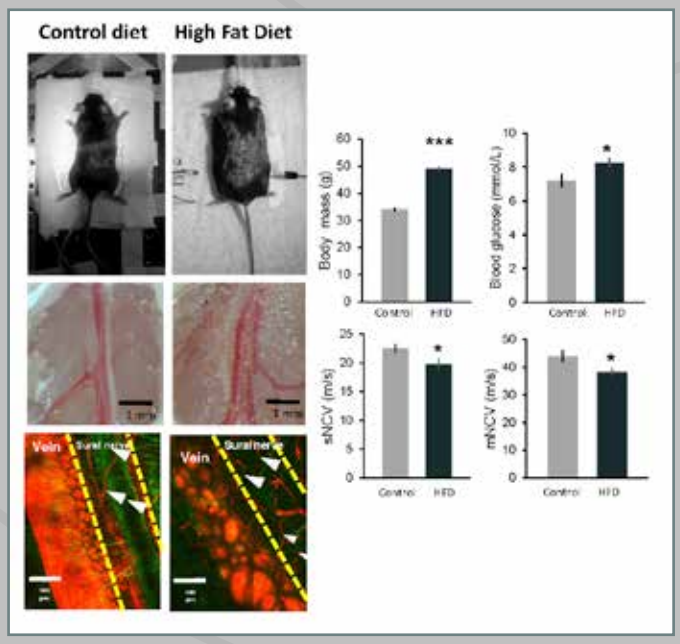



**Figure 6**
Mouse model of diet induced obesity.

## Diabetic Neuropathy

In addition to the brain pathology and hemodynamic research, we have recently established an approach to assess microvascular perfusion and function in peripheral nerves of mice. Our first studies have shown that local limb temperature affects peripheral nerve perfusion in mice, and it is therefore of crucial importance to keep the peripheral nerve within physiological range of temperatures during experiments (see Figure 5).

Susanne Smith Christensen in the training lab with mouse. Photo: Tonny Foghmar, AUH Foto

We have further applied this approach to study the role local microvascular dysfunction plays in development of diabetic peripheral neuropathy in animal models. For this, we established a working mouse model of diet induced obesity in our lab. These mice develop obesity, type 2 diabetes, and, consequently, diabetic peripheral neuropathy (see Figure 6). In addition, they display increased perivascular fat deposition. We are currently working on characterizing microvascular function and tissue oxygenation in peripheral nerves of these mice using two photon *in vivo* microscopy.

This study is supported by the Novo Nordisk Foundation.

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## NEW FACES at CFIN

**Christian Damsgaard**, joined CFIN in November 2019 as a postdoctoral researcher cosupervised by Nina Kerting Iversen (Pre-clinical Optical Group) and Tobias Wang (Section for Zoophysiology).

He received his PhD in comparative physiology from Aarhus University in 2016, where he combined biomedical imaging techniques, hemoglobin characterization, and phylogenetics to show how improvements in retinal oxygen delivery supported the evolution of improved vision across vertebrates.

His postdoctoral project seeks to uncover the physiological mechanisms that supply oxygen to the bird retina using *in vivo* two-photon microscopy. The bird retina has an exceptionally high metabolic rate but lacks an internal microcirculation, and, therefore, it may provide insight into novel mechanisms to improve oxygen supply to neural tissues.

**Halvor Guldbrandsen**, BSc.

Halvor joined CFIN in February 2020 as a research year student supervised by Nina Kerting Iversen.

He recently received his Bachelor's degree in medicine from Aarhus University, and his focus is on vascular physiology in cerebral tissue.

Halvor's current project aims to investigate the role of penumbral arterioles in late cerebral ischemia following stroke. In this project he will use stroke mice models, laser speckle imaging and myography to evaluate the behaviour of arterioles within the penumbra after ischemic stroke.

# MCN Lab

## CFIN Molecular and Cellular Neuroscience Laboratory

by Kim Ryun Drasbek

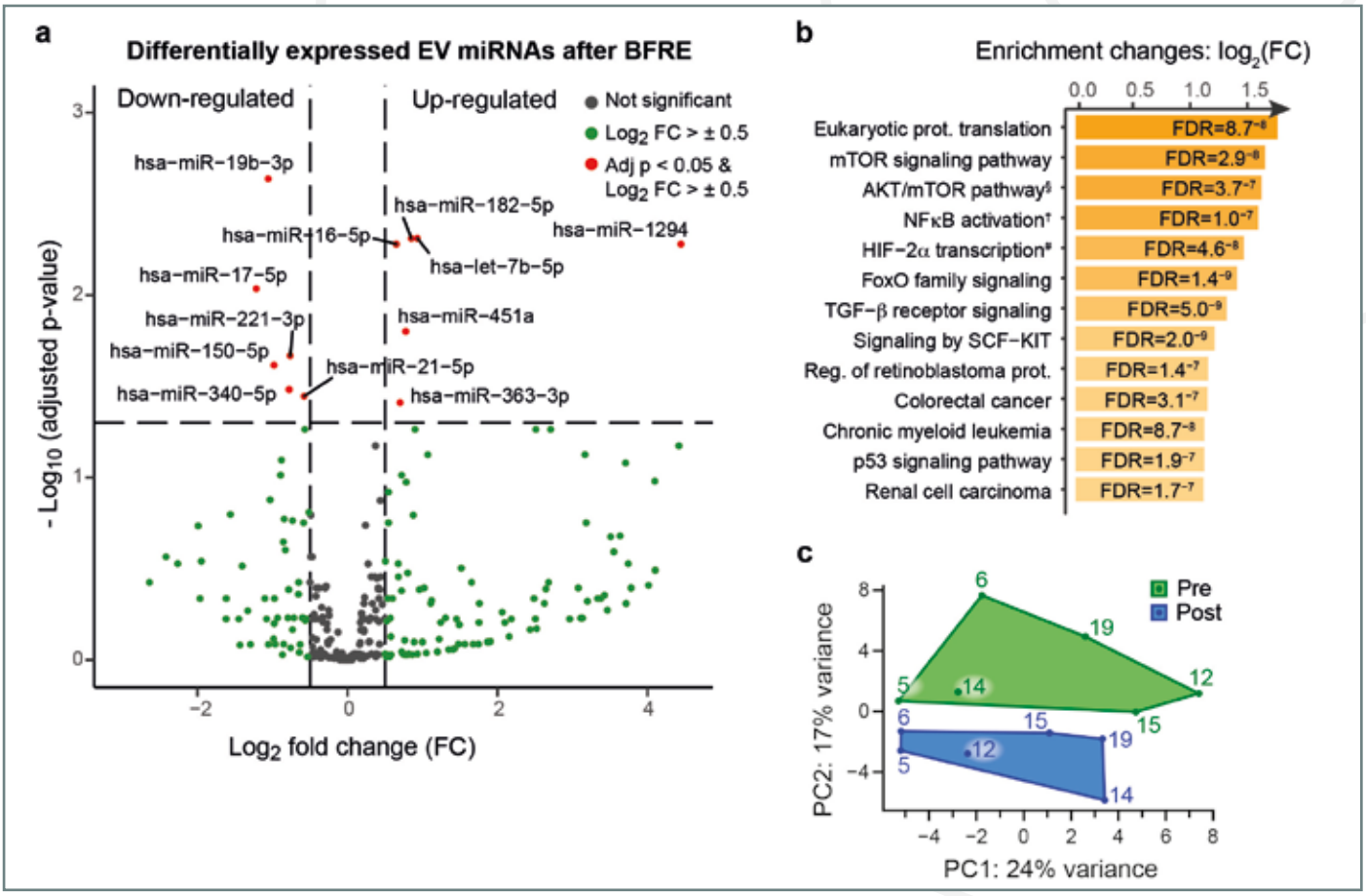
Understanding ischemic diseases such as stroke and acute myocardial infarction (AMI) is the focus of the Molecular and cellular neuroscience lab (MCN Lab) at CFIN. In addition, the lab studies the effect of inflammation during stroke and how that impacts brain activity controlled cerebral blood flow changes. The lab uses a multitude of molecular techniques in combination with cellular assays and animal models.

Several of the projects in the lab is conducted as part of a large Novo Nordisk Synergy project, Conditioning based intervention strategies (ConBIS) that investigates the molecular response to different interventions in relation to stroke and AMI. This consortium facilitates the collaboration with researchers at CFIN, AU, Cardiology, AUH, iNANO, AU, Sport Science, AU and Medical Gastroenterology, OUH.

Specifically, in this project we study and compare the molecular effects of remote ischemic conditioning (RIC), blood-flow restricted exercise, (BFRE) and traditional resistance training (TRT) as all of them are thought to elicit protective effects on prolonged ischemic events such as stroke and AMI.

RIC is induced by repeated 5-minute periods of controlled hypoxia in e.g. the arm using an auto-RIC device or simply a blood pressure cuff, while TRT is carried out at 80% of maximum load until exhaustion. BFRE is a combination of the two other interventions. Here, exercise is performed with a tourniquet that stops the venous blood flow to the leg with a training load of only 20% of maximum and the person performs as many cycles as possible with short resting periods.

In our search for molecular signaling components in the blood, we concentrate our attention on extracellular vesicles (EVs), as they are released by many cell types, with molecular tags reflecting their origin and the state of the secreting cell. These small nanosize particles ideally function as long distance signaling carriers by virtue of their release into the blood and



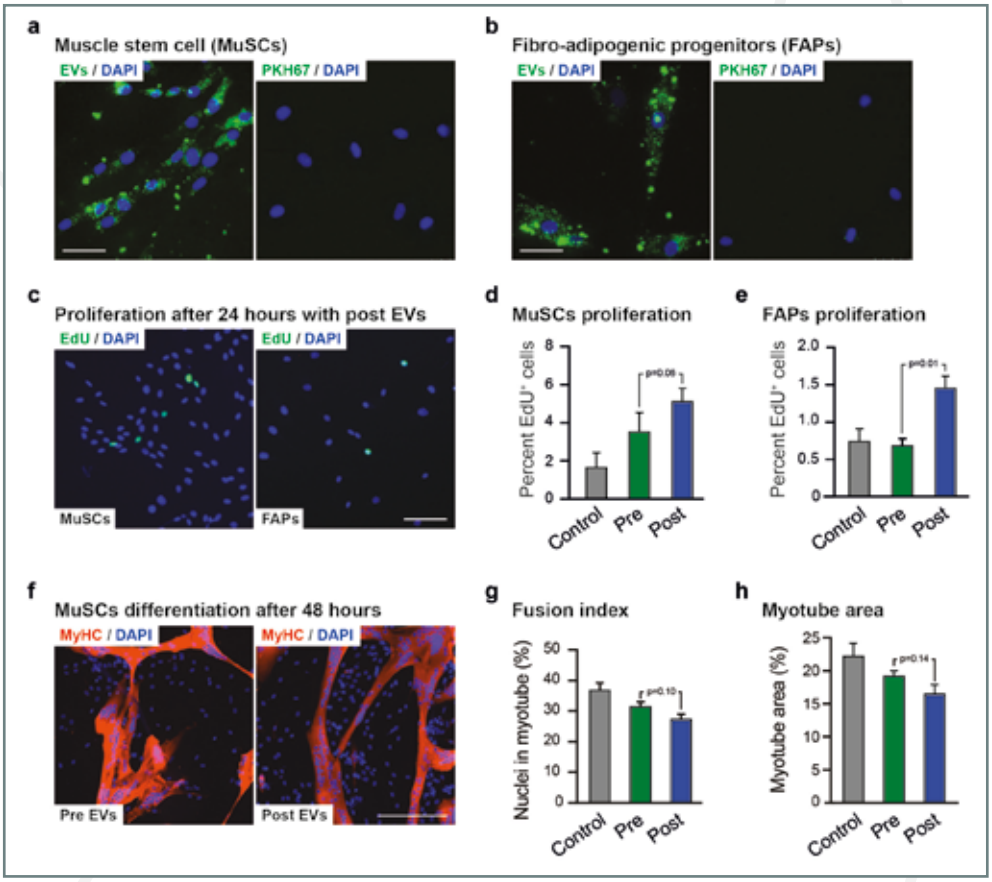



**Figure 2**
Fluorescently labelled BFRE EVs (green) were taken up by muscle stem cells (MuSCs, a) and fibro-adipogenic progenitors (FAPs, b) during 24 hours of incubation. Only a small amount of signal was observed in the negative control (PKH67 fluorescent dye only, right panel). Scalebar = 50 µm. Proliferation after 24 hours was estimated based on EdU incorporation (c) in MuSCs (d) and FAPs (e) incubated with either pre- or post-exercise BFRE EVs or non-EV control (PBS). MuSC differentiation into multi-nucleated myotubes after 48 hours when cultured with the pre- or post-exercise EVs (f). Differentiation estimations were based on the fusion index (g) (percentage of nuclei in MyHC+ (red) myotubes containing more than three nuclei) and the myotube area (h). ($1.0 \cdot 10^{10}$ EVs were added per well) (mean +/- SEM, n=6).
Illustration from Just et al. Blood flow-restricted resistance exercise alters the surface profile, miRNA cargo and functional impact of circulating extracellular vesicles. Sci Rep 10, 5835 (2020).

their ability to carry information to other organs in the body where EVs are readily taken up by other cells. Interestingly, EVs carry miRNAs that are post-transcriptional regulators and play an important role in fast cellular protein expression regulation. As each miRNA targets several proteins, they have the potential to re-program the recipient cells. Due to their biological impact on the recipient cells, miRNAs present an interesting future treatment strategy. Using bioinformatic tools, we have found several miRNAs, which are differentially expressed following the conditioning procedures in human subjects. We test the impact of EVs purified from conditioned blood and selected miRNAs in cellular assays as well as in animal models. Here, we study the effect of EV administration on infarct progression and -size in a stroke animal model as well as changes in inflammation following stroke. We also study inflammation in relation to blood flow changes and neural activity in mice, using chemogenetics to manipulate neuronal activity. Meanwhile, we use calcium imaging to visualize activity patterns in the brain using 2-photon microscopy as well as other optical techniques, in awake animal studies.

**Figure 1 (previous page)**
Next generation sequencing of small non-coding RNAs purified from EVs. Differentially expressed plasma EV miRNAs after BFRE presented as a volcano plot (a). The miRNA counts from NGS were normalised and tested for differential expression (DE) using the R Bioconductor package DESeq2, implementing a model design testing for differences between pre and post BFRE while correcting for inter-person variability. DE miRNAs (red) were considered significant with an FDR adjusted p-value < 0.05, a log2 fold-change > ±0.5 and a base mean count > 100. Under these assumptions, 12 miRNAs were differentially expressed (6 were up-regulated and 6 were down-regulated). Pathway enrichment analysis (b), showing top 15 enriched pathways from KEGG, REACTOME, BioCarta and PID collected in the MsigdbC2Pall pathway gene sets with FDR < 0.05. [§]Skeletal muscle hypertrophy is regulated via AKT/mTOR pathway. [†]NFkB activation by Non-typeable Hemophilus influenzae. PCA plot based on the counts of all detected miRNAs (c). A green (pre-samples) and blue (post-samples) polygon denotes the smallest space to contain the pre and post samples, respectively.
Illustration from Just et al. Blood flow-restricted resistance exercise alters the surface profile, miRNA cargo and functional impact of circulating extracellular vesicles. Sci Rep 10, 5835 (2020).

In 2019, we participated in the launching of the Danish Society for Extracellular Vesicles (https://www.dsev.dk) with Kim Ryun Drasbek taking the position as secretary. We formed the local organizing committee for the 1st Annual DSEV Symposium with Peter Nejsum and Anne Borup, Dept. Clinical Medicine, AU. At the symposium, vesicle researchers from all of Denmark attended with talks and poster presentations to facilitate national collaborations within this research field. The symposium concluded with a dinner in central Aarhus. The next symposium will take place at Vejle Sygehus.

DSEV
The Danish Society for Extracellular Vesicles

## NEW FACE at CFIN

**Katrine Tang Stenz**, joined CFIN in May 2018 as a PhD student in the Molecular and Cellular Neuroscience Lab, supervised by Kim Ryun Drasbek.

She received a Master's degree in Molecular Biology from Aarhus University. During her master's degree, she studied the degeneration of dopaminergic neurons in the model organism C. elegans in relation to Parkinson's disease. After her master's degree, she worked for 2 years with fertility equipment and quality control.

Katrine is now working on the project named "Beneficial effects of remote ischemic conditioning and blood flow restricted exercise in stroke", where she uses cell assays to evaluate the protective effect of Extracellular vesicles and miRNA from different conditioning methods. Part of her PhD will be conducted at the Institute of Genetics and Developmental Biology in Beijing as she is partly funded by the Sino-Danish Center for Education and Research.

## ECVs in ischemic exercise

Ischemic exercise conducted as low-load blood flow restricted resistance exercise (BFRE) can lead to muscle remodelling and promote muscle growth, possibly through activation of muscle precursor cells. Cell activation can be triggered by blood borne extracellular vesicles (EVs) as these nano-sized particles are involved in long distance signalling.

In this study, EVs isolated from plasma of healthy human subjects performing a single bout of BFRE showed changes in their surface profile and miRNA cargo as well as having an impact on skeletal muscle precursor cell proliferation. We found that after BFRE, five EV surface markers and 12 miRNAs were significantly altered. Furthermore, target prediction and functional enrichment analysis of the miRNAs revealed several target genes that are associated to biological pathways involved in skeletal muscle protein turnover. Interestingly, EVs from BFRE plasma increased the proliferation of muscle precursor cells. In addition, alterations in surface markers and miRNAs indicated that the combination of exercise and ischemic conditioning during BFRE can stimulate blood cells to release EVs.

These results support that BFRE promote EV release to engage in muscle remodelling and/or growth processes.

*Blood flow-restricted resistance exercise alters the surface profile, miRNA cargo and functional impact of circulating extracellular vesicles*

Authors: Just J, Yan Y, Farup J, Sieljacks P, Sloth M, Venø M, Gu T, Vincenzo de Paoli F, Nyengaard JR, Bæk R, Jørgensen MM, Kjems J, Vissing K, Drasbek KR. Sci Rep 10, 5835 (2020).

Jesper Just in the lab.
Photo: Tonny Foghmar, AUH Foto

# Moving South

by Henriette Vuust

CFIN and MIB researchers who did not move north to Aarhus University Hospital in Skejby, also moved out of the now former Danish Neuroscience Center at Nørrebrogade.

After 10 years in the DNC building everything was packed in hundreds of boxes and transported down hill to the former Århus Kommunehospital's oldest building - Building 1.

This building was designed by architecht Thomas Arboe in 1893 and comprised the original core of the hospital in Aarhus. The first Chief Physician, Christian Weis, two hospital doctors, four sisters, a housekeeper, a student from the Red Cross, forteen maids and three farmhands comprised the entire staff back in the end of the 19. Century. Later, the hospital grew in several stages, and Building 1 has been used for many purposes over the years - among these, it was a childrens ward for many years.

Today CFIN and MIB researchers fill the halls and former hospital rooms with new life, and we consider ourselves quite priviledged to live in the midst of the history of Aarhus. CFIN and MIB marked the move to our new South-home in June 2019 with a social event of fun and games in the beautiful old garden in front of the building.

Moving South.
Photos: STENOSELSKABET/Medicinsk Selskab for Fyn og Jylland, Vibeke Sauer Panyella, Henriette Vuust

# APPLIED IMAGING AND MODELLING

by Simon Fristed Eskildsen

The applied imaging and modelling (AIM) group investigates pathological and developmental brain changes by combining both conventional and novel imaging techniques with sophisticated analysis methods. The AIM group is involved in several studies on neurodegenerative diseases, such as Alzheimer's disease and multiple sclerosis. One of the group's focus areas is to study and improve imaging biomarkers of the brain. In 2018 and 2019, the group worked on furthering the understanding of white matter hyperintensities[1] and validating structural connectivity[2], which are both widely used MRI based biomarkers. Within neurodevelopmental research, the AIM group is involved in understanding the effect of congenital heart disease on microscopic and macroscopic brain abnormalities.

## Alzheimer's disease

In our collaboration project on Alzheimer's disease (AD) with the PET-Centre at Aarhus University Hospital, we are working to uncover the pathogenesis of the disease and

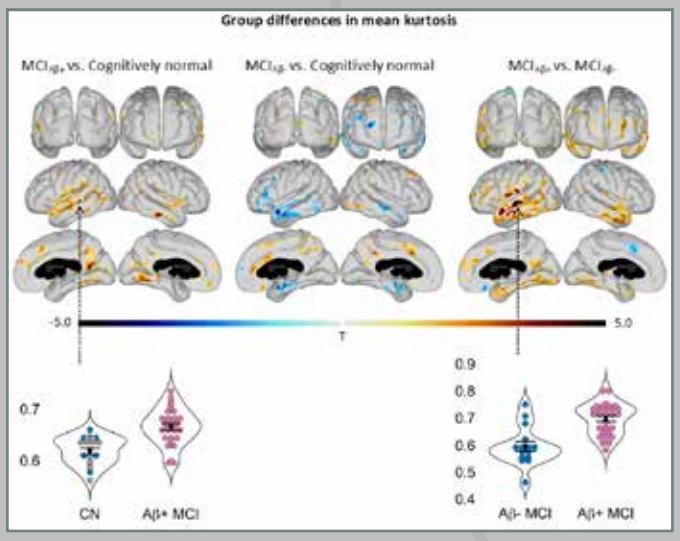



**Figure 1**
Statistical t-maps of significant (p<.05) differences in cortical mean kurtosis between patients with mild cognitive impairment (MCI) and healthy controls and between subgroups of MCI patients. Negative t-values indicate decreases (blue nuances), while positive t-values indicate increases (red nuances) in patients. The white outlining marks clusters surviving family-wise error correction for multiple comparisons (p<.001). Age-adjusted region of interest mean values from clusters, as indicated with the black arrows, are shown in the lower panel, including mean (black dot) and standard error of the mean (whiskers). Patients were sub-grouped as amyloid positive (Aβ+) or amyloid negative (Aβ-) based on their 11C-PiB (Pittsburgh Compound B) status, defined by an atlas based composite regional 11C-PiB SUVr (standard uptake value ratio) >1.5 and ≤1.5, respectively. Statistics were adjusted for age using linear regression. From Nielsen et al. 2020.[5]

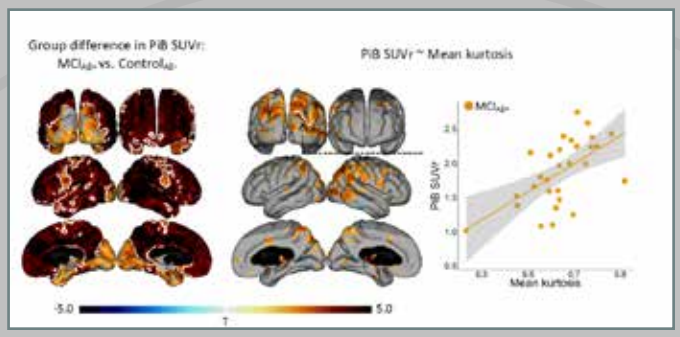



**Figure 2**
Statistical t-value maps showing significant (p<0.05) differences in PiB SUVr and vertex-wise linear correlation between mean kurtosis and PiB SUVr, in amyloid positive (Aβ+) patients with mild cognitive impairment (MCI) adjusted for age. Negative t-values indicate decrease in Aβ+ MCIs or negative correlation (blue nuances), while positive t-values indicate increase in Aβ+ MCIs or positive correlation (red nuances). The white outlining marks clusters surviving family-wise error correction for multiple comparisons (p<.001). From Nielsen et al. 2020.[5]

investigating MRI biomarkers of disease progression. PhD student Rune Bæksager Nielsen studied both clinically diagnosed AD patients and individuals suffering from mild cognitive impairment (MCI), a condition typically preceding a clinical diagnosis of AD. In the fall 2018, Rune successfully defended his PhD. During his studies, Dr. Nielsen showed that vascular impairment is a key element in AD and reported disturbances in the brain's microcirculation of both diagnosed AD patients[3] and of individuals with MCI suspected of AD[4]. Then, he went on to study the application of diffusion weighted MRI (DWI) for detecting cellular injury caused by cerebral protein deposits, such as amyloid and tau, in the prodromal phase of AD[5]. Sensitive imaging biomarkers are crucial to improve our understanding of AD's preclinical phases, and to offer early, preventative therapies to patients. DWI is sensitive to the micrometer-scale Brownian motions of water molecules, and thereby to tissue microstructure as these water molecules collide and interact with cell membranes and organelles. In the study, Dr. Nielsen calculated mean diffusivity (MD) and mean kurtosis (MK) from the DWI to characterize the microstructure of the cerebral cortex. MD measures the degree of diffusion, while MK informs about the deviation from free diffusion and may potentially provide additional sensitivity towards early erratic loss of cells, dendrites and axons in AD. In 29 patients with prodromal AD, characterized by MCI and a positive amyloid PET scan, Dr. Nielsen found significantly higher MK in the left temporal lobe compared to 23 cognitively normal controls and compared to 15 MCI patients with a negative amyloid PET scan (suspected non-AD pathology) (see Figure

1). Higher MK was associated with higher load of amyloid (see Figure 2), while MD was primarily associated with age. The microstructural changes observed with MK may reflect toxic effects of amyloid pathology in the prodromal phase of AD. This indicates that diffusion kurtosis imaging is a potential biomarker of Alzheimer's disease bridging the gap between protein and atrophy markers in the brain.

### White matter hyperintensities

Cerebral white matter hyperintensities (WMHs), often referred to as white matter lesions, are frequent findings on T2-weighted magnetic resonance imaging (MRI) in the elderly, with a reported prevalence of up to 95% in large population-based studies of people aged 60–65 and older. Once considered an incidental finding, increasing evidence show that the presence and extent of WMHs play an important role in cognitive and functional impairment. Higher prevalence of WMHs are associated with increased risk of stroke, dementia, late-life depression and death. The pathogenesis of WMHs is complex and not yet fully established. In general, WMHs are considered a marker of cerebral small vessel disease (SVD). SVD may result from a range of pathological processes that affect the small arteries, arterioles, capillaries, venules and small veins of the brain. In particular, the involvement of capillaries are thought to result in disturbed blood brain barrier permeability and transient, repeated episodes of white

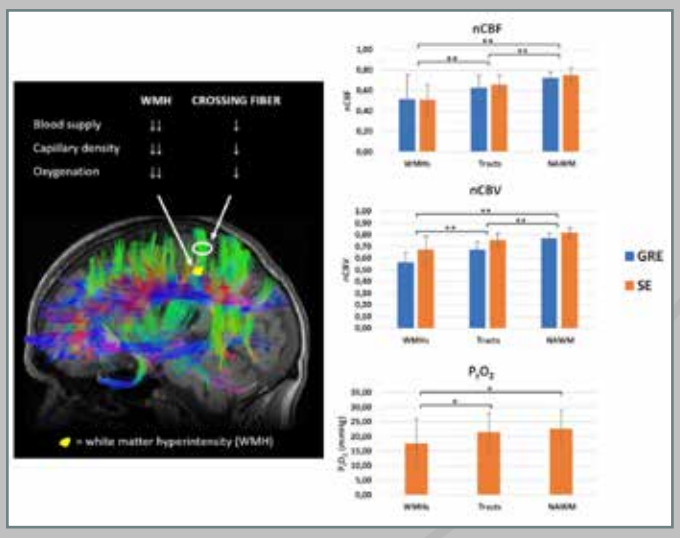



**Figure 3**
Perfusion in white matter hyperintensities (WMHs). Compared to normal appearing white matter, WMHs have reduced blood flow, blood volume and oxygenation. Fibers (tracts) crossing WMHs follow the same pattern, but to a lesser extent. From Dalby et al. 2019.[1]

# FACTS

## Core group members

- Simon Fristed Eskildsen, Head of Group
- Rune Bæksager Nielsen, Postdoc
- Robert Dahnke, Postdoc
- Mikkel Karl Emil Nygaard, PhD student
- Lasse Stensvig Madsen, PhD student

## Affiliated group members

- Leif Østergaard
- Torben Ellegaard Lund
- Sune Nørhøj Jespersen
- Brian Hansen
- Kim Mouridsen
- Jakob Udby Blicher
- Irene Klærke Mikkelsen
- Erhard Næss-Schmidt
- Rikke Dalby
- Benjamin Asschenfeldt
- Martin Langeskov-Christensen

matter hypoperfusion, perivascular alterations, and eventually demyelination, loss of oligodendrocytes, and axonal damage. Given the evidence of capillary changes in SVD[6]; Dr. Rikke Dalby and the AIM group set out to investigate capillary function and predicting oxygen availability within WMHs. In the study, we used structural, perfusion- and diffusion-weighted MRI from 21 patients with late-onset depression and 21 controls. WMHs were manually outlined and white matter tracts intersecting WMHs were found using tractography. Using dynamic susceptibility contrast perfusion MRI and CFIN's advanced methods for estimating hemodynamic parameters at the microscopic level[7], we showed that WMHs have lower blood flow and blood volume than normal-appearing white matter, resulting in reduced tissue oxygen tension (see Figure 3). Tracts intersecting WMHs showed a similar pattern of lower blood flow, blood volume and tissue oxygen tension compared to normal-appearing white matter, but to a lesser extent[1]. We speculate that aging and vascular risk factors impair WMH perfusion and capillary function to create hypoxic tissue injury, which in turn affect the function and metabolic demands of the white matter tracts they disrupt. This finding may aid in understanding the impact of WMHs in neurological diseases and normal aging.

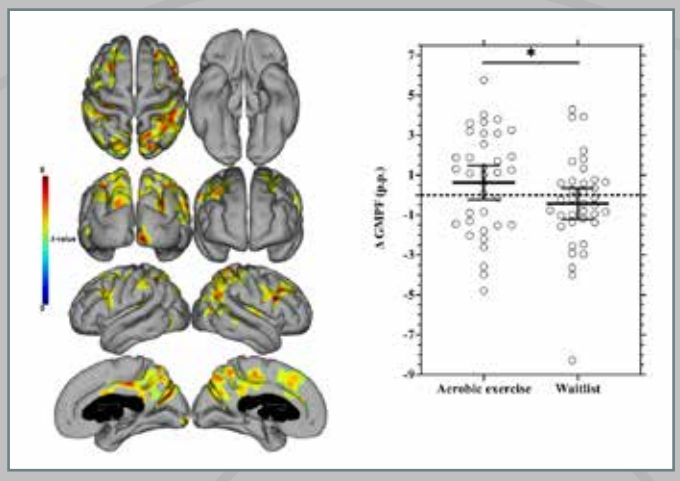



**Figure 4**
MRI biomarkers and effects of aerobic exercise in multiple sclerosis (MS) patients. Left: Performance of the six-spot step test correlates with mean diffusivity in a cohort of relapsing-remitting MS patients (n=75). From Nygaard et al. (2020)[8]. Right: Grey matter parenchymal fraction changes over 24 weeks in MS patients performing high-intensity aerobic exercise (n=43) and a matched groups of MS patients continuing their habitual lifestyle (n=43). From Langeskov-Christensen et al. (2020)[9].

## Multiple sclerosis

In collaboration with Sport Science at Department of Public Health, we examined effects of high-intensity aerobic exercise on MRI-derived markers of neuroplasticity in a cohort of multiple sclerosis (MS) patients. Eighty-six MS patients were enrolled in a randomized, controlled, phase 2 trial. Baseline measurements showed clear correlations between physical performance and MRI diffusivity in the cerebral cortex[8] (Figure 4, left). After 24 weeks of high-intensity aerobic exercise, the cardiorespiratory fitness in the exercise group improved 14% and zero relapses were detected. We found significant increase in grey matter parenchymal fraction (GMPF) compared to a placebo group[9] (Figure 4, right). This effect was not detectable on whole brain using the widely used SIENA tool. This is however not surprising as we, in another study, showed that the sample size per arm for SIENA measurements should be more than 150 to detect significant annualized percent brain volume change[10]. Dr. Martin Langeskov-Christensen, who successfully defended his PhD in the fall 2019, carried out the study on aerobic exercise in MS. The results from the study hold promise of exercise as a potential neuroprotective intervention in multiple sclerosis.

## Congenital heart defects

Children born with a heart defect have greater risk of neurodevelopmental impairments affecting cognitive and social functions and mental health. Benjamin Asschenfeldt from the Department of Cardiothoracic & Vascular Surgery, Aarhus University Hospital examined 66 adult patients with a congenital heart defect (CHD) who underwent childhood surgery for isolated atrial septal defect (n=34) or ventricular septal defect (n=32). These were examined by a standard battery of neuropsychological tests and brain MRI and compared to healthy matched peers (n=40). Benjamin worked with the AIM group to analyse the data and found the total and regional brain volumes of CHD patients to be smaller than the volumes of controls without reaching statistical significance after correcting for multiple comparisons. However, CHD patients had significant impairments, with lower scores on full-scale intelligence quotient, verbal comprehension, perceptual reasoning, and working memory compared with controls. In addition, the CHD group had poorer visuospatial abilities, verbal memory, executive function, and social recognition compared with controls. The study shows that children operated for simple CHD have poorer neurodevelopmental outcomes in adulthood when compared with healthy

controls and expected population means. The study was published in Journal of the American Heart Association[11] with an editorial comment[12]. The AIM group continues the collaboration with Benjamin Asschenfeldt and Vibeke Hjortdal to investigate whether CHD patients' brains are affected on the microstructural level using diffusion MRI.

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# FACTS

## National & International collaborators

- Professor David J. Brooks, Positron Emission Tomography Centre, Aarhus University Hospital
- Professor Vibeke Hjortdal, Department of Cardiothoracic Surgery, Rigshospitalet
- Professor Thomas Thymann, Department of Veterinary and Animal Sciences, University of Copenhagen
- Professor Ludvig Muren, Department of Medical Physics, Aarhus University Hospital
- Associate Professor Kenneth Jensen, Danish Center for Particle Therapy, Aarhus University Hospital
- Associate Professor Ulrik Dalgas, Department of Public Health - Sport Science, Aarhus University
- Associate Professor Tim Dyrby, Diffusion Imaging Group, Danish Research Centre for Magnetic Resonance
- Dr. Tanja Sikjær, Department of Endocrinology and Diabetes, Aarhus University Hospital
- Dr. Per Qvist, Department of Biomedicine, Aarhus University
- Dr. Lars Evald, Hammel Neurorehabilitation Centre and University Research Clinic
- Professor Louis Collins, McConnell Brain Imaging Center, Montreal Neurological Institute, McGill University
- Professor Ellen Grant, Fetal-Neonatal Neuroimaging and Developmental Science Center, Children's Hospital Boston
- Professor Nicola Pavese, Clinical Ageing Research Unit, Newcastle University
- Professor Risto Kauppinen, School of Experimental Psychology, University of Bristol
- Professor Christian Gaser, Structural Brain Mapping Group, University of Jena
- Professor José Manjon, Instituto de Aplicaciones de las Tecnologías de la Información y de las Comunicaciones Avanzadas (ITACA), Universitat Politècnica de València
- Dr. Pierrick Coupé, Laboratoire Bordelais de Recherche en Informatique, Université de Bordeaux
- Dr. Anna Tietze, Institute of Neuroradiology, Charité Universitymedicine, Berlin
- Dr. Eduardo A. Garza-Villarreal, Institute of Neurobiology (INB), UNAM campus Juriquilla, Querétaro

## Events

- Visit by Professor Jose Manjon and Dr. Pierrick Coupé, April 2018
- FIOL meeting at oncology, April 2018, Invited talk, Simon Eskildsen
- MICCAI conference, Granada, September 2018, Simon Eskildsen
- Invited talk at Neurological Department, October 2018, Simon Eskildsen
- Rune's defense, November 2018
- Brain Prize meeting 2018, Lasse Madsen and Simon Eskildsen
- PhD Day 2019, Simon Eskildsen (Chairman)
- Visit by Dr. Anna Tietze, February 2019
- Brain Prize meeting 2019, Robert Dahnke and Simon Eskildsen

## NEW FACE at CFIN

**Mikkel Karl Emil Nygaard**, MSc (Biomedical Engineering), PhD Student.

Mikkel joined CFIN in as Research Assistant in September 2018 after completing his Master in collaboration with CFIN and Section for Sport Science, Aarhus University. During his master's studies, he investigated the relationship between cortical GM diffusion kurtosis imaging (DKI) and cognitive and physical performance in patients with multiple sclerosis (MS). The results suggest, that abnormalities in cortical GM DKI reflects both cognitive and physical performance.

As Research Assistant, he has been working with segmentation, DKI and perfusion while trying to fund his interdisciplinary PhD project in collaboration with Section for Sport Science, Aarhus University. In January 2020, the project was completely funded and thus Mikkel was enrolled as PhD Student in February 2020.

The aim of Mikkel's project is to identify magnetic resonance imaging markers capable of quantifying disease severity and exercise-induced neuroplasticity in patients with MS and Parkinson's disease.

## NEW FACE at CFIN

**Lasse Stensvig Madsen**, MSc in Biomedical Engineering.

Lasse completed his Master in January 2019 at Aarhus University. His master's thesis was conducted in collaboration with CFIN in a project aiming to utilize machine learning in order predict the development of different biomarkers in early Alzheimer's disease (AD). During his Master, Lasse was also employed as a student worker at CFIN, working on hippocampus subfield segmentation.

After completing his Master, he was employed as a Research Assistant at the Department of Nuclear Medicine and PET-Centre at Aarhus University Hospital. Here, he worked on a project involving subjects with mild cognitive impairment (MCI), a prodromal stage of AD. Subjects had multiple PET and MRI scans, including DCS-MRI to evaluate cerebral perfusion. Results from this study suggest that capillary dysfunction plays an important role in the early development of AD.

Lasse is now a PhD student on a project aiming to evaluate AD pathology in asymptomatic elderly APOE4 carriers with raised cortical amyloid deposition. His focus will be on analyzing perfusion MRI and PET scans in order to determine how capillary dysfunction, cortical amyloid deposition and neuroinflammation is affected at the preclinical stage of AD. This study will resolve if findings from the MCI study can be detected at an even earlier disease stage. The PhD study is conducted in a close collaboration between the PET-Centre and CFIN.

## NEW FACE at CFIN

**Robert Dahnke** is a guest researcher from the Jena University in Germany.

Robert is working on an enhanced gyrification index to describe cortical folding. His research focuses on the development of computational tools for the analysis of structural brain data that are mostly integrated in the Computational Anatomy Toolbox (CAT) of the Statistical Parametric Mapping (SPM) software. In particular, he is intensively involved in the development of algorithms and tools for processing voxel- and surface-based imaging data, including segmentation, spatial registration, surface reconstruction, cortical measures, and image quality control in humans but also other primates.

Besides brains he is also interested in art drawing and painting people and landscapes - and seeking models.

Robert can be reached at robert.dahnke@uni-jena.de

# FACTS

### Selected research projects

- Magnetic resonance imaging biomarkers in Alzheimer's disease: investigating capillary dysfunction and neurodegeneration for diagnosis and prediction. Rune B. Nielsen, Simon F. Eskildsen, Leif Østergaard.
- The relationship between Aβ, inflammation and capillary dysfunction in amnestic mild cognitive impairment. Peter Parbo, Rola Ismail, Simon Eskildsen, Nicola Pavese, Leif Østergaard, David Brooks.
- The temporal and spatial inter-relationships between β-amyloid deposition, tau tangles, inflammation, and cognition in elderly subjects with preclinical Alzheimer's disease and the influence of the noradrenergic system. Pernille L. Kjeldsen, Lasse S. Madsen, Malene F. Damholdt, Joel F. A. Aanerud, Simon F. Eskildsen, David J. Brooks.
- Is vascular injury a herald of Alzheimer's disease? Investigating in vivo the relationship of cerebral microcirculation to amyloid, tau deposition, and to inflammation in preclinical cases. Lasse S. Madsen, Pernille L. Kjeldsen, David J. Brooks, Leif Østergaard, Simon F. Eskildsen.
- Cerebral perfusion in patients with late-onset major depression. Rikke B. Dalby, Simon F. Eskildsen, Poul Videbech, Leif Østergaard.
- Cortical thickness and structural connectivity in the Vervet monkey brain. Simon F. Eskildsen, Henrik Lundell, Tim Dyrby.
- The implication of the schizophrenia-associated gene, BRD1, in behavior, cognition and brain development in genetically modified mice. Per Qvist, Steffen Ringgaard, Simon F. Eskildsen, Jens R. Nyengaard, Gregers Wegener, Jane H. Christensen, Anders Børglum.
- Effects of aerobic exercise on brain health in multiple sclerosis. Martin Langeskov Christensen, Simon Eskildsen, Ulrik Dalgas.
- Brain Matters in Heart Matters – from early fetal development. Mette Høj Lauridsen, Steffen Ringgaard, Simon Eskildsen, Vibeke Hjortdal.
- Magnetic resonance imaging biomarkers of disease severity and impact of exercise training in neurodegenerative diseases. Mikkel K. E. Nygaard, Martin L. Christensen, Ulrik Dalgas, Louis Collins, Simon F. Eskildsen.
- Quantification of cerebral gyrification in the primate brain. Robert Dahnke, Christian Gaser, Simon F. Eskildsen.
- The effect of congenital heart disease on cerebral function and comorbidity in adult-hood. Benjamin Asschenfeldt, Lars Evald, Johan Heiberg, Leif Østergaard, Simon F. Eskildsen, Vibeke Hjortdal.
- Impaired Quality of Life and cognitive function in patients with hypoparathyroidism might be explained by disturbed capillary flow patterns in the brain. Tanja Sikjær, Lars Evald, Simon F. Eskildsen, Leif Østergaard, Line Underbjerg, Lars Rejnmark.
- Bioactive formula to improve gut, immunity and brain development in preterm pigs. Karina Obelitz-Ryom, Steffen Ringgaard, Sune Nørhøj Jespersen, Anders Brunse, Simon F. Eskildsen, Thomas Thymann.
- Image-based biomarkers for radiation-induced brain damage in pediatric brain tumors. Laura V. Toussaint, Oscar Casares-Magaz, Simon F. Eskildsen, Ludvig P. Muren.
- Cross Sectional Study of Late Toxicity after Intensity-Modulated Radiotherapy for Sinonasal Cancer. Maja B. Sharma, Kenneth Jensen, Ali Amid, Simon F. Eskildsen, Cai Grau.
- Cerebral microcirculation in isolated rapid eye movement sleep behaviour disorder. Kristian Stær, Morten G. Stokholm, Simon F. Eskildsen, Arne Møller, David J. Brooks, Leif Østergaard, Nicola Pavese.

# CNRU

## Consciousness and its correlates

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, it is usually also what is used by consciousness researchers to explain consciousness – by understanding its systematic relations to its correlates.

### Cognitive correlates of consciousness

Over the last two decades, we have worked towards the development of precise subjective measures that at the same time are exclusive (i.e. that they do not measure any unconscious states) and inclusive (i.e. that they measure all conscious states). As we are still developing and refining these methods, we are able to provide still more evidence about the fundamental relationship between (degrees of) subjetive experience and behaviour.

For many years, cognitive scientists have considered consciousness as the ”tip of the iceberg” in an almost Freudian sense. From this perspective, consciousness is ”something special” – something unusual that ”arises” under very specific circumstances. As a consequence of our method development, one of our most controversial findings has been that much cognition that has been considered unconscious in fact is not. In one recent experiment (Lohse & Overgaard, 2019), we showed that awareness of emotional faces is gradual rather than dichotomous, and that the effects of emotional priming are predicted by the level of perceptual awareness of emotional faces, with effects when reported unseen. The results question how much unconscious perceptions can influence behaviour. As priming is one of the most well-established phenomena believed to occur unconsciously, the results suggest that even the most well-established and historical paradigms that have provided evidence in favour of unconscious cognition need to be re-evaluated.

The consequences of this is not simple as it fundamentally relates to the question about the kind or type of relation consciousness can be said to have to cognition. Where one standard view in the field seems to be that only few or parts of certain cognitive functions are conscious, our findings reveal to an increasing degree that ”degree” of cognitive processing correlate with the degree of conscious experience. These findings seem to be in line with a different view that consciousness is ”special” – the somewhat more rare view that consciousness is not special at all, but rather a natural and integrated part of cognition. This view may of course still take many forms – one may as one example speculate that any information processing that relates to e.g. overt behaviour (Mogensen et al, 2018) is conscious.

### Beyond neural correlates of consciousness

The idea of a “neural correlate of consciousness” has been around in decades and was probably first used in print by Francis Crick and Christof Koch in 1990. In some cases, it has meant looking for correlations between certain events in the brain – under a certain representation as described on

### NEW FACE at CFIN

**Asger Kirkeby-Hinrup,** PhD. The advances in neuroscience and cognitive science in the recent decades has opened the door for developing and comparing theories of consciousness from a new, viz. empirical, perspective. Asger’s research is situated at the intersection between philosophy and related empirical sciences - primarily cognitive science and cognitive neuroscience - in the domain of consciousness studies, with special attention to the way empirical evidence is leveraged as arguments for or against theories of consciousness.

Asger was awarded a three-year international postdoc grant by the Swedish Research Council to stay at CFIN for his project titled: Access consciousness, phenomenal consciousness, and their neural correlates.

After completing his BA and MA degrees in Philosophy from Aarhus University, Asger completed his PhD in theoretical philosophy at Lund University in Sweden. His PhD was supervised by Professor Ingar Brinck and Professor Peter Gärdenfors.

a certain neurobiological level of analysis – and for certain events in the ongoing dynamics of phenomenal experience – under a certain representation, as described by the subject, usually in the everyday terminology of "folk phenomenology". In other cases, it has meant looking for correlations between the occurrence of events of the first kind – again, as neuroscientifically described – and the occurrence of events of the second kind – as only indicated in a nonlinguistic manner by the subject, such as in pushing a button. In yet other examples, it has meant looking for correlations between states usually associated with being "alert and awake" contrary to other states taken to be associated with a reduced level of consciousness, e.g. the vegetative state. Generally speaking, the epistemic goal – what we really want to know – in the type of correlation studies relevant to consciousness research is to isolate the minimally sufficient neural correlate for specific kinds of phenomenal content. Such a correlate, however, will always be relative to a certain class of systems and to internal as well as external conditions. In this empirical context, it will be the minimal set of properties, described on an appropriate level of neuroscientific analysis that is sufficient to activate a certain conscious content in the mind of the organism.

While there has been much development in the attempt to find neural correlates of consciousness, there have been surprisingly few attempts to understand or interpret these correlates by the same scientists. Mapping does not mean reduction, and correlation does not mean explanation. This is not to say that consciousness researchers generally believe that the identification of a correlation is an explanation in itself, yet, in practice, the research field appears as if this is exactly the hypothesis. But once strict, fine-grained correlations between brain states and conscious states have been established, a number of theoretical options are still open. Additional constratins therefore will eventually be needed.

Our current research is preoccupied with how to move this area forward – to go beyond the attempt to just isolate correlates in physical matter, but to use them as theoretical arguments in order to understand structure-function and mind-body relations. Some of this work will be published in the book *Beyond Neural Correlates of Consciousness* that is expected to be published in 2020.

# FACTS

## Core group members

- Morten Overgaard, Professor, head of CNRU
- Peter Fazekas, Postdoc
- Asger Kirkeby-Hinrup, Postdoc
- Martin Dietz, Postdoc
- Timo Kvamme, PhD student

## Affiliated group members and collaborators

- Michael Lohse, Postdoc, MIT
- Thomas Alrik Sørensen, Associate Professor, Aalborg University
- Georgina Nemeth, Postdoc, Eötvös Lorand University
- Qian Janice Wang, Food Science, Aarhus University

# Dimensions of conscious experiences

by Peter Fazekas

In 2019 we have continued to work on our model of the dimensions of conscious experiences. In contemporary cognitive neuroscience the two major issues related to consciousness concern the neural correlates of consciousness, i.e. what the neural underpinnings of having conscious experiences might be, and the graded versus dichotomous nature of conscious experience, i.e. whether consciousness is an all-or-nothing kind of phenomenon or it comes in degrees. Our work is tightly connected to both of these issues.

First, with regard to the neural correlates of consciousness, our work fits into a recent trend that tries to move beyond mere correlational claims. It has been forcefully argued that for a scientific understanding of consciousness, over and above identifying neural correlates of consciousness, explanatory links between neural mechanisms and features of conscious experiences would be required (Seth, 2009, 2010). According to an influential account from philosophy of science (Bechtel & McCauley, 1999; McCauley & Bechtel, 2001) such explanatory links can be established by first proposing hypothetical correspondence relations between features of the two phenomena, and then by extending this initial mapping to further feature-pairs. From this perspective, our focus was on proposing and exploring the viability of hypothetical correspondence relations between certain characteristics of conscious experiences and their neural basis.

To form such hypothetical correspondence relations we have analysed the fine-grained characteristics of the contents of conscious experiences. There is a recent shift in contemporary discussion from a unidimensional view regarding global states of consciousness (wakefulness, dreaming, mind wandering, sedation, hypnosis, minimally conscious state, vegetative state, etc.) towards a multi-dimensional approach, according to which global states of consciousness are to be characterised in terms of a multi-dimensional feature space, including such dimensions as the gating of conscious content (i.e. the range of contents that can enter consciousness), and the accessibility of conscious content (which cognitive processes can access the contents entering consciousness) (Bayne et al., 2016).

We amend this picture by emphasising that the way the contents entering consciousness appear in a conscious experience — what we call the quality of the experience — is also a crucial factor (Fazekas & Overgaard, 2016, 2018a, 2018b), which itself can be characterised along multiple dimensions. The subjective intensity of an experience is determined by how much content-element of a stands out from the perceived background, and can change along sub-dimensions like contrast, saturation and brightness. The subjective specificity of an experience is determined by how distinguishable a content-element is from other content-elements, and can change along sub-dimensions like precision, blurriness and detailedness (Fazekas & Overgaard, 2018a; Fazekas, Nemeth & Overgaard, 2019, forthcoming).

The hypothetical correspondence relations we propose connect these fine-grained characteristics to neural features. We argue that the neural underpinning of subjective intensity is the strength of the response function of those populations of neurons that encode the relevant attributes of the content of perception, while subjective specificity corresponds to the precision of the underlying neural representations and the level of involvement of early visual processing.

To explore the theoretical significance of this model, we have investigated how the correspondence relations proposed affect the original interpretations of recent groundbreaking empirical findings. We have shown that they imply substantive

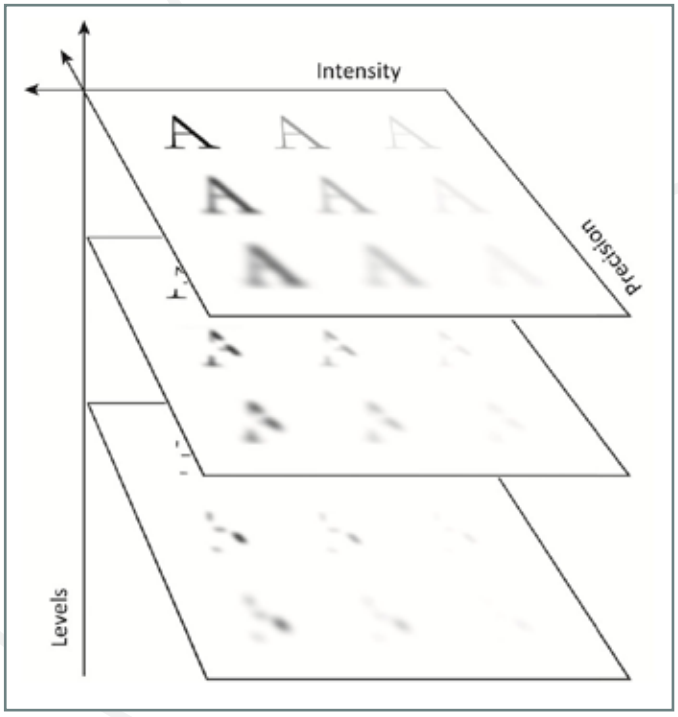


**Figure 1**
Specific dimensions of our multi-dimensional model of the quality of consciousness.

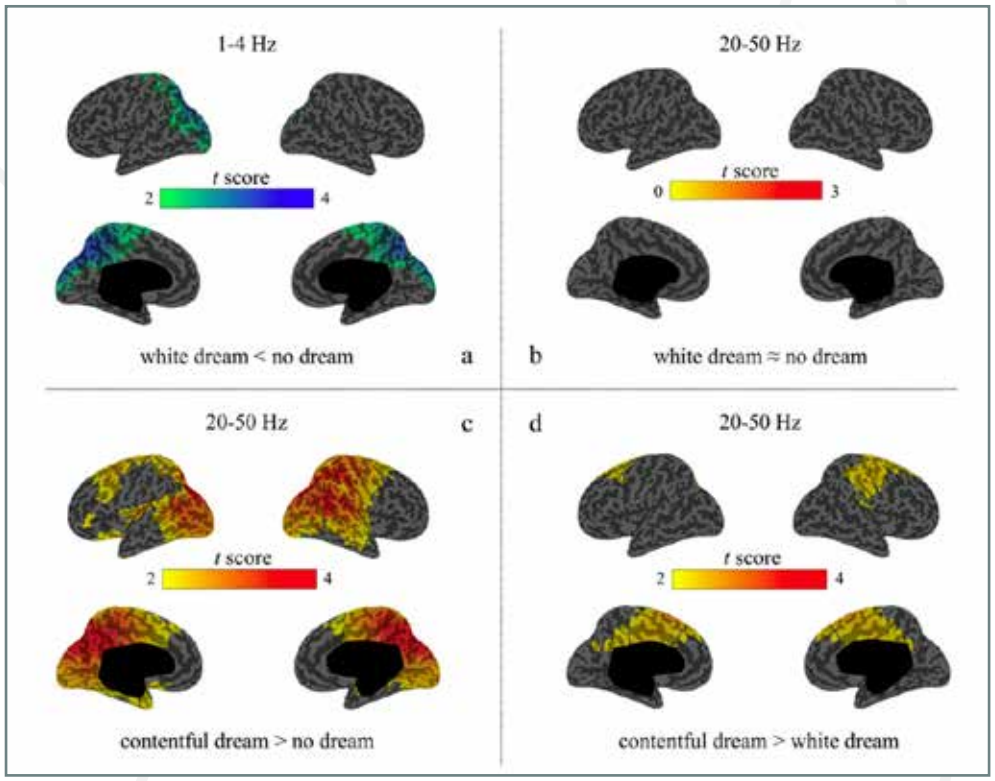


**Figure 2**
Comparison of local changes in EEG signal showing that the level of activity of the neural substrate of white dreams is between the levels of activity characteristic of normal dreams and dreamless sleep.

re-interpretations affecting how one should think about so-called white dreams (when one is certain that one had a dream experience but is unable to recall any detail about it) and mind wandering. White dreams are typically claimed to be either forgotten normal dreams (Siclari et al. 2017) or instances of a special kind of contentless experiences (Windt et al. 2016). Relying on the data presented in an influential recent study that compared EEG signatures of white dreams, normal dreams and dreamless sleep, we have demonstrated that white dreams are, in fact, dream experiences in which the content-elements appear with decreased subjective intensity (Fazekas et al. 2019). Similarly, we could show that the findings of a groundbreaking study that identified the neural basis of mind wandering are in tension with the standard interpretation that connected the strength of its activity to the frequency of the occurrence of mind wandering. We argued for an alternative view, according to which the elevated activity in the implicated brain regions reflected the increased subjective intensity of the content of mind wandering. That is, the minds of those subjects who, on the basis of questionnaire-based self-reports, appear to have low mind wandering proclivity might still wander just as often as those who report high frequency mind wandering (Fazekas et al. forthcoming).

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# ECG

## Embodied Computation Group

by Micah Galen Allen

### A Computational Approach to Understanding Interoception

Our inaugural year was a big one for the ECG. In February 2019 I returned to Aarhus after almost 7 years of postdoc abroad at UCL and Cambridge. It felt great to come home, and I had a very warm welcome thanks to my dual AIAS and Lundbeckfonden Fellowships. Although it was a strange time to come back to CFIN, as we were just in the process of moving offices, it was wonderful to see so many old friends and colleagues again.

Once we settled into our new home, the ECG got to work straight away. First, we expanded our team, hiring two new postdocs, Dr Camile Correa and Dr Nicolas Legrand. Camile came to us having just completed a PhD on computational approaches to consciousness at the University of Amsterdam, and Nicolas arrived from the University of Caen with a freshly minted PhD on machine learning, heart-rate variability, and neuroimaging. Camile took on the job of developing our ethics application, which was no small task. As part of the Lundbeckfonden grant, our overarching project is to scan as many as 500 healthy Danish participants in a massive individual differences study. In line with our group's commitment to best practices in open science, we intend to eventually release these data as the first ever "DK Brain-Body Biobank", sharing anonymized brain, behaviour, and psychophysiology data openly. Realizing this goal meant that we had to do extensive work developing all new participant information and consent protocols, which is something that Camile took a leading role in from the beginning of her time at CFIN.

As part of this project, Camile developed a multi-modal metacognition battery, including a novel "trivia" task probing participant's ability to monitor their own knowledge in different domains, such as example for the nutritional contents of different foods, or on socio-economic questions. Using this battery, she then carried out our first large scale study at COBE Lab, collecting metacognition data from 350 participants in just 30 days. This dataset will be invaluable for our overall project, where we will use structural equation modelling and other computational techniques to estimate the hierarchical structure of metacognition, and relate these 'hidden variables' to psychiatric symptoms and interoceptive sensitivity.

Meanwhile, Nicolas got to work straight away developing some of our core experimental protocols. An overarching theme for our group is understanding the mechanisms underlying "interoception", i.e., the sensation, perception, awareness, and control of homeostatic signals arising from the body's viscera. Our vision is that by better understanding these mechanisms, we can leverage them as explanatory tools to better understand and manage a wide variety of psychiatric and physical illnesses. However, current methods to measure interoception are plagued by methodological issues, such as poor construct validity and measurement reliability. Nicolas set out to develop a new set of tasks which utilize psychophysically adaptive Bayesian procedures, in order to model how participants, perceive their heartrate, respiration, and other bodily sensations. As part of this project, Nicolas developed and launched our open-source software package "Systole", which provides a one-stop shop for pre-processing, analysing, and synchronizing cardiac data

This was a tough nut to crack, but our team has developed a robust set of tools which we are now validating against 'gold standard' measures such as the heartbeat counting task. As

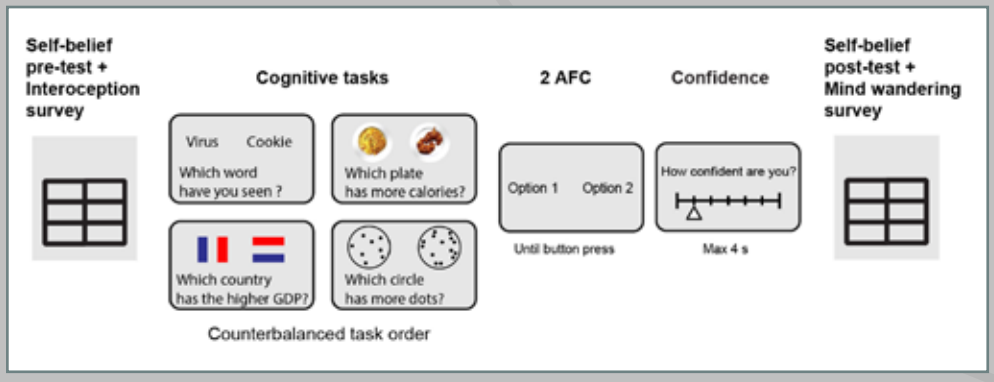


**Figure 1**
The Domain General Metacognition Battery

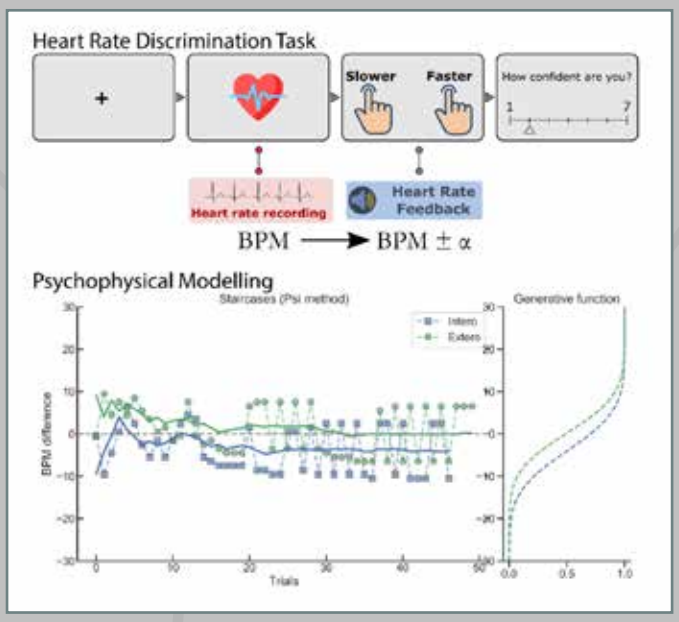


**Figure 2**
Our adaptive measure of cardiac interoception.

an exciting sign of our progress here, on the basis of these new measures the ECG has initiated a stunning number of new collaborations at Cambridge Psychiatry, UCL, Imperial College, Vanderbilt University, Aarhus University, and Dresden University. These collaborations will make use of our tasks to investigate interoceptive dysfunction in a variety of psychiatric patient populations (ADHD, Autism, and Sleep deprivation), and will also examine for the first time the influence of psychedelic drugs such as LSD and Psilocybin on bodily self-awareness!

We are eagerly preparing for our large-scale imaging study, which will identify the neural correlates of interoceptive perception using our novel tasks. The lab has continued to expand and in the Fall of 2019, we hired Nanna Kildahl Mathiasen, an MSc student in Cognitive Science, as a part-time research assistant. Nanna came to us with a lot of expertise in experimental design, scientific programming, and decision-making, and she has been an invaluable team member working on everything from translating ethics protocols, to programming new experiments. We keep our fingers crossed that we find a place for Nanna in the PhD program, but she is also looking at possible industry jobs as a place for her strong talents. In spring 2020, we also welcomed Dr Malthe Brændholt Sørensen to the team as a PhD candidate. Malthe holds a medical degree, and as such

# FACTS

## Group members

- Micah Galen Allen
- Camile Costa Correa
- Nicolas Legrand
- Niia Nikolova
- Nanna Kildahl Mathiasen
- Malthe Brændholt Sørensen

## Affiliated researchers and collaborators

- Francesca Fardo, CFIN, Aarhus University
- Paul Fletcher, Department of Psychiatry, University of Cambridge, UK
- Ray Dolan, Imaging Neuroscience, UCL Queen Square Institute of Neurology, UK
- Tobias Hauser, University College London (UCL), UK
- Karl Friston, Wellcome Trust Centre for Neuroimaging, UCL, UK

## Active and Ongoing International Collaborations

- *Psychedelics and Interoception*
  Robin Carhart Harris & Chris Timmermans, Imperial College London
- *Gamified Computational Phenotyping*
  Ray J. Dolan & Tobias Hauser, UCL Max Planck Centre for Computational Neuropsychiatry and Aging Research
- *Quantitative MRI, Brain-Body Phenotyping, & Interoceptive Active Inference*
  Martina Callaghan, Karl J. Friston, UCL Wellcome Centre for Human Neuroimaging
- *Psychosis and Interoceptive Inference*
  Phil Corlett, Yale University
- *Health-Harming Disorders, Gastrectomy, Inflammation and Computational Psychiatry*
  Paul Fletcher, Ed Bullmore, Hisham Ziauddeen, Cambridge Psychiatry
- *Interoceptive Inference in Anxious Teens*
  Marie Louise Schrieter, Dresden University
- *Interoceptive Inference in Autism Spectrum Disorder*
  Carissa Cascio, Vanderbilt University
- *Project Webheart: No-contact web-based measurement of cardiac interoception*
  Manos Tsakiris, Royal College Holloway

ECG
embodied computation group


**Figure 3**
Example psychometric function and stimuli from Niia Nikolova's Emotion Discrimination Task.

brings essential clinical knowledge to the team. Malthe's PhD proposal "Breathing in the Brain: A Computational Approach", will utilize innovative MEG scanning protocols, tasks, and modelling approaches to test specific hypotheses about how respiratory rhythms entrain neural activity and behaviour. We are really excited to work on this rapidly unfolding new frontier of research.

Rounding out our team, in March 2020 we recruited Dr Niia Nikolova to head up our perceptual decision-making research. Niia recently completed her PhD at City, University of London, and the Max Planck Institute for Metabolism Research (Cologne, Germany), and brings to the lab substantial expertise in neuroimaging methods, psychophysics, and perceptual decision-making. Even though she arrived in Denmark the day before the borders shut, she wasted no time making her mark in the group, developing a new emotion discrimination task using adaptive psychophysical procedures. Niia's project is to develop this task into a probabilistic perceptual learning task, which we will use in a variety of projects to probe how expectations and interoceptive signals interact to shift affective biases, in both healthy participants and controls. Although the task is brand new, we already have a collaboration applying it to patients with Borderline Personality Disorder and Psychosis at our Cambridge Psychiatry sister lab and we are looking forward to scanning it this summer. It should also be mentioned that Niia launched the "psychophysics @ home" initiative, which brings together perception scientists from around the world to share their tasks, so that perception science can continue even in a shutdown. This amazing initiative now has 180 international members and has proven to be an invaluable resource for piloting our tasks. We really look forward to what Niia will do next!

Any yearly report would be amiss without mentioning our intrepid cognitive science students. In our first year we saw an amazing level of interest and enthusiasm from students in the BSc and MSc programs. Our lab meetings are regularly attended by 3-6 CogSci students, who bring invaluable enthusiasm, creativity, and talent. Along the way we've supervised some impressive thesis projects, including the colourful Sebastian Scott Engen's project on modelling how emotion influences metacognition, which is shaping up to be an excellent future publication, Phila von Porthan who investigated emotional experiences in virtual reality, and Lena Hansen who investigated computational models of the thermal grill illusion. We also enjoyed a great contribution from Esben Kran who designed our new Lab Logo, and from Peter Thustrup Waade who is leading our online survey study of interoceptive experience during the COVID-19, and will hopefully visit Karl Friston at UCL this fall, as part of a collaboration on computational modelling and inter-social interoceptive inference. We are eternally grateful for all of our cognitive science students, who really do super charge the lab with their talent and energy.

That just leaves me! As for my contributions, learning to run a group is one of the most exciting experiences of my life. There have been plenty of victories and pitfalls along the way, but I am absolutely honoured to lead such an amazing group of young minds. We have a lot of hill left to climb to realize our ambitions, but this year has seen us plant so many promising 'seeds' that I simply cannot wait to realize that future harvest. I've also had a lot of fun finishing some projects left over from my postdoc, including new first authored publications in Trends in Cognitive Science and Behavioural and Brain Sciences, and our new preprint detailing an innovative computational model of cardiac interoception and heart-rate variability, together with Thomas Parr and Karl Friston. I can promise you that more big things are on the way for the ECG, and I welcome all of our colleagues to come chat with us about how we can help you bring brain-body measurement into your own research.


**Figure 4**
Our new lab logo, designed by CogSci student Esben Kran.

## NEW FACES at CFIN - ECG Group

**Micah G. Allen**
Associate Professor, AIAS-COFUND Fellow
Group leader

**Camile Costa Correa**
Postdoc

**Nicolas Legrand**
Postdoc

**Niia Nikolova**
Postdoc

**Malthe Brændholt Sørensen**
PhD student

**Peter Thestrup Waade**
Student helper

**Nanna Kildahl**
Research assistant

# FUNCTIONAL HEMODYNAMICS

## Ten years of capillary (dys)function research

by Leif Østergaard

The 2010 CFIN annual report described our first analysis of the effects capillary transit time heterogeneity (CTH) have on blood-tissue oxygen transport, combining a biophysical model developed by Sune Nørhøj Jespersen with estimates of blood flow and CTH from the literature. Our conclusion read

> *"Thorough analysis of reported changes in transit time characteristics suggest that capillary transit time heterogeneity is crucial in order to secure the tissue oxygenation during functional hyperemia"*

and went on to speculate

> *"The implications of this finding may be wide-ranging: The effects of CTH have gone unnoticed by current neuroimaging techniques - and therefore its role in health and disease remains unknown. The phenomenon […] challenge[s] the notion that blood flow reflects tissue oxygenation. Can tissue with normal CBF suffer poor oxygenation due to abnormally high CTH?"*

The manuscript on this analysis would not be published until the following year[1] and it took a few more years until we could develop and publish the first approaches to measure CTH in humans[2] and animal models[3]. We would learn that some felt it difficult or even perilous to abandon the paradigm that tissue oxygen availability is determined by its blood supply blood alone. Mostly, however, we benefited from the curiosity, open-mindedness, and knowledge of many, world-leading experts on the microcirculation and vascular physiology of the brain. They provided invaluable insights and ideas, as well as methodological support to the development of our ideas, partly at the 2012-15 Aarhus CTH Meetings[4] and other venues, partly in the writing of a range of reviews in which we examined whether a range of disease phenomena might be understood from the perspective of dysfunctional capillaries.

We are particularly grateful to the VELUX Foundation, who dared to provide us with the support needed to examine our models' predictions in further detail, particularly in the context of capillary function in aging and dementia. With their generous DKK 10M Aarhus Research Center for Brain Aging and Dementia (ARCADIA) program grant donation, we were able to develop methods to examine the function of individual capillaries in the brains of rodents by means of two-photon microscopy, and to demonstrate changes in capillary flow patterns in aging and dementia. In 2019, the VELUX Foundation generously donated DKK 10M for ARCADIA II, a program during which we will target the microcirculation by over-the-counter drugs in an attempt to improve capillary function and brain oxygenation in animal models of Alzheimer's Disease.

I am delighted to report that we will be able to launch additional research regarding capillary dysfunction in 2020, thanks to a major donation by the Lundbeck Foundation. Read more about this in next year's Annual Report.

### Capillary flow distributions – and why they matter

The proposition, that not only organ blood supply, but also its microscopic distribution, determines whether sufficient oxygen reached every cell in our body, owes to a fundamental property of individual capillaries: While the availability of oxygen in blood depends on erythrocyte velocities, and hence the amount of oxygen passing by, blood-tissue transport of oxygen is limited by the time available for diffusion exchange before blood leaves the tissue to return to the heart – the capillary transit time. These two opposing effects give rise to the nonlinear relation between erythrocyte velocities and oxygen availability in tissue shown in Figure 1

This single property means that the unloading of oxygen to tissue is most efficient if blood is evenly distributed across the capillary bed, as illustrated in Figure 2A (top), where the color represents blood saturation (deep red 100% deep blue 65%). This ideal scenario corresponds to negligible CTH,

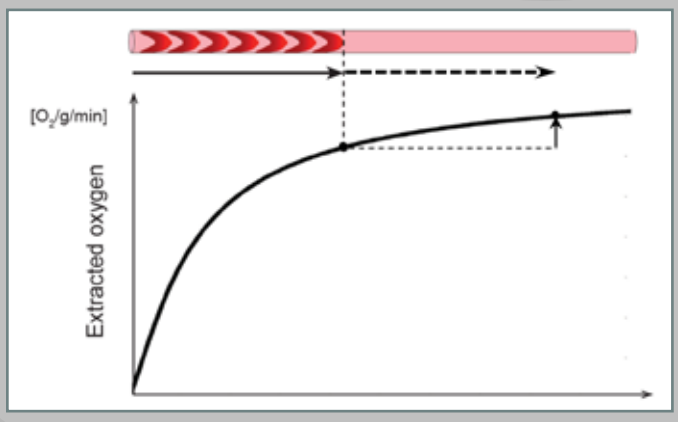


**Figure 1**
The amount of oxygen that tissue can extract from a capillary increases as erythrocyte flow-through increases – mostly for slow or modest erythrocyte velocities. Note how doubling erythrocyte velocity has little effect on oxygen availability.

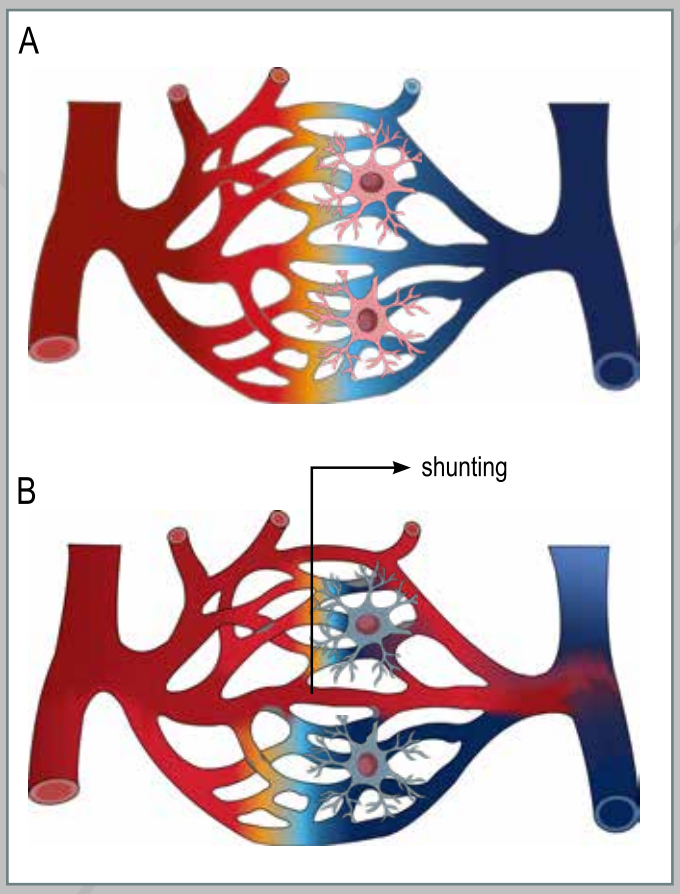


**Figure 2**
(A) Oxygen extraction across the capillary bed is most efficient if all capillary paths possess identical extraction properties.
(B) Changes in capillary patency can disturb capillary flow patterns and prevent their normal homogenization during increases in blood flow – so-called capillary dysfunction.

while increasing CTH, such as in Figure 2B, is associated with poorer oxygen unloading, partly because blood flow through some capillaries is limited, possibly causing 'micro-ischemia'.

Observing Figure 2B, another feature becomes apparent: With a constant blood supply through the arteriole and blood's passage through some regions of the capillary bed hindered, a disproportionate amount of blood has to pass through tissue via other capillary pathways. Even in normal tissue, blood typically spends less than a second within the capillary bed, providing little time for blood-tissue diffusion exchange. This 'shunting' of oxygenated blood through the capillary bed, away from the 'micro-ischemia' near narrow capillaries, is the central phenomenon that cause age- or disease-related changes in the blood flow through individual capillary to impact oxygen availability in tissue – by limiting oxygen uptake into tissue,

# FACTS

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- Jens Christian Hedemann Sørensen, Dept. Neurosurgery, Aarhus University Hospital
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rather than blood flow. The actual impact of this shunting depends on whether local blood flow control compensates for the lack of oxygen in subregions of the tissue downstream. We revisit this somewhat paradox blood response below.

## What is a 'vascular' disease?

The notion, that capillary flow patterns may affect the proportion of diffusible molecules extracted while blood passes through the capillary bed has been touched upon before, see e.g.[5-10], but failed to make it into physiology textbooks. According to these, tissue *blood flow*, capillary *surface area*, and capillary wall *permeability* limit the uptake of diffusible molecules into tissue. In the context of human disease, this misconception has wide-ranging ramifications: While *reduced blood flow* results in a graded reduction in oxygen availability, only capillary *occlusions* are predicted to affect oxygen availability, as they reduce capillary surface area. In most organs, the capillary bed offers multiple, highly connected parallel pathways for blood to pass through tissue, and the occlusion of individual capillary segments is therefore unlikely to alter capillary surface area or the overall resistance for blood to pass through tissue to any great extent. Herein lies the reason why we – so far – only consider vessels that may limit blood flow, i.e. arteries and arterioles, when we speak of vascular disease. Importantly, within this paradigm, 'vascular disease' can be verified by demonstrating vascular occlusions or limited tissue perfusion. Conversely, a vascular disease is generally ruled out if such changes cannot be found.

## In search of capillary dysfunction – what to look for?

While we developed means of detecting capillary flow disturbances, we also worked with medical experts from different disease areas to search for indirect evidence of capillary dysfunction in diseases of the brain[11-17], peripheral nervous system[18, 19] and heart[20], including cancer[21] and critical illness[22] in the literature. So what did we look for? In most organs, blood supply is closely regulated to maintain constant oxygen levels. As capillary dysfunction begins to limit the passage of oxygen into tissue, we therefore expect blood flow to *increase* to compensate for the relative lack of oxygen – contrary to the notion that vascular disease changes exclusively *limit* blood supply. Importantly, this blood flow increase may compensate for deteriorating capillary function up to a certain level, so this compensatory flow response would, at least initially, be expected to *mitigate* symptoms and tissue damage. Other than this telltale *pre-symptomatic hyperemia*, we also searched for histopathological reports of disease-related changes in capillary patency (e.g. compression, constriction or damage to the glycocalyx, endothelium, pericyte, or basement membrane) or blood properties. The luminal diameter of capillaries is generally smaller than the size of a red blood cell (RBC) and much smaller than those of leukocytes. Parallel changes in symptom severity and the deformability of RBC on one hand, and leukocyte number and adhesion to capillary endothelium, on the other, may therefore be indicative of fluctuating tissue oxygenation due to capillary flow disturbances.

We found evidence of presymptomatic hyperemia in a range of conditions[13, 18, 19], perhaps most striking in Alzheimer's Disease[11]. The risk factors of Alzheimer's Disease (AD) are mainly vascular – similar to those for developing a stroke or a heart attack. However, AD patients' large blood vessels do not appear different from similarly-aged healthy individuals, and their cerebral blood flow only starts to decline shortly before they develop dementia. Importantly, young carriers of the APOE-ε4 gene, which increases the risk of developing AD manyfold and is present in most AD patients, show areas of *elevated* cerebral blood flow (CBF), several decades before some develop dementia. These findings lead many to rule vascular disease changes out as contributors to AD, whereas the findings might in fact signify that capillaries do contribute to AD.

**Figure 3**
As capillary dysfunction grows more severe, blood-tissue oxygen transport can be improved by reducing flow – allowing more time for blood-tissue oxygen exchange. This happens at the expense of tissue hypoxia and inflmmation.

Perhaps the most counterintuitive property of capillary dysfunction is that, as capillary flows become very heterogeneous, tissue's access to oxygen may actually improve if blood flow – and thereby the shunting of oxygenated blood – is reduced. This is illustrated in Figure 3. The resulting drop in tissue oxygen tension improves local blood-tissue concentration gradients and thereby net oxygen extraction, while longer blood transit times allow more time for blood-tissue diffusion exchange. This pattern of low flow and high fractional oxygen extraction is also characteristic of 'traditional' ischemia, caused by a primary restriction of blood supply. However, in the case of capillary dysfunction, the limited flow represents an intrinsic adjustment of blood flow to meet metabolic demands. Notably, in the absence of such attenuation of blood flow responses, tissue function is expected to deteriorate if capillary flow changes worsen, or if a blood flow increase is forced upon a dysfunctional microvasculature.

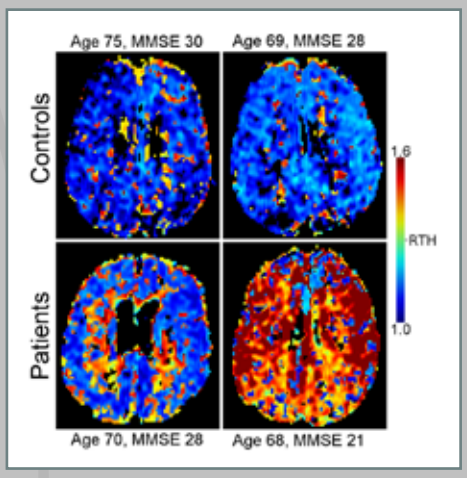


**Figure 4**
Parametric maps of the relative transit time heterogeneity (RTH) in two healthy controls (upper row) and in patients with mild cognitive impairment (MCI) and Alzheimer's Disease (AD), respectively (lower row, left to right)[25]. Maps were calculated from dynamic susceptibility contrast MRI data[2]. Due to the tendency for CTH and MTT to co-vary, their ratio, RTH, is a convenient index of microvascular flow disturbances. MMSE denotes Mini-Mental State Examination (MMSE) score.

We found multiple instances of paradox symptoms and 'ischemic' tissue injury at normal or elevated blood flow in conditions where histopathological evidence also show severe changes in capillary morphology. Prominent examples are cases of physical nerve tissue damage[14, 18], reperfusion injury[12, 20], critical illness[22], and some types of cerebral small vessel disease[16].

Coronary microvascular dysfunction[20] and stress cardiomyopathy[23] are other striking instances of symptoms, historically considered 'non-vascular' for lack of detectable, large vessel changes by contemporary methods. These patients suffer from angina and display reduced coronary flow reserve, and electrocardiographic and biochemical evidence of tissue hypoxia while their conditions are associated with changes in microvascular morphology and blood properties[20, 23]. Due to our incomplete understanding of vascular disease pathology and the absence of demonstrable vascular occlusions, however, a considerable fraction of the medical literature on these conditions can be found in psychiatry, rather than cardiology journals.

## What causes capillary dysfunction?

Capillary function deteriorates over time, as these delicate, thin-walled blood vessels are exposed to the wear and tear of billions of RBCs and leukocytes squeezing through. In addition to aging, cardiovascular risk factors, such as smoking, high cholesterol, and high blood glucose, directly impair capillary function. Interestingly, *endothelial dysfunction*, the gradual attenuation of small blood vessels' response to vasodilators, antedates hypertension and is considered the earliest, systemic sign of vascular disease pathology, including those that affect the brain[24]. Our findings thus far suggest that this phenomenon may reflect progressing capillary dysfunction and serves to attenuate microvascular 'shunting' of oxygenated blood – at the expense of long-term, oxidative injury to resistance vessels upstream[11, 12]. We hope future research will tell us whether high blood pressure is in fact a sign of advancing capillary dysfunction in key organs, and whether antihypertensive drugs, which relax both arterioles and capillary pericytes, show even greater benefit when administered *before* blood pressure increases.

## Measuring capillary flow disturbances

Having developed means of detecting capillary flow disturbances, we were thrilled to observe the microvascular flow disturbance we had hypothesized years earlier, in fact exist and correlate with symptom severity in AD patients[25, 26] and can be detected in animal models of aging and AD[27] – See Figure 4. More recent data from patients with mild cognitive impairment (MCI), acquired and analyzed in a collaboration between David J. Brooks and Simon F. Eskildsen, suggest that the dramatic transition from asymptomatic hyperemia to attenuated CBF may coincide with the onset of memory problems[28] – See 2017 Annual Report. In a study by Rasmus Aamand Olesen, we now find that microvascular

flow disturbances can be detected in young, asymptomatic APOE-ε4 carriers, several decades before some develop AD – read more in next year's Annual Report.

In 2018, Maryam Anzabi demonstrated the early, capillary flow disturbances after subarachnoid hemorrhage[29] we had predicted 5 years earlier[13]. Importantly, her thesis work also addressed the puzzling suppression of blood flow described above, which we predict sets in as capillary flow patterns become severely disturbed to better extract oxygen during bloods capillary transit. In a literature review on the peculiar reductions in blood flow that occur during so-called cortical spreading depolarization (CSD), which is characteristic of migraine aura and hypoxic tissue injury[15], we had proposed that these flow changes are caused by rapidly emerging capillary flow patterns. The capillary flow changes could, however, instead be the result of reductions in blood flow, the cause of which would then remain unknown[15]. Working with Cenk Ayata, Sava Sakadzic, and David Boas from Harvard Medical School and Boston University, Maryam found that the capillary flow disturbances indeed occur several seconds prior to changes in arteriolar diameter – compelling confirmation that upstream resistance vessels respond to changes in capillary flows patterns – See 2017 Annual Report.

Working with international collaborators, 2018-19 also brought important new insights into the interplay between microvascular flow disturbances and large vessel disease[30, 31], see Figure 5. We were proud that the capillary dysfunction phenomenon was included into a prestigious position paper on how stroke and dementia must be considered together as we try to reduce the impact of these devastating conditions on human health[32].

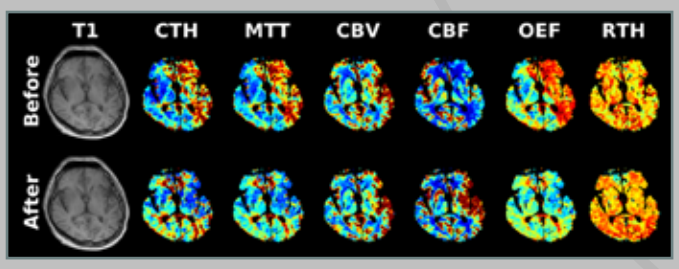


**Figure 5**
Anatomical and hemodynamic maps from a carotid artery stenosis patients, before and after carotid stenting[30].

## Why is the capillary dysfunction concept important?

When we try to treat diseases, to detect them before they inflict irreparable damage to our organs, and to even prevent them, our chances of success are far greater if we know why, where, and how they develop. This knowledge is incomplete or unavailable for the disease conditions, we reappraised for signs of capillary dysfunction. The fact, that this overlooked phenomenon seems to play important roles in the early phases of all these conditions, indicates to us that the microcirculation may be a promising target as we try to prevent or delay the chain of molecular or cellular events that ultimately lead to these diseases.

To illustrate how this knowledge matters, consider past decades' effort to cure or prevent Alzheimer's disease. AD is characterized by the presence of abnormal proteins deposits in brain tissue. These proteins, called Aβ and tau, are toxic to nerve cells, and the predominant strategy to treat AD in this millennium has been to remove Aβ from the brain tissue or prevent its formation. While these efforts now succeeded in humans, the removal of amyloid from brain tissue has not provided the expected benefits to patients. While scientists now work with pharmaceutical companies to examine whether these drugs may prove efficient when given earlier in the course of the disease, our research suggest that capillary changes may still limit the oxygen needed for brain cells to function and survive in these patients' brains. Therefore, any benefits of these drugs may require that the underlying capillary dysfunction is addressed in parallel. In fact, Aβ and tau proteins are thought to form more easily in brain tissue with poor oxygenation – while amyloid, in turn, constrict capillaries[11, 33]. Understanding the relation between capillary dysfunction, tissue oxygenation, and Aβ and tau pathology is therefore very important to our current research. If capillary dysfunction indeed represents an early contributor to the development of AD, the microcirculation might provide a target for early diagnosis, drug development, and prevention – delaying the disease process *before* it causes symptoms.

In acute ischemic stroke, which by definition arises from reduced blood flow, our data also suggest that the capillary distribution of residual blood flow matters. Indeed, gradual deterioration of capillary flows and capillary collapse seem to contribute to the rapid progression of tissue injury after symptom onset – to an extent that does not depend on residual blood supply *per se*[34] – See 2017 Annual Report.

Today, only a fraction of acute stroke patients are eligible for therapies that restore their blood flow – and such therapy can only be administered after careful examinations at highly specialized hospitals. Medicines that prevent capillaries from closing irreversibly during the first, critical hours after a stroke may prove safe to administer to stroke patients by ambulance crew – and our data suggest that this could save brain function in all stroke patient, irrespective of whether they later receive treatment to restore blood flow.

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# MEG & NeDComm Lab

by Yury Shtyrov, Head of MEG/EEG and PI of NeDComm Lab

## MEG@CFIN: a story of continued success

The MEG Laboratory has continued to grow and flourish at CFIN. Just like the rest of our imaging facilities, the MEG lab had to be relocated to the new Aarhus University Hospital location in Skejby, including the MEG setup and the other equipment we have as parts of the same facility, most importantly EEG and TMS. The move was done in a record time of about two months, and in the summer 2019 the lab resumed its normal function. Various improvements to the data acquisition and stimulation procedures, lab setup and work space were introduced during the move.

The lab continues to see an influx of new users and new experimental and clinical recordings. This includes large-scale projects on music perception, sleep, schizophrenia, epilepsy, vision, language, consciousness disorders, investigations into Parkinson's disease, olfactory processing etc, etc. Among others, the MEG user group was expanded by the arrival of Assoc. Professor Diego Vidaurre and his group, whose innovative ERC-funded research on modelling brain states will use a combination of neuroimaging and sophisticated computational and statistical methods.

We continue to develop tools and algorithms for MEG and EEG data analysis, actively contributing to the international development of open-source scientific software.

Furthermore, CFIN scientists are actively involved in developing next-generation MEG systems based on optically-pumped magnetometers (OPMs), which do not use superconductivity and thus do not need liquid helium and thermal insulation. The first OPM recordings at CFIN have been successful. When fully developed, OPM systems will allow for much more flexible recordings, including wearable MEG, foetal, spinal and retinal recordings, higher spatial resolution, etc. etc, and CFIN is proud to be at the forefront of these developments.Ongoing research includes multiple other projects dealing with various cognitive and clinical questions, while the MEG is also routinely used for clinical diagnostic purposes, most importantly for pre-surgical mapping in epilepsy patients.

## New research group joins CFIN MEG community

CFIN have been very happy to welcome a new MEG-focussed group, headed by Diego Vidaurre, who has recently moved from Oxford University to join Aarhus University as an Associate Professor. Diego has won a prestigious ERC Starting Grant and a Novo Nordisk Hallas Møller Award to establish his research group at CFIN.

Diego and his group are interested in the development and application of computational methodology for characterising and understanding the complex dynamics of activity in the brain, and for relating these to behaviour in a meaningful way. In particular, using data from different sources (MEG, EEG, fMRI), they will be developing models of stimulus processing that can describe the cascade of information processing in the brain with high temporal and spatial specificity. Having

### MEG

Magnetoencephalography (MEG) is one of the key brain imaging facilities at CFIN. This technique can monitor brain activity with sub-millisecond temporal precision; it does so by recording miniscule magnetic fields generated by electric currents in neurons, the brain's main working cells. These tiny magnetic fields are picked up by the so called super-conductive quantum interference devices, sophisticated miniature sensors, distributed around a person's head in a helmet-shaped device and kept at super-low temperatures near the absolute zero. As the magnetic fields freely permeate through human tissues and air, there is no need for a solid conductor between the head and the measuring device, which makes MEG recordings easy, convenient and time-efficient.

The technique is entirely non-invasive and does not involve any currents, fields or substances "injected" into the participant's body. Its operation is completely silent with participant seated in a comfortable chair in a spacious magnetically-shielded room. Furthermore, MEG allows for more direct estimates of not only the timing but also of the spatial location of neuronal activation, thus showing in real time the complex interplay of various brain areas as they are processing the information coming to our central nervous system.

CFIN's MEG Laboratory is the first installation of its kind in Denmark and Scandinavia. It uses a Triux™ device (Megin Oy, Finland), which incorporates 306 MEG sensors of different types, 128 EEG channels and various other data outputs, capable of yielding the most accurate spatial-temporal image of the brain activity currently possible. It also includes a zero-boiloff liquid helium recirculation system, which ensures its economical use independent of regular cryogen supplies.

contributed to the study of vision with this type of methodology in his previous work, he is now planning to apply these models to the field of pain processing in order to get a better understanding of how the complex interplay between brain regions gives rise to the subjective experience of pain. Further work will revolve around how to associate these subject-specific models of stimulus- (or pain-) processing to clinical phenotypes. That is, can we use these to characterise and understand, for example, the abnormal processing of pain by chronic pain patients? We look forward to having Diego's contrition to the CFIN research!

Professor Sarang S. Dalal from the NEMOlab group in the newly installed MEG facility at AUH, Skejby.
Photo: Tonny Foghmar, AUH Foto

### New MEG study by NedComm Lab: Machine Learning Classifies Word Type Based on Brain Activity

Pairing machine learning with neuroimaging can determine whether a person heard a real or made up word based on their brain activity, according to a study published at eNeuro. These results lay the groundwork for investigating language processing in the brain as well as for the development of an imaging-based tool to assess language impairments in various conditions. Many brain injuries and disorders cause language impairments that are difficult to establish with standard language tasks because the patient is unresponsive or uncooperative, creating a need for a task-free assessment method.

Using magnetoencephalography (MEG), CFIN scientists Mads Jensen, Rasha Hyder and Yury Shtyrov examined the brain activity of participants while they listened to audio recordings of similar-sounding real words with different meanings and made up "pseudowords". Using machine learning algorithms, the team were able to determine, based on the participant's brain activity in MEG, when they were hearing a real or made up word, as well as determine the meaning of the particular word and whether it was grammatically correct or incorrect. They also identified specific brain regions and neural activity frequencies responsible for processing different types of language information.

# FACTS

### NeDComm Lab members

- PI: Yury Shtyrov
- Andreas Højlund
- Christopher Bailey
- Mads Jensen
- Marie Louise Holm Møller
- Milena Osterloh
- Rasha Hyder

### Visiting scientists

- Alina Leminen
- Eino Partanen
- Nikola Vukovic
- Malte Henningsen

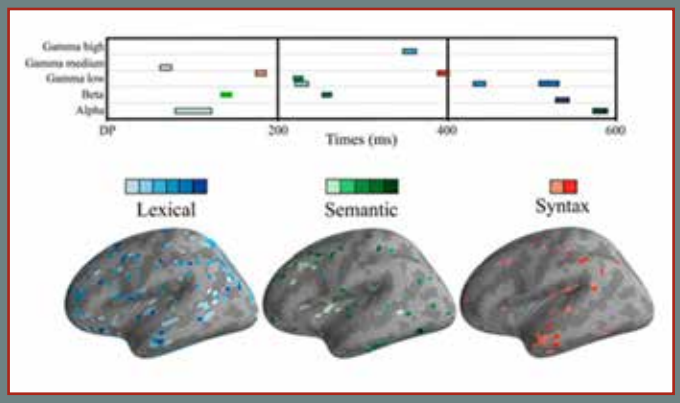


**Figure 1**
Heatmap of significant clusters across three linguistic contrasts, five frequency bands, and time. Lexical condition in blue colors, semantic in green, and syntax in red. Bottom, Surface topography of significant effects. For all conditions, colors go from lighter to darker as latency becomes longer.

**For full details, please see:**
Jensen, M., Hyder, R., & Shtyrov, Y. (2019). MVPA analysis of intertrial phase coherence of neuromagnetic responses to words reliably classifies multiple levels of language processing in the brain. ENeuro, ENEURO.0444-18.2019. https://doi.org/10.1523/ENEURO.0444-18.2019

# NEMOlab

## 2018 and 2019

by Sarang S. Dalal

These were two busy years for the NEMOlab. In these two years, we launched several experiments under the umbrella of my ERC Starting Grant project, *The Retina as a Window to the Brain*. Our lab primarily makes use of magnetoencephalography (MEG) and electroencephalography (EEG) to measure the brain's visual responses, as well as electroretinography (ERG) to measure the retina's responses.

The response to light flashes can be measured even through closed eyelids, and in fact ERG is often performed this way to test retinal function in infants and sedated patients. Together with EEG, this makes it possible to measure the retina's and brain's visual responses during sleep, and postdoc **Alexandra Vossen** conducted an experiment to do just that. The slow waves of deep sleep are thought to reflect alternating phases of heightened and depressed cortical excitability, and so may in turn enhance or inhibit responses to visual stimuli, depending on the timing of the stimulus relative to a given sleep slow wave. Alexandra's project aimed to determine whether this is indeed the case, and determine whether that may happen as early in the visual pathway as the retina. The experiment required developing a unique pair of goggles that contained LEDs to alternately stimulate the left and right eyes throughout the night. Analysis of this data are ongoing, but preliminary results suggested that the retina's high frequency oscillations are modulated by the precise time of arrival of a light flash relative to a sleep slow wave, as are the subsequent responses of visual cortex.

Through a collaboration with Valerie Goffaux at UC Louvain in Belgium, we hosted a visiting PhD student, **Kirsten Petras**, to perform an MEG experiment investigating how the visual system makes use of redundant information across spatial scales. She hypothesized that low spatial frequencies – broader, more general features of an image – inform the visual cortex about where to focus resources to process high spatial frequency content – sharper edges and other fine details. She implemented a study making use of photographs of human faces, along with images derived by scrambling those faces while maintaining similar image statistics. In the context of faces, the shading in the general region of the eyes would correspond to low spatial frequencies, and are also informative of where to find sharper details of high spatial frequency content, such as the eyelids, iris, and eyelashes. The scrambled faces had the distinction that lower spatial frequencies would *not* be informative of features likely to contain high spatial frequencies. The MEG results indeed provided evidence that feedback driven by low spatial frequency processing from fusiform areas (specialized in face perception) guide high spatial frequency processing in early visual cortex. This sort of feedback could be one mechanism that enables the fast and efficient processing of visual objects.

**Sigbjørn Hokland**, a master's student in biomedical engineering at DTU, joined our group to perform research for his master's thesis and subsequently stayed on to further develop his project. Sigbjørn was inspired by initial findings showing that 40 Hz light flicker may reduce amyloid load in a rodent model of Alzheimer's disease. Due to the striking results from that study, there has naturally been interest in

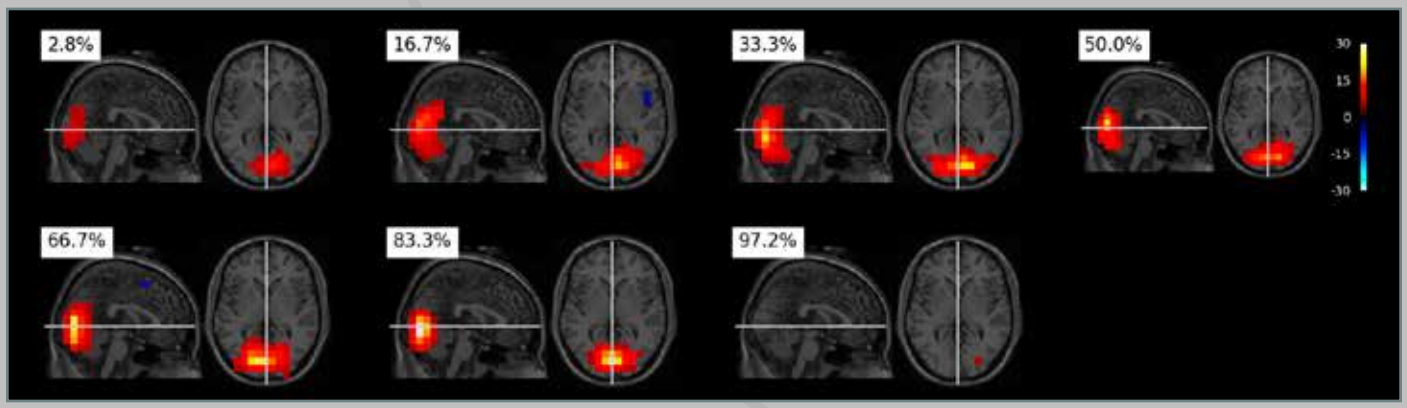


**Figure 1**
The brain volume activated by 40 Hz flicker of duty cycles varying from 2.8% to 97.2%, as reconstructed from statistical analyses of MEG source maps. While the largest and strongest responses occurred at 33.3% and 50%, it is compelling that a 2.8% duty cycle flicker could still activate a sizable volume, as it is subjectively more comfortable to view.

investigating whether flickering light could be an effective non-pharmaceutical therapy for human Alzheimer's patients. Indeed, the brain's responses to light flicker have long been investigated with EEG and MEG to study the visual system. However, the duty cycle of the light flicker (i.e., relative proportion of light to dark during the flicker sequence) could impact both the brain's responses as well as subjective viewing comfort, two key factors in evaluating the feasibility of using a 40 Hz flicker in Alzheimer's disease treatment. Sigbjørn set out to understand these aspects of light flicker in a group of healthy participants, recording both MEG and electroretinography (ERG) to understand how responses to light flicker evolve at different stages of the human visual system. Although flicker with duty cycles between 33-50% indeed elicited the strongest brain responses, the responses to duty cycles between 3-17% were still substantial while participants reported them being more comfortable to view (Figure 1).

We welcomed two new PhD students, **Jordan Alves** and **James Lubell**, who launched MEG+ERG investigations into other aspects of vision. Based on preliminary results showing that the human retina's responses to natural images (digital photographs) may vary according to spectral content, James designed an experiment to characterize that relationship and how the retina's processing (measured with ERG) informs the responses of visual cortex (measured with MEG). Jordan designed an experiment to measure how the responses of visual cortex to motion may likewise be driven by retinal processing. Counterintuitively, the human retina's responses to natural images and motion are not well understood, despite evidence of their involvement in the animal retina. We look forward to the results of their analyses!

Most MEG and EEG experiments rely on averaging across repeated trials in order to enhance the visibility of the brain's weak signals. However, it would be ideal to evaluate brain responses for each individual event, especially for certain applications such as neural prosthetics, or to study responses that can change over the course of a longer experiment. Working with collaborators at Donders Institute in the Netherlands and the University of Birmingham in the UK, postdoc **Britta Westner** devised a novel method combining the random forest machine learning algorithm with MEG source analyses in order to decode from the brain's high-frequency responses whether the participant was either hearing a word spoken, or seeing it visually on a screen. Her algorithm achieved a remarkable 66% success rate in

# FACTS

## Group members and students

- Group leder Sarang S. Dalal
- Alexandra Vossen, postdoc
- Britta Westner, postdoc
- James Isaac Lubell, PhD student
- Jordan Alves, PhD student
- Lau Møller Andersen, postdoc
- Marie Louise Holm Møller, research assistant
- Martin Dietz, postdoc
- Sigbjørn Hokland, research assistant

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- M Bourguignon, V Jousmäki, SS Dalal, K Jerbi, X De Tiège. Coupling between human brain activi-ty and body movements: Insights from non-invasive electromagnetic recordings. NeuroImage 203, 116177.
- S Leske, SS Dalal. Reducing power line noise in EEG and MEG data via spectrum interpolation. NeuroImage 189, 763-776.
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- E Ruzich, M Crespo□García, SS Dalal, JF Schneiderman. Characterizing hippocampal dynamics with MEG: A systematic review and evidence□based guidelines. Human brain mapping 40 (4), 1353-1375.
- BU Westner, SS Dalal, S Hanslmayr, T Staudigl. Across-subjects classification of stimulus modality from human MEG high frequency activity. PLoS Computational Biology 14 (3), e1005938.


## Pre-prints


- Westner BU & Dalal SS. Faster than the brain's speed of light: Retinocortical interactions differ in high frequency activity when processing darks and lights. bioRxiv 153551; https://doi.org/10.1101/153551
- LM Andersen, K Jerbi, SS Dalal. Can electro-and magnetoencephalography detect signals from the human cerebellum? PeerJ Preprints 7, e27901v1.
- A Jaiswal, J Nenonen, M Stenroos, A Gramfort, SS Dalal, BU Westner. Comparison of beamformer implementations for MEG source localization, ... BioRxiv, 795799

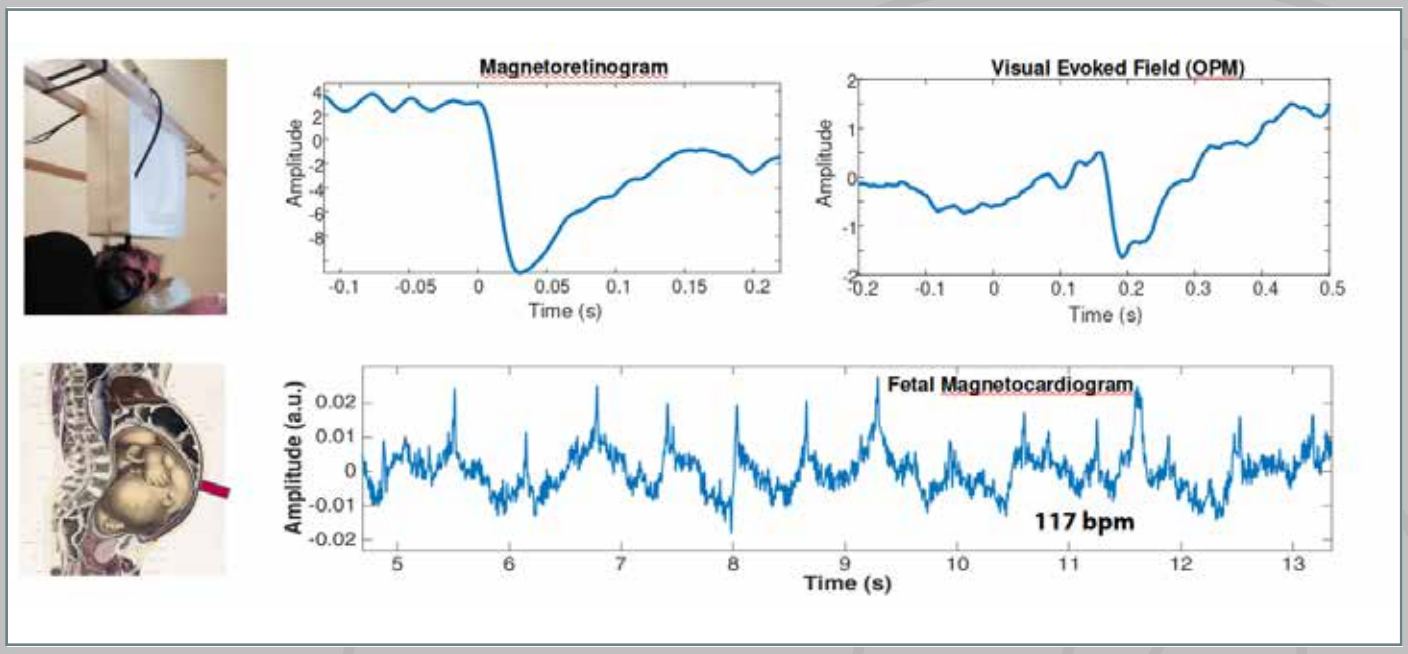


**Figure 2**
Pilot recordings with a prototype OPM in our laboratory. Upper row: the first magneto-retinogram ever recorded with an OPM, along with a visual evoked response from occipital cortex. Lower row: A fetal magnetocardiogram measured from a healthy fetus at 33 weeks of gestation, with an OPM placed on the mother's abdomen.

classifying individual trials, which is a remarkable achievement for high-frequency MEG data. The details of her method and study can now be read in her article in *PLoS Computational Biology* (Westner et al., 2018).

These two years also saw the NEMO group's efforts contributing to the development of open source software for MEG/EEG analysis and visualization continue and expand. Partly funded through a Seed Grant from the International Neuroinformatics Coordinating Facility, together with Karim Jerbi (University of Montreal), Alexandre Gramfort (INRIA Saclay), Denis Engemann (INRIA Sac-lay), and Caroline Witton (Aston University), Montreal-based postdoc Mainak Jas added important MEG visualization functionality to the popular software *MNE Python*.

Through collaboration with Alexandre Gramfort and funding from the Google Summer of Code, **Tommy Clausner**, research assistant in the NEMOlab, developed functionality in *MNE Python* to perform group statistics on volumetric data such as MEG beamformer reconstructions. Finally, **Britta Westner** overhauled the beamformer source reconstruction functionality in *MNE-Python*, standardizing its API, adding support for different variants, and validating results compared to another popular MEG analysis toolbox, *FieldTrip*.

## New frontiers in MEG and magnetophysiology with optically pumped magnetometers

Prevailing MEG systems employ sensitive magnetometers based on superconductors (SQUIDs) that need to be cooled to -269°C with liquid helium. SQUID-based MEG systems are consequently quite large and constrained to a rigid one-size-fits-all shape; ultimately, this implies that many of the SQUID sensors are located farther away from their sources in the brain and body, leading to a reduction of signal strength, and that participants must remain still for optimal signal quality.

Optically pumped magnetometry (OPM), a rapidly emerging technology for sensitive measurements of magnetic field fluctuations, have the potential to free MEG from these constraints as they operate near room temperature and

are compact. They can therefore be placed directly on the head in any desired configuration, boosting signal strength due to their closer proximity to the underlying sources. The flexibility of OPMs further enables the same system to measure electromagnetically active sources throughout the body – not only the brain, but also, for example, the retina, heart, and possibly the spinal cord. Compellingly, it can even record the heart and potentially brain of a fetus in the mother's womb (Figure 1, lower). OPMs furthermore have minimal maintenance requirements and increased longevity, substantially reducing both start-up and running costs. The cost-benefit ratio of an OPM array is therefore considerably more favorable than that of specialized SQUIDs.

In Spring 2019, we tested a prototype OPM system in our laboratory. Thanks to lots of hard work from the vendor and our own *ad hoc* OPM crew (Britta Westner and Mads Jensen), we successfully recorded responses to visual stimuli, including a typical evoked field over occipital cortex and, to our knowledge, the first successful demonstration of an OPM to capture the human retina's responses (Figure 2, upper). We also managed to replicate the use of OPMs to detect the heartbeat of a fetus at 33 weeks of gestation (Figure 2, lower).

Our final 16-channel OPM system arrives in early 2020, and we are excited to follow up on these results as well as develop new applications to use them for neuromagnetic measurements from the brain as well as throughout the body.

## NEW FACES at CFIN

**Jordan Nicolas Alves**, joined CFIN in May 2018 as a PhD student co-supervised by Sarang S. Dalal (NEMOlab), Andreas Højlund (Dept.of Clinical Medicine) and Britta Westner (NEMOlab).

He graduated with a Masters in Cognitive Neuropsychology from the University of Lyon, France, in 2017. There he studied changes in the resting state networks of adults, children, and children diagnosed with Autism Spectrum Disorder (ASD) while they learned a new motor sequence and were recorded using magnetoencephalography.

His PhD project falls into the framework of vision neuroscience and studies the relation between retinal neurons and the Occipital cortex. It aims to elucidate motion processing mechanisms in the retina and cortex by recording electrical potentials from retinal neurons and using beamforming processing techniques to link retinal activity to the human visual motion cortical area MT+.

**James Isaac Lubell**, joined CFIN in September 2019 as a PhD student supervised by Sarang Dalal (NEMOlab).

Before joining CFIN, James received his Masters in Cognitive Neuroscience at the University of Oslo and received a dual Bachelors degree in Cognitive Science and Philosophy at the University of California at Berkeley. A continuing theme throughout his research have been advanced methodologies in electro- and magnetoencephalography as they pertain to neuronal oscillations.

His current PhD project focuses, broadly, on the retinal cortical relationship. Specifically, James uses MEG, electroretinograms, and optically pumped magnetometers to explore potential top-down cortical-retinal interactions and bottom-up retinal-cortical responses to the spatial frequency of natural stimuli. Retinal oscillations remain a largely untapped domain of inquiry in humans and hopefully can provide insight into how oscillations through out the brain help enable cognition.

# NEUROINFORMATICS & CERCARE

by Kim Beuschau Mouridsen

## Update from a CFIN spin-out

Cercare Medical was established in 2013 by CFIN researchers Kim Mouridsen, Mikkel Bo Hansen and Kartheeban Nagenthiraja. As a spin-out company from Aarhus University, Cercare was established to bridge the gap between research and clinical practice.

Over the years, the Neuroinformatics group and colleagues from CFIN and MIND*Lab* have developed novel techniques to map the capacity of tissue for extracting oxygen and sustaining metabolism using MR and CT imaging. Research has shown that regulation of microvascular flow heterogeneity may be a fundamental mechanism by which tissue modulates oxygen uptake and which may be altered in the early phases of many different diseases, including tumors and neurodegenerative disease, as well as being predictive of further disease development and response to treatment.

Therefore, the ability to seamlessly create high-resolution images that characterize capillary function may be valuable in clinical practice. However, medical software must satisfy a wide range of safety, robustness and regulatory requirements, while also integrating with a diversity of clinical workflows and routines. Therefore producing 'clinical grade' software is a major task which requires many different competences, and extensive funding.

Starting out as only a 'virtual' company in 2013 with the founders and one additional employee with commercial background, the company had grown to 12 employees in 2018 and 20 by end of 2019. With an increasing demand on space, Cercare Medical relocated from Aarhus University Hospital to Navitas, which, as part of INCUBA, is a science park and offers office space for startups and scaleups.

**RSNA 2019 Cercare**
Radiological Society of North America. The 105th Scientific Assembly and Annual Meeting was held in Chicago, December 2019.

Having spent the first years developing the technology and validating it, 2018-2019 focused on establishing contacts and partnerships with major healthcare providers. In 2018 we successfully engaged in a partnership with Siemens Healthineers and got to be among the first few companies worldwide to become available on the global Syngo.via platform, which has an outreach to a very large number of hospitals. We launched the first products together at RSNA in

**Navitas**
The home of Cercare Medical

**Philips Global Healthcare Breakthrough award**
Kim B. Mouridsen presenting Cercare Medical at the Philips HealthWorks Breakthrough Day event in Eindhoven, Netherlands, 12 December 2018.

Chicago in 2018 and in 2019 we participated for the first time with our own stand and several presentations.

In 2018 we were a handful of candidates selected from among more than 500 companies globally for participation in a prestigious accelerator program by Philips Healthcare. After successful completion of the program we were amongst the winners of the overall Philips Global Healthcare Breakthrough Program, an event with over 300 invited C-level guests and live broadcast.

Building a company to produce clinical grade medical software requires substantial funding. Cercare Medical is fortunate to have the Smedvig family office as a main investor since 2016, signing a larger investment agreement with them in 2018. The Smedvig family is from Norway with Peter Smedvig starting his first company in shipping in 1915, and later taking over a canning company. Today Smedvig Capital manages over 1.6 billion USD of assets in technology companies as well as property and private equity. Cercare is grateful to the Smedvig family as well as Smedvig Capital for their strong support and expertise.


# FACTS

**Smedvig**

Smedvig's story began with shipping and canning. The company backed the oil business by investing in tankships and oil rigs. They have also backed the steel industry, the equities market and property.
Today, Smedvig invests in disruptive and innovative businesses in addition to real estate, private equity and investment funds. Through four generations, their legacy has been characterised by change and renewal.

Smedvig invests across a wide range of business areas, but these share the same key characteristics: entrepreneurial spirit, operational experience and capital, combined with a long-term mindset

Assests under managment: 1.6 bn USD.
Offices in Stavanger, Norway and London, UK.

Cercare Medical

SIEMENS Healthineers

# NEUROPHYSICS 2018-2019

by Sune Nørhøj Jespersen

## Introduction

Tissue microstructure imaging is a thriving field within neuroscience[1]. In fact, as shown in Figure 1, the field's scientific activity increases exponentially, with a doubling of the number of papers every 2.9 years since 1995.

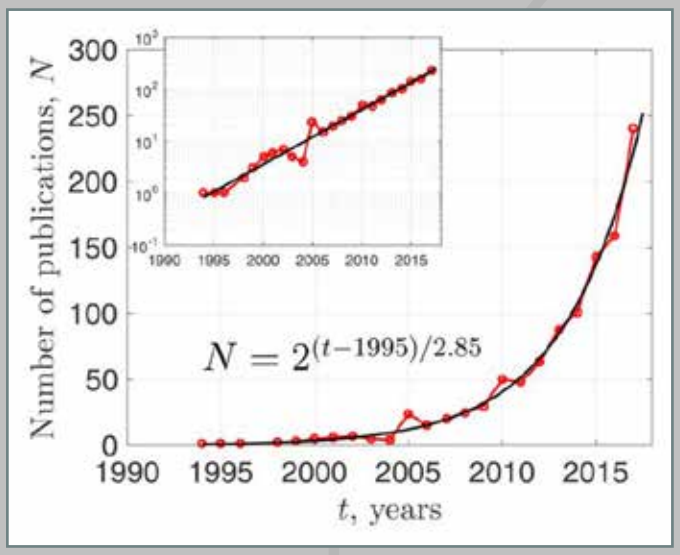


**Figure 1**
The exponentially increasing field of microstructural mapping, reproduced with permission from[1].

So what is microstructural mapping, and why is it useful? As the name suggests, microstructural mapping aims to image tissue properties on the micrometer scale. With MRI, this is possible to do noninvasively, and can supply valuable information about early stage pathological processes, aiding disease understanding and diagnosis, and informing drug development. However, the resolution of MRI is typically ~1 mm, so quantifying properties on a scale 1000 times smaller is indirect and relies on biophysical modeling. For example, the diffusion of water molecules which can be mapped with diffusion MRI, depends sensitively on micrometer scale structure[2]. Biophysical models predict for example how the diffusion coefficient decreases with time in different types of systems, and comparing to MRI data of time-dependent diffusivities therefore allows us to quantitatively characterize microstructural properties of brain tissue in patients. Example parameters (see Figure 2) are axonal densities, orientations, and diameters, myelin fraction, as well as intra- and extra-axonal diffusivities. Microstructural imaging aims to map these properties in 3D across the whole brain noninvasively. This is why we sometimes refer to these techniques as "virtual microscopy".

## The Neurophysics group

The members of the Neurophysics group changed a lot over the last 2 years. We said goodbye to Assistant Professor Ahmad Raza Khan, who after more than 4 years with us took up a Ramalingaswami Fellow position at the Centre of Biomedical Research (CBMR), SGPGI Campus, Lucknow, in India. Likewise, Andrey Chuhutin is now employed as a research software engineer at the Department of Bioscience, Aarhus University, after having completed both a PhD and a postdoc with us. Fortunately, 2 new PhD students enrolled during 2019, Jonas Olesen (financed by VELUX foundation) and Anders Dyhr Sandgaard (financed by Independent Research Fund Denmark), after successfully finishing their Masters' projects in physics at Aarhus University (AU). Nikoline Hummelmose, also a physics student from AU, initiated her masters project in the Neurophysics group in the fall of 2019.

## Research outputs

In 2018-2019, the Neurophysics group co-authored 17 papers, most of them related to microstructure imaging ranging from basic research to applications.

Our paper "On Modeling" published in Magnetic Resonance in Medicine in 2018[1], was an invited opinion piece written in collaboration with Dmitry Novikov and Valerij Kiselev. In view of the exploding interest in modeling of diffusion MRI, and the plethora of models proposed, we presented our view on the "art" of modeling and validation, its role in our field, and gave some advice on how to do it. This paper, which is cited 89 times (March 2020), is currently the 2nd most downloaded paper from the Journal in 2019.

Another long-standing collaboration with Dmitry Novikov, Valerij Kiselev, and Els Fieremans culminated in 2018 with the publication of our 53 page invited review "Quantifying brain microstructure with diffusion MRI: Theory and parameter estimation" in NMR in Biomedicine[2]. In it, we give a comprehensive overview of the field of diffusion MRI modeling. This paper is currently the 2nd most accessed paper from the Journal, and is among the Journal's top cited papers (114 citations as of March 2020) from that year.

A third review-like paper, "White matter biomarkers from diffusion MRI"[3], was published in a Festschrift issue of Journal

of Magnetic Resonance celebrating 2 decades of Joseph Ackerman editing the Journal.

A reoccurring theme in these papers, and a central theme of research in the group, is the so-called standard model of diffusion in the brain, which was developed in part by us in a 2007 paper in NeuroImage[4]. The term now encompasses a class of models under which many current biophysical models belong, and is currently probably the best description we have of diffusion in the brain. The model enables estimation of intra-axonal diffusivity $D_a$, extra-axonal parallel and perpendicular diffusivities $D_e^{\parallel}$ and $D_e^{\perp}$, and of axonal water fraction $f$.

In a 2018 NeuroImage paper[5], we built on our previous work[6] and developed a method to estimate model parameters using fast diffusion kurtosis imaging (DKI) data[7-9]. This type of data are routinely acquired on clinical scanners in a matter of minutes, in contrast to the original framework which required a much larger data set using very high gradients, making it infeasible in a human population. With the new method, the biophysical parameters can be quantitatively mapped over much of white matter with standard diffusion MRI.
(see Figure 2)

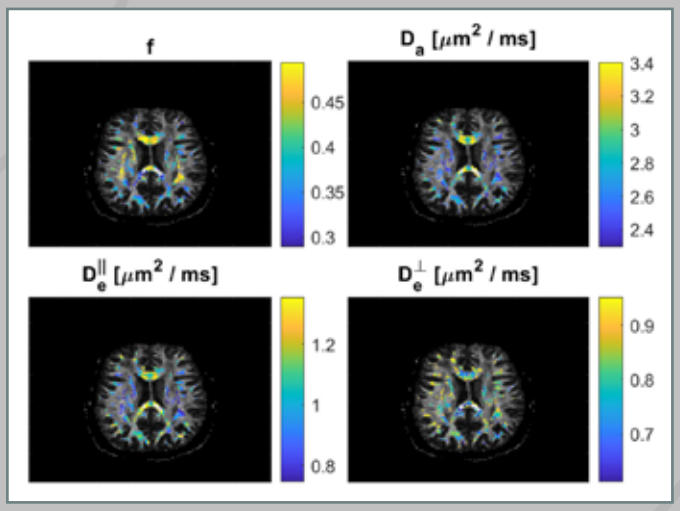


**Figure 2**
Example of parameter maps in a healthy human subject.
Axonal signal fraction (f), intra-axonal diffusivity ($D_a$), extra-axonal axial diffusivity ($D_e^{\parallel}$) and extra-axonal radial diffusivity ($D_e^{\perp}$).

# FACTS

## Group members and students

- Sune N. Jespersen (group leader, Professor)
- Brian Hansen (head of high field lab, Associate Professor)
- Mikkel Petersen (Postdoc)
- Jonas Lynge Olesen (PhD student)
- Anders Dyhr Sandgaard (PhD student)
- Nikoline Nørby Hummelmose (Master student)

## Teaching and outreach

- MR physics, graduate course in spring 2018 Department of Physics, Aarhus University.
- Lectures for high school classes about MRI
- GPU programming, graduate course in fall 2019, Department of Physics, Aarhus University.

## Conferences

- EU CONNECT CLUB: March 7-9 2018, Villa Thalassa, Helsingborg, Sweden. (Presentations by Sune Jespersen)
- ISMRM annual meeting: June 16-21, 2018, Paris, France. (Presentations by Ahmad Khan, Sune Jespersen)
- ISMRM annual meeting: May 11-16, 2019, Montréal, Canada. (Presentations by Ahmad Khan, Sune Jespersen, Andrey Chuhutin, Jonas L Olesen)
- Gordon Research Conference on tissue microstructure imaging: July 7-12, 2019, South Hadley, Massachusetts, US. (Sune Jespersen discussion leader)
- 5th International Workshop on MRI Phase Contrast & Quantitative Susceptibility Mapping: September 25 – 28, 2019, Seoul, Korea (Presentations by Anders Dyhr Sandgaard)

## Grants


- We thank the following funding agencies for their generous research support: the Lundbeck foundation (R291-2017-4375), Aarhus University Research Foundation, Augustinus foundation (18-1456), Dagmar Marshalls foundation, Independent Research Fund Denmark (grant number 8020-00158A), and the VELUX foundation (ARCADIA).

In[5], we were able to use this new strategy to acquire diffusion maps at multiple diffusion time points in a fixed pig spinal cord, enabling us to investigate the time dependence of these parameters. We found strong time dependence in all diffusivities, largely consistent with a recent theory proposing universal power law time dependence in biological tissues[10]: this time dependence is believed to be primarily caused by axonal caliber variations, and can therefore potentially be used as a biomarker of axonal beading[11]. Axonal beading is known to happen for example as a result of hypoxia.

The standard model and DKI were also used in several studies to detect pathological changes due to stress. Ahmad Khan was lead author on 3 papers looking at metabolic, macro- and microstructural alterations and recovery in rat models of stress depression[12-14]. Despite the mild but realistic paradigm, he found widespread changes in e.g. auditory and prefrontal cortex, amygdala and hippocampus. The fast diffusion kurtosis imaging protocol was also used in two studies led by Erhard T. Næss-Schmidt to examine postconcussion changes after mild traumatic brain injury, where DKI revealed altered microstructure in patients compared to controls[15, 16].

When estimating the standard model parameters from DKI data, and inherent so-called parameter degeneracy (ambiguity) must be circumvented, and this is currently done by assuming that intra-axonal diffusivity is faster than the extra-axonal parallel diffusivity. While this is supported by independent data, a fully data-driven approach is desirable for robustness, e.g. in the presence of pathology. Santiago Coelho showed that incorporating generalized diffusion weighted sequences, specifically double diffusion encoding (DDE)[17] can resolve this degeneracy, and produce more robust maps[18, 19]. The double diffusion encoding sequences have other uses, notably the detection of microscopic (i.e. sub-voxel) diffusion anisotropy[20-23] arising e.g. in an isotropic distribution of axons. In a paper first authored by Andrada Ianus, an efficient protocol for DDE using oscillating gradients was developed and used to reveal frequency dependent microscopic diffusion anisotropy, a novel probe of tissue microstructure[24].

**Sabbatical 2018-2019**

Thanks to the generous support of the Lundbeck Foundation, Aarhus University Research Foundation, New York University (NYU Langone), and Augustinus Foundation, Sune Jespersen was able to spend a one-year research sabbatical at the Center for Biomedical Imaging, New York University, working with Drs. Dmitry Novikov and Els Fieremans. The research topic of this sabbatical was so-called double diffusion encoding (DDE) sequences, which are a new form of magnetic resonance imaging diffusion-weighted techniques sensitive to other aspects of brain tissue microstructure compared to traditional techniques. Specifically, we have recently shown that this type of sequences can help constrain the inference of microstructure from MRI.

During this research stay at NYU, we made significant progress in the understanding of the signal encoded by this type of sequences (and their generalization), and their correspondence to tissue microstructure.

Specifically, we developed for the first time a complete theory for the diffusion signal from an arbitrary diffusion encoding sequence using effective medium theory. In this framework, tissue is characterized by its statistical properties, specifically the two point (and higher) correlation function(s) characterizing the distribution of barriers/obstacles, such as cell membranes, to diffusing water molecules. The result is a very fundamental and general relation between signal and structure, analogous to the relation between the narrow pulse diffusion signal from a conventional sequence and the so-called diffusion propagator, developed by Paul Callaghan in the 1980s, and underlying most diffusion MRI since then. As such, we can expect the results to have a large impact on diffusion research in the future, by clearly elucidating the link between all possible diffusion MRI probes and microstructure. The results will therefore be key in analyzing the microstructural information content in nonconventional diffusion sequences, as well as for designing novel sequences.

Our results were developed using advanced theoretical tools from statistical physics, specifically diagrammatical perturbation theory (Feynman diagrams) of the diffusion equation in a disordered environment (see Figure 3). They were further validated using massive GPU simulations on the BigPurple high-performance computing cluster at NYU.

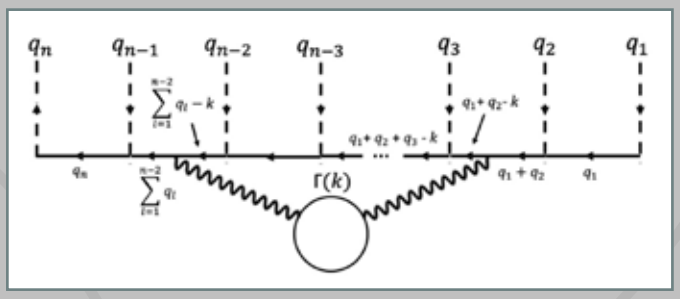


**Figure 3**
Feynman diagrams describing contributions to the diffusion signal for completely general diffusion MRI sequence. Presented as a PowerPitch at ISMRM 2019 in Montreal.

We are currently extending our results through our continuing collaboration, but preliminary results were presented by Sune Jespersen in a so-called PowerPitch at the annual meeting of the International Society of Magnetic Resonance in Medicine (ISMRM) in Montréal in May 2019.

Besides this main work, two other manuscripts are being written together with the group at NYU. One, “The impact of real axonal shapes on axon diameter estimation using dMRI” has been submitted to NeuroImage, and the other one “Optimal experimental design in multidimensional diffusion MRI for parameter estimation of biophysical tissue models” is submitted to Magnetic Resonance in Medicine.


**Collaboration with a view**
Sune Jespersen and Dmitry Novikov at the One World observatory (102nd Floor) in New York City.

# FACTS

## Talks

- 2019, Roskilde, Denmark, Roskilde University
- 2019, Massachusetts, USA, Harvard University
- 2018, Montréal, Canada, ISMRM
- 2019, St. Louis, USA, Washington University
- 2019, Nashville, USA, Vanderbilt University
- 2018, New York City, USA, New York University
- 2018, Middelfart, Denmark, Dansk Fysisk Selskab årsmøde
- 2018, Aarhus, Denmark, Aarhus University Oncology
- 2018, Paris, France, ISMRM

## Collaborators

- Noam Shemesh, Rafael Neto-Henriques and Andrada Ianaus, Champalimaud Research, Champalimaud Centre for the Unknown, Lisbon, Portugal
- Dmitry Novikov, Els Fieremans, Santiago Coelho, and Hong-Hsi Lee, Center for Biomedical Imaging, NYU Langone, New York, US.
- Mark Does, Biomedical Engineering, Vanderbilt University.
- Valerij Kiselev, Freiburg University Hospital, Freiburg, Germany.
- Leif Østergaard, CFIN/MIND*Lab*, Aarhus University.
- Sarang Dalal, CFIN/MIND*Lab*, Aarhus University.
- Lau Møller Andersen, CFIN/MIND*Lab*, Aarhus University.
- Yury Shtyrov, CFIN/MIND*Lab*, Aarhus University.
- Torben Lund, CFIN/MIND*Lab*, Aarhus University.
- Kristian Sandberg, CFIN/MIND*Lab*, Aarhus University.
- Jens Randel Nyengaard, Section for Stereology and Microscopy, Aarhus University.
- Erhard Trillingsgaard Næss-Schmidt, Hammel Neurorehabilitation Centre and University Research Clinic, Hospital Midt, Denmark.
- Ove Wiborg, Neurobiology, Aalborg University.
- Donald Kuhn, John D. Dingell VA Medical Center, Wayne State University, US.

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### NEW FACE at CFIN

**Jonas Lynge Olesen** joined CFIN in February 2019 as a PhD student in the Neurophysics group supervised by Professor Sune Jespersen. He is stationed at the first floor of CFIN south (our Nørrebrogade offices).

He has a Master's degree in physics and is specialized in diffusion models as applied within MRI. At typical MRI measurement times, the diffusion length of water molecules matches the characteristic length scale of cells. Therefore, diffusion MRI provides microstructural information accessible through modeling. Currently, model validation is a challenge and Jonas' thesis work was focused on addressing this by using imaging sequences additional to ordinary single pulse diffusion encoding.

Now, Jonas continues the work on diffusion modeling and explores what lies beyond the standard model of diffusion. This revolves around the analysis of extensive data from high field experiments as well as Monte Carlo simulations of spin trajectories in realistic neuron geometries.

## NEW FACE at CFIN

In September 2019, **Anders Dyhr Sandgaard** began his PhD studies in the Neurophysics group, headed by Professor Sune N. Jespersen.

Anders received his Master's degree in physics from the Department of Physics & Astronomy, Aarhus University. His thesis work focused on how the magnetic properties of white matter can be used as a probe of important biophysical information such as demyelination, neuronal loss, iron accumulation and segmenting brain regions in MRI experiments.

Anders is now continuing his pursuit of developing and validating biophysical models of magnetic microstructure of brain tissue, and how to construct realistic in silico models of e.g. white matter using electron microscopy co-registered to real ex-vivo MRI measurements.

Anders's office is at CFIN south (Nørrebrogade), first floor.

## NEW FACE at CFIN

**Nikoline Nørby Hummelmose**, BSc joined CFIN in September 2019 as a master student in the Neurophysics group led by Sune N. Jespersen.

She achieved a bachelor's degree in physics in 2018 from Aarhus University, Department of Physics and Astronomy. She is currently writing her master thesis in neurophysics.

The aim of the thesis is to examine the behavior of noise in EEG and/or MEG measurements, and how denoising the signal can lead to higher signal-to-noise ratio, and hence more precise source reconstructions. She will use principal component analysis (PCA) and random matrix theory (RMT) to predict the behavior of noise components. Furthermore, she will investigate if and how the noise is correlated in EEG and MEG measurements and how this correlation will affect the noise components.

# Neurotransmission

## Gambling disorder

by Arne Møller, Casper Schmidt and Catharina Blocher

### Gambling disorder – impulsivity and compulsivity

Addiction as a phenomenon has existed for centuries in the forms of substance use and behaviour, and is demarcated by impulsivity and compulsivity, leading to clinical symptoms of tolerance and withdrawal. In numerous western countries such as the U.S., addiction is one of the costliest public health problems, and present technological advances have paved the way for new addictive phenomena, which rely on behaviour rather than drugs of abuse. These addictive processes are primarily guided by the neurotransmitters dopamine (DA) and serotonin (5-HT), which play crucial roles in aspects of reward processing in the human brain, where overconsumption can lead to addiction. It is therefore of the highest relevance to assess more precisely the underlying mechanistic neurobiological aspects of reward processing, and assess addictive disorders in order to improve their options for treatment.

In Casper Schmidt's PhD study which was carried out between 2016 and 2019, we examined the roles of DA and 5-HT in reward processing, and the neural properties of gambling disorder (GD); a behavioural addiction demarcated by deficits in impulsive and compulsive behaviours.

In the pharmacological study of the dissertation, the effects of increasing DA and depleting 5-HT were studied separately and in combination in healthy volunteers (HV) during active reward processing, different phases and forms of reward, in order to mimic the underlying neurobiology of addictive disorders. Increasing DA and depleting 5-HT in HV increased neural activity to erotic rewards.This may imply that a neurochemical endophenotype of high DA and low 5-HT represents a core neurochemical component of GD.

In the gambling study, we examined the functional neural correlates of reward processing in treatment-active GD by testing the effect of active treatment on GD. We found that, relative to HV, GD subjects undergoing active treatment, exhibited increased reward-related neural activity towards erotic relative to monetary reward anticipation in HV, suggesting a shift in reward balance as a function of treatment. This was well in line with the fact that GD subjects from the study were abstaining from their detrimental gambling behaviours.

In conclusion, we found intriguing results highlighting the pharmacological roles of DA and 5-HT in reward, suggesting an effect of treatment through the functional neural changes observed in GD.

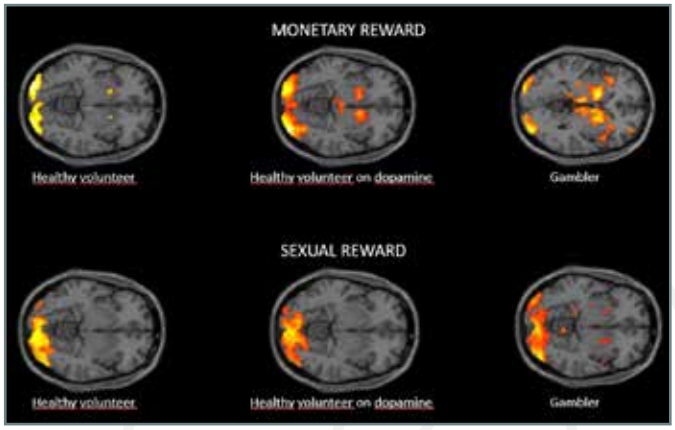


**Figure 1**
Pharmacological priming. There is an increased activety in the striatal reward areas during both monetary and sexual rewards in the brains of healthy volunteers treated with DA compared to baseline (column 2 vs column 1). An even stronger effect is seen in the gamlers brain (column 3). Schmidt et al., 2020

### Gambling disorder – dopamine and GABA

Gambling disorder is known to be associated with maladaptive gambling behaviors, where problems concerning self-control and diminished self-awareness seem prominent. Previous studies have shown that dysfunction of the prefrontal cortex plays an important role in addictions. A reduced recruitment of the prefrontal cortex may lead to failure of behavior regulation, resulting in problems with self-awareness and self-control. A previous study has investigated whether a change in the paralimbic interactions between the medial prefrontal/anterior cingulate and medial parietal/posterior cingulate cortices is found in pathological gamblers as compared to healthy controls. Using magnetoencephalography and a stop-signal task, the results show prolonged stop-signal reaction time in pathological gamblers in comparison to healthy controls, confirming impaired self-control in pathological gamblers (Rømer Thomsen, K., et al. 2013). Could the prolonged reaction time be described by a change in sensitivity in a gamblers brain?

It has previously been shown that an interaction between the medial prefrontal and parietal cortices – via synchronizing oscillations in the gamma range – is crucial in promoting self-awareness. These oscillations stem from intermittent GABA stimulation of pyramidal cells and are modulated by dopamine release. In a previous paper, it was found that the synchronization of gamma oscillatory activity between medial prefrontal and parietal regions is reduced in individuals suffering from gambling disorder (Lou, H. C., et al. 2016). It is therefore of interest to determine whether the dopaminergic regulation of GABA release is attenuated in problem gamblers, resulting in maladaptive gambling behaviors.

In a double-blinded controlled study consisting of 10 male problem gamblers and 10 age-matched healthy male controls, the participants were either given oral doses of 100 mg L-dopa or a placebo. By using co-registration with 3T MRI and [$^{11}$C]-Ro15-4513 PET, a ligand of benzodiazepine α1/α5 receptor availability in the GABA receptor complex, the changes in synaptic GABA levels in response to exogenous dopamine was measured.

As seen in Figure 2(a), the study found a dopaminergic activation of GABA release leading to decreased $^{11}$C-Ro15-4513 binding to GABA-A/BZD in healthy controls.
In Figure 2(b) the effect of exogenous dopamine was seen to be attenuated or even reversed in most of neocortex, thereby decreasing the synaptic GABA release in problem gamblers in response to dopamine (Møller, A., et al., 2019).

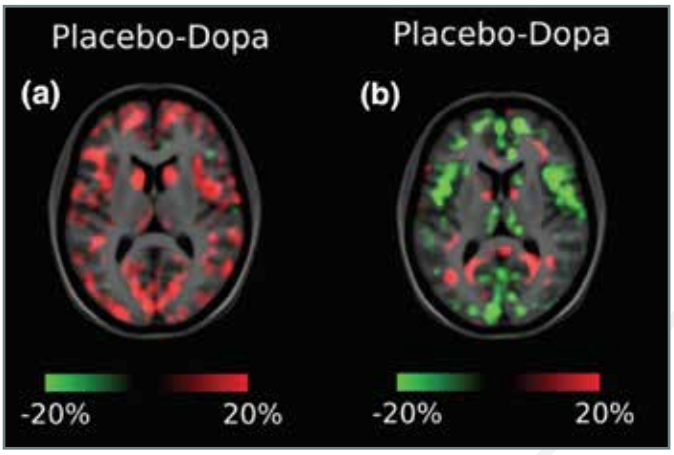


**Figure 2**
(a) Distribution of the effect of dopaminergic activation of GABA release demonstrated by reduced GABA□A/BDZ receptor availability in healthy controls. This effect was prominent in prefrontal regions and insula and present throughout neocortical regions and cerebellum.
(b) In problem gambling this effect of L□dopa was generally attenuated or even reversed in most of neocortex.
Møller, A., et al., 2019

The prolonged reaction time for pathological gamblers in the stop-signal task might therefore stem from a dysfunctional dopamine regulation of synaptic GABA release, possibly contributing to impaired self-control.

Based upon these findings, it may be beneficial in the future to test the effect of GABA-enhancing medications in gambling disorder, and study whether GABA agonists are able to adjust some of the maladaptive behaviors in males with gambling disorders.

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### NEW FACE at CFIN

**Catharina Blocher**, is currently finishing her Master's Degree in Medicine at Aarhus University. She has always been fascinated by neurology, and joined Arne Møller's Gambling Addiction Group as a research assistant in 2018.

Her current research project examines whether randomized item generators used in computer games (so-called loot boxes) are a risk factor for the development of Pathological Gambling.

The project is based upon a series of studies indicating similarities in response mechanisms when comparing loot boxes to gambling slot machines.

# PLASTICITY AND DISEASE

by Jakob Udby Blicher

The Plasticity and Disease group focuses on clinical and translational neuroscience, using techniques such as Magnetic Resonance Spectroscopy, Diffusion weighted MRI, EEG and Transcranial Magnetic Stimulation. During 2018 and 2019 we have published papers on Amyotrophic Lateral Sclerosis (ALS)[1], Depression[2], Migraine[3], Concussion[4], Parkinsons disease[5], Transient ischemic attack (TIA)[6], and Pathological Gambling[7]. Our focus is better disease understanding, with the aim of developing future disease prevention, cure and rehabilitation.

## ALS - Pathophysiology

Despite the severity of ALS, the underlying cause and pathophysiology is still largely unknown. The dominant hypothesis is that cortical hyperexcitability causes neuronal death that spreads from the cortex to the spinal cord. Cortical excitability is controlled by the main excitatory and inhibitory neurotransmitters, Glutamate and GABA respectively. Using Magnetic Resonance Spectroscopy we can measure relative or absolute concentration of several metabolites. Using specifically designed sequences (as MEGA-PRESS) or ultra high fieldstrengt (7T), it is possible to quantify both GABA and Glutamate. In 2019 we published the first study in ALS using a novel ultrashort-TE Spin Echo Full Intensity Acquired Localized (SPECIAL) sequence to measure both GABA and Glutamate in ALS[1]. The neurotransmitters were measured in the hand area of the primary motor cortex, and somewhat surprisingly we found that the excitatory neurotransmitter Glutamate was low, as opposed to what would be expected with hyperexcitability. This is likely explained by the fact that patients was on average more than 2 years after their first symptom, and consequently, a larger proportion of neurons have already died leading to lower production of the neurotransmitter. To clarify the role of Glutamate and GABA in ALS, it is necessary to examine patients very early after symptom onset and follow patients over time as the disease progresses. This will be an important area of research for our group going forward.

## Rehabilitation and assistive devices and the power of social media

The Plasticity and Disease group coordinates the project "Restore motor function through robotic arm exoskeleton and brain computer interface" (REMAP). The project is a collaboration between CFIN, Department of Neurology, Aarhus University Hospital, Aalborg University, The Danish National Rehabilitation Center for Neuromuscular Diseases (RCMF) and the Swedish company BioServo. The project is supported by the Innovation Fund Denmark.
The project aims to develop robotic devices controlled by brain activity registered using electroencephalography (EEG). The project is still ongoing and to-date, REMAP scientist have examined more than 40 patients suffering from ALS with EEG.

**Figure 1**
ALS patient during EEG recording.

Patients have been eager to contribute to the research, and in 2018, one of the participating patients shared his experience in research on Facebook, sharing a picture of him during our EEG recordings (Figure 1). The post was shared in the ALS community in Denmark and Norway and was read by Margo Lien and his brother Professor Terje Lien from Trondheim. Professor Lien shares our interest in assistive devices and had built a robotic arm for his ALS affected brother Margo. A contact from Margo and Terje Lien led to efforts to establish a Danish-Norwegian collaboration, and in April 2018 Professor Terje Lien participated, together with REMAP investigators, in a seminar on "Assistive Robotics for ALS patients" at Center for Sensory-Motor Interaction (SMI) at Aalborg University. We are thankful for the willingness of patients to participate in our research despite their very severe disease, and positively surprised by the new opportunities for research collaboration through dissemination of our work through social media as Facebook.

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## NEW FACE at CFIN

**Tobias Glaston Stærmose,** Bsc Med.
Tobias is a Masters degree student in Medicin at Aarhus University, and a PhD Student at CFIN, with Jakob Blicher as his main supervisor. Tobias has previously done a research year at CFIN in a MRS (Magnetic Resonance Spectroscopy) project.

He is now doing his PhD with focus on motor function in ALS patients, using both MRS and functional MEG. The study is part of the REMAP project that focuses on development of BCI aids for ALS patients.

## NEW FACE at CFIN

**Nikolaj Bøgh,** MD, is a PhD student at the MR Research Center, Aarhus University. He is affiliated to CFIN through Jakob Blicher, who supervises his PhD.

Nikolaj graduated as a medical doctor from Aarhus University in 2019. During his studies, he has conducted a series of preclinical research projects in MRI.

In his PhD, he is combining his knowledge in MRI with interest in neurology. Nikolaj will examine ALS patients with a novel technique termed hyperpolarized MRI. Further, he will continue his preclinical work in the field of metabolic MRI of neurological disorders.

# FACTS

### Core and affiliated group members

- Jakob Udby Blicher
- Erhard Næss-Schmidt
- Krystian Figlewski
- Tobias Glaston Stærmose
- Christina Shen-Zhuang Nielsen
- Mia Heintzelmann
- Nikolaj Bøgh

# PNM

## Perception and Neuroarchitectural Mapping Group

by Kristian Sandberg

The Perception and Neuroarchitectural mapping group is a relatively new research group focusing on basic as well as clinical research. In 2018-19, Kristian Sandberg started the SkuldNet consciousness consortium to initiate a large-scale effort of linking MRI-based estimates of neural architecture to individual differences in conscious perception/memory as well as more general cognitive phenomena like intelligence and personality. Late 2018, he was awarded an EU Cooperation of Science and Technology (COST) Action grant (CA18106) of around €500.000 to support the consortium, which has subsequently grown to include more than 100 scientists globally.

Much of the work in 2018-19 has focused on designing experiments and preparing the start-up of large-scale data collection sites, each of which test 200-300 participants for 10-20 hours, incl. 1 hour of MRI. Currently, data collection is ongoing in Aarhus, and another 4 sites are expected to commence data collection in 2020-21. An important part of the reasoning behind conducting large-scale studies is that the number of statistical tests that can be made within a dataset increases exponentially as a function of sample size whereas the number of comparisons you need to make when adding more experiments increases linearly. It is thus substantially more efficient in terms of costs and labour to conduct many experiments simultaneously with one large sample.

Large datasets do not only have adequate power to examine many behavioural/cognitive phenomena, but also to relate them to multiple brain characteristics. MRI provides a time-efficient, non-invasive method for examining these brain characteristics. In SkuldNet/CA18106, we use a range of different sequences. The results of our current pipelines are shown in Figure 1, which also illustrates how they, in combination, form a complex data structure that we call a neuroarchitectural map. This structure can then be examined with a range of univariate and multivariate statistical methods, incl. machine learning. Furthermore, it can form the basis of more complex computational, neuroarchitectural modelling approaches where the mechanisms of specific neural features can be examined. These two approaches will form the bulk of the work of the Perception and Neuroarchitectural mapping group over the next years.

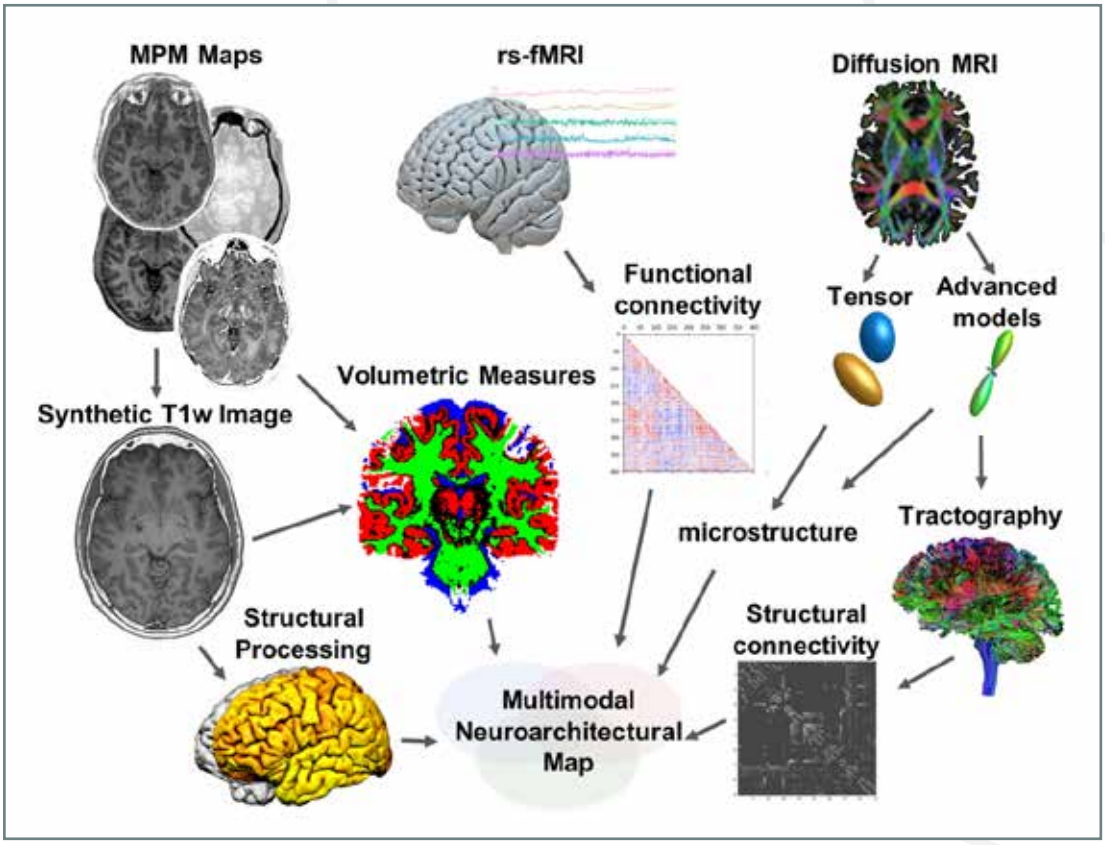
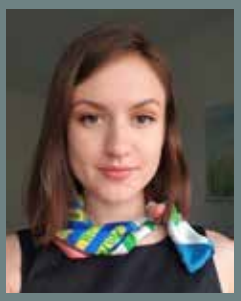



**Figure 1**
Neuroarchitectural mapping. Schematic of a key subset of MRI processing pipelines used in the SkuldNet consortium leading to multimodal neuroarchitectural maps.

## NEW FACE at CFIN



**Katarina Vulić**, MSc. Katarina holds a Bachelor's degree in Psychology and a Master's degree in Experimental Psychology from the University of Belgrade, Serbia.

During her master studies, she explored the effects of noninvasive brain stimulation (tDCS, otDCS) of posterior parietal cortex on encoding and associative memory. Katarina's research interests include memory assessment, cognitive aging and associative decline, while her main focus is behavioral and neural differentiation between memory sub-processes.

She is currently pursuing a PhD, focusing on neural underpinnings of the domain-general binding component and modality-specific processes of associative memory. Her PhD project is conducted within COST Action The neural architecture of consciousness, which brings Katarina to CFIN.

At CFIN, Katarina is working under the supervision of Kristian Sandberg. She is involved in behavioral assessment for neuroarchitectural mapping of memory and other cognitive functions.

Although the group spends the majority of its time on neuroarchitectural mapping at the moment, it is not its sole focus. Particularly modelling and empirical examination of conscious perception remains a key topic. In a paper within this topic, for example, Maria Hernández-Lorca et al. (2019) used EEG to contribute to the long-standing debate of whether consciousness is related to late frontal activity or earlier sensory processing by showing that conscious experience pertaining to the emotional content of a stimulus is reflected in perceptual areas at an early time point.

## On the role of the posterior cortex in human conscious perception

In September 2019, **Kristian Sandberg** defended his Higher Doctoral Dissertation (D.M.Sc.) entitled "On the role of the posterior cortex in human conscious perception". The defense was a great opportunity for interesting scientific discussions with the two opponents, Professors Giulio Tononi and Juha Silvanto, who are leading international experts on consciousness.

### About the thesis:

One of the key issues in the neuroscience of consciousness has been whether consciousness requires activation of higher order areas in the frontal cortex or whether signals in, for example, sensory areas are sufficient. Over the last decades, data has often been interpreted as supporting the theory that consciousness is linked to an all-or-none signal in the prefrontal cortex. In his higher doctoral thesis composed of 9 publications, Kristian Sandberg argue how his own research along with results from other laboratories support the opposite view.

First, behavioral results are presented indicating that conscious experiences are primarily non-dichotomous and thus should not be described as originating from all-or-no signals. Next, a series of studies using magnetoencephalography (MEG) are presented. These indicate that the neural signatures that are closest to conscious experiences are not the relatively late pre-frontal all-or-none signals that earlier studies have indicated but instead sensory signals that vary gradually with the clarity of the conscious experience. Finally, studies are presented which investigate the correlation between individual variations in the neuroarchitectural properties of the sensory cortex (specifically GABA concentration and grey matter volume) and conscious experience.

Taking these findings together, he argues for a paradigm shift in the field of consciousness research and presents a general methodological framework that can be used in in the future to bring consciousness research to a level where we can provide adequate basic scientific explanations and make clinically relevant predictions.

# Neuroscience in China

by Kim Ryun Drasbek & Vibeke Sauer Panyella

Researchers at CFIN have contributed greatly to the SDC university collaboration between Denmark and China over the past years and continues to be deeply involved in both the SDC Master programme in Neuroscience and Neuroimaging as well as in research collaborations within SDC Life Sciences theme. We have had a steady uptake of Danish, Chinese, and international students resulting in classes of 20+ students every year of this master programme embracing all aspects of neuroscience and neuroimaging. Many of the graduates have continued their career within research as PhD students, several have obtained funding through the SDC to pursue collaborative project ideas combining expertise of Danish and Chinese labs. A student from the first cohort (2011) has now finished a joint SDC PhD and is now employed as MR Clinical Scientist at Philips. Currently, we have several SDC Neuroscience and Neuroimaging candidates conducting their PhD at CFIN with co-funding from SDC. Some of them are quite close to finishing while others have just started their projects.

While the Danish and international students experience a foreign culture and work environment during the master programme as it takes place in China, the Chinese students experiences an international work atmosphere while visiting Denmark for 2 months during their master project period. CFIN hosts several student lab stays and with the great help of Program coordinator, Vibeke Sauer Panyella, CFIN arranges a tour of Danish neuroscience and neuroimaging facilities as well as workshops for all the Chinese students to train their presenting and writing skills.

## Research collaborations

In the summer of 2018, Kim Ryun Drasbek was appointed Principal Coordinator of research collaborations within the SDC Life Science theme that also includes the Omics research subtheme as well as the Master programme in Life Science Engineering and Informatics placed at DTU. He has introduced several initiatives to facilitate research collaboration between the different research groups within SDC Life Sciences with a goal of bridging educational and research traditions. Here, the 1st annual SDC Life Sciences symposium took place in the SDC Building at the Yanqihu campus in the Fall of 2019 with MSc students, PhD students, and scientist from both Denmark and China. The symposium included joint sessions, parallel sessions with student presentations as well as dedicated scientific sessions for the SDC involved researchers from both countries.

In August 2018, a group of five of the core researchers from the SDC collaboration visited their Danish partners. Among them was the Chinese Head of Educational Programme, Professor Xue Rong. The visit aimed to strengthen their existing connections with Danish research environments and to extend their network. During their stay, the Chinese researchers gave presentations to Danish research colleagues within the field of neuroscience at Aarhus University, Technical University of Denmark and University of Copenhagen.

Through 2018, we explored new research institutes in China. In the spring of 2018, a delegation of researchers visited

Chinese SDC students visiting H.C. Andersens Hus in Odense.
Photo: Vibeke Sauer Panyella

Chinese SDC researchers visiting CFIN, and eating Danish 'smørrebrød'.
Photo: Vibeke Sauer Panyella

SDC Life Sciences Symposium 2019 in Beijing, China.
Photo: Vibeke Sauer Panyella

HUST-Suzhou Institute for Brainmatics, to learn more about their facilities for mapping brain structures and connections using a highly sophisticated automated technology. The Innovation Attaché, Martin Bech, at Innovation Centre Denmark in Shanghai, facilitated this meeting. The visit also aimed at raising awareness of SDC within the industrial technology research center.

In the fall of 2018, a delegation of Neuroscience researchers visited the Beijing Institute of Technology, who work with robotic prosthetics. We had a look at their version of a robotic arm, which was of special interest to MD and CFIN researcher Jakob Blicher.
Read more about Jakob Blicher's research in the Plasticity and Disease group at page 58-59.

Chinese SDC researchers and Danish hosts cruising Aarhus coastline during Sailing World Championship, 2018.
Photo: Kim Ryun Drasbek

Jakob Blicher at the Beijing Institute of Technology.
Photo: Vibeke Sauer Panyella

### A different take on a PhD course

In the fall of 2019 the SDC Neuroscience & Neuroimaging programme hosted a PhD course in the SDC building. The course was staged as the Neuroscience PhD Symposium – Neuroscience Challenge 2019. 28 PhD students from China and Denmark met with several international speakers within the field of neural functions, brain information processing and behavior, to foster novel ideas, generate technical developments and create a platform for future collaborations. Along with this great opportunity, the PhD students received points from the Graduate School of Health at Aarhus University.

# CENTER FOR MUSIC IN THE BRAIN

by Peter Vuust

2018 and 2019 has been extremely productive years at Center for Music in the Brain (MIB) in terms of publications, international collaborations, and outreach. We have published a high number of peer-reviewed papers with an increasing impact on the field of neuroscience and music and an increasingly strong effect on decision makers with regards to strategies for the use of music within the educational and health care systems in Denmark.

Central to the MIB research is the tenet that music, structured around the unifying theme of prediction, can advance our understanding of prediction as a fundamental brain principle across a range of functional domains, as expressed in our Predictive Coding of Music (PCM) model. In 2019, the model was featured in a review paper in the prestigious journal, Trends in Cognitive Science, and presented orally at the predictive coding conference in Marseille in September.

Through the process of studying PCM as the basis of perception, action, emotion, and learning at the individual level a new direction of research has emerged at MIB, which focuses on understanding the predictive mechanisms involved in how music becomes meaningful when it is communicated between humans. Hence, in 2019 we suggested a new oscillator-based model for understanding perception/action brain processes related to interpersonal synchronization, which applies successfully to people tapping together and the related brain responses. In a more ecologically valid context, we are using musical improvisation as a model for studying non-verbal communication as well as creativity through music analyses, mathematical modelling, and with behavioural and neuroscientific experiments; most often using jazz as the prime example.

At a greater scale we published a paper in the high impact journal eLife, which is now featured at videnskab.dk, showing how structure in music evolves over centuries, possibly millennia, partly through the process of intergenerational transmission, “adapting” to the brains of its users, i.e. transmitters and receivers. We are also using a novel social entrainment video paradigm to show how music can provide a meaningful context for social interactions and hereby strongly influence the experience of social closeness even though participants may not be aware of this effect. These findings suggest that how much we enjoy a musical context is more relevant for the influence of temporal social cues on affective social bonding than how familiar we are with this context.

These basic research studies feed into our clinically oriented research branch, with the work on understanding music as an interpersonal phenomenon bearing great potential for being translated into clinical applications. One of the highlights was our publication in Nature Communications showing that by moving beyond the state-of-the-art and developing a completely data-driven Hidden Markov Model (HMM) it is possible to characterise the spatiotemporal complexity of whole-brain networks and state transitions. Here, we used a prediction-based method to discover the dynamic choreography of different whole-brain networks across the wake-sleep cycle and are in the process of translating this knowledge into our research on the role of music listening for sleep disorders. Other important clinical applications include listening interventions to improve mood, mental health, and to alleviate pain perception and cancer-related anxiety. We are also involved in active rehabilitation interventions in patients diagnosed with chronic lung disease and in patients with Parkinson’s disease, and record brain activity, with the aim of mapping out the music related hearing capabilities of cochlear implant-users.

MIB values international collaborations and during the years, we have hosted a number of doctoral, postgraduate and undergraduate students from abroad and prominent guest speakers and collaborators, such as professors Martin Lotze, Petri Toiviainen, Edward Large, Eckart Altenmüller and Mari Tervaniemi. 2019 also saw new national and international collaborations e.g. as an outcome of our work on cortical feedback mechanisms in relation to musculoskeletal pain in musicians, recently funded by the Lundbeck foundation and performed together with Danish National Research Center for Neuroplasticity and Pain (University of Aalborg). We also initiated a collaboration with Anne Caclin and Barbara Tilmann, University of Lyon in which we are recording EEG in amusics, and with Bob Knight at UC Berkeley, where we use intracranial recording to understand the underlying brain mechanisms of music memory.

2019 saw the successful PhD defenses of Ole Adrian Heggli and Maria Celeste Fasano, who were part of the first brood of PhD students hired at MIB back in the beginning in 2015. Ole continues in a postdoc position at MIB, while Maria Celeste has been employed as postdoc at the Psychology Department at Aarhus University. In December, David Quiroga defended his thesis and was subsequently hired to continue his post-doctoral research at MIB. As a new addition to our postdoc group, we welcomed Alexandre Celma-Miralles from University

Pompeu Fabra. Since September 2019, Professor Marcus Pearce had to move back to the UK for family reasons, but he still remains an important collaborator and PhD supervisor at MIB.

In the spring of 2019, the scanners and technical staff of CFIN moved to Aarhus University Hospital in Skejby, and shortly after, MIB and the rest of CFIN moved to another building at Nørrebrogade – the oldest building at the old "Kommunehospitalet". After a short period with minor turbulence, we have now settled in at the new facilities and the collaboration with the technical staff works seamlessly.

Working with the Mariani Foundation, lots of effort has gone into organising the upcoming Neurosciences and Music Conference taking place in Aarhus June 2020, for which we received 300.000 DKK from the Lundbeck Foundation in 2019. We have planned an Aarhus Summer School to precede the conference with an impressive lineup of renowned speakers, including Professors Robert Zatorre, Virginia Penhune and David Huron, and exciting hands-on workshops. Unfortunately, both events have been postponed to 2021 due to the Covid-19 epidemic.

In December 2019 we received the wonderful news that MIB will be granted a second period by DNRF from 2021-2026.

With the latest Music in the Brain Annual Report, we highlight scientific progress and key events in 2019 and wish to thank MIB and CFIN scientists and collaborators, the Danish National Research Foundation, Central Denmark Region, the Department of Clinical Medicine at Aarhus University, The Royal Academy of Music Aarhus/Aalborg, Aarhus University and other generous funding sources for their continued support.

All Center for Music in the Brain Annual Reports can be found and downloaded from the MIB website:
https://musicinthebrain.au.dk/annual-reports/

# FACTS

## Mission Statement

The Danish National Research Foundation's Center for Music in the Brain (MIB) is an interdisciplinary research centre aiming at addressing the dual questions of how music is processed in the brain and how this can inform our understanding of fundamental principles behind brain processing in general.

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

MIB retreat 2019. This year the annual retreat was held at Skanderborghus, and besides 'make time to think' group work, there was also time for a boat ride on the Skanderborg Lake and of course the obligatory MIB group photo. Photos: Hella Kastbjerg

# CENTER FOR MUSIC IN THE BRAIN

## Examples of MIB research from the 2019 Annual Report

### The four strands of research at MIB cover:

#### Perception

Perception can be described as the process of minimizing prediction errors between higher-level "prediction units" and lower-level "error units" in the hierarchically organized brain. The dynamic interplay between predictable structures in music and predictive brain processing is a key determinant of perception and cognition of music. The Perception group tests hypotheses derived from PCM (predictive coding of music hypothesis) by varying the intramusical features of music (e.g. in rhythm, melody, harmony, form, instrumentation, and acoustics) and the extra-musical factors influencing the brain's model. In this way, the work in this group bridges the gap between musicology, psychology and neuroscience and lays out the foundation for the work in the other groups.

#### Action

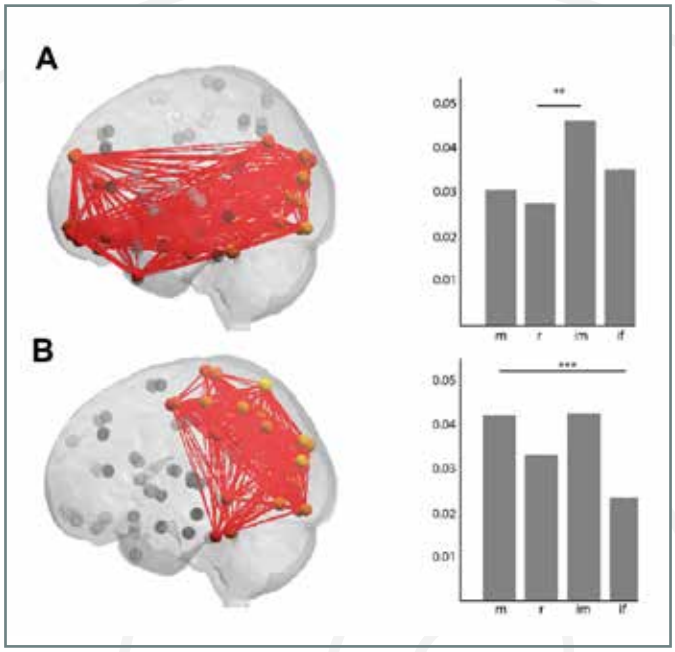
Action is the active engagement of the motor system to resample the environment in order to reduce prediction error. Music action centered around rhythm is a focus of MIB for several reasons. Rhythm provides a powerful tool for investigating the relation between perception and action, since there is a direct link between listening to musical rhythm and motor behavior. Our work will be based on the hypothesis that action aims at minimizing prediction error. Equally important, performance and music listening have social and communicative functions in which rhythm plays a key role. Hence, in a musicological perspective such studies touch upon the crucial question of whether music is an evolutionary adaptation designated for social cohesion.

#### Emotion

Emotion, attention, and motivation act as weights or modulators of the prediction error itself, guiding behaviour, action and learning through neurotransmitters such as dopamine. Emotion is fundamental to human life, survival and well-being, and music is one of the strongest and most universal sources of human emotion and pleasure. Meyer formulated the idea that musical anticipation and incongruity, i.e. elements that do not fit with schematic, veridical or short term memory-based predictions, may be a fundamental source of music emotion and pleasure, an idea that was later pursued and expanded on by Huron. The Emotion group investigates predictive mechanisms related to emotional and pleasure processing in the brain.

#### Learning

Learning is the long-term influence on the prediction units. Playing music is a highly specialized skill that places immense demands on the underlying neural substrates, making music an important model for studying brain plasticity and development. The Learning group investigates the influence of long and short term training on predictive processing and how predictive mechanisms for music are shaped by music training, expertise, and individual cultural factors such as listening history, music-stylistic preferences, or biological factors such as personality and genotype.




### Action

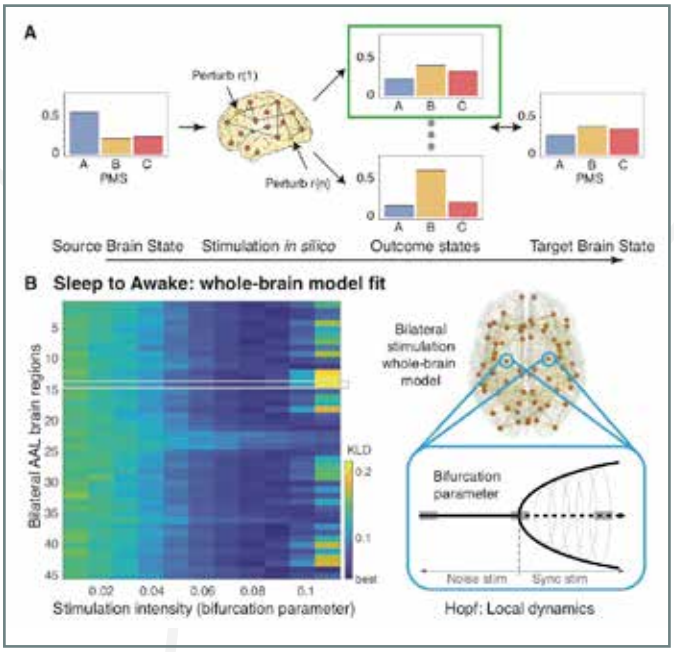
Professor Peter Vuust

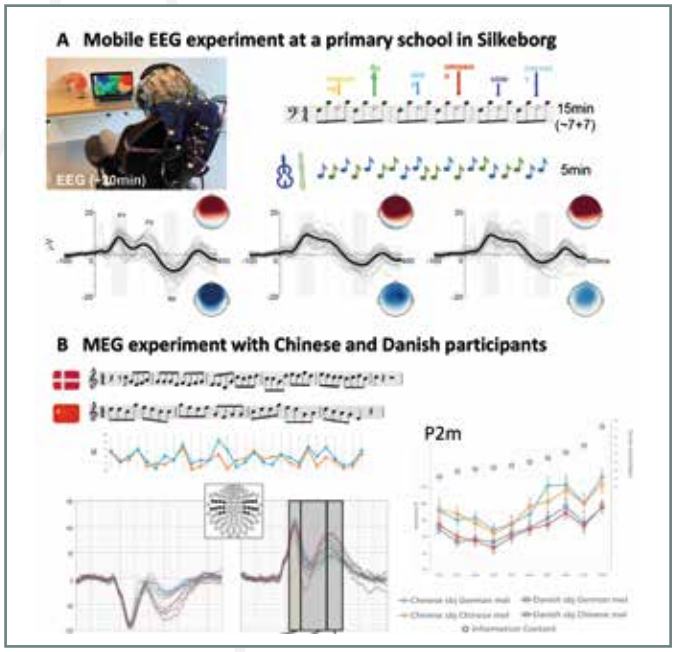
**The dynamical repertoire of functional connectivity brain states during musical improvisation.**

Music is a social phenomenon, in that we make, listen or dance to music together. An important form of musical interaction and meaningful communication during playing take the form of improvisation. In jazz, in particular, the act of improvisation is the central, defining element. In collaboration with the other strands of MIB, the action strand used musical improvisation as a model for studying non-verbal communication, combining structural and functional neuroimaging data with connectomics and whole-brain computational modelling. PhD student Patricia da Mota have fMRI scanned expert jazz piano players and contrasted their improvising over a well-known jazz song (Figure above).

A) When participants (pilot data, n=16) improvise based on a melody (im) they engage a brain state comprising the visual, default-mode and reward/pleasure with a significantly higher occurrence probability than when they read music (r) .

B) When they play from memory (m) they engage more often a brain state comprising visual, sensorimotor, default-mode and attention networks than when they improvise freely (if).




## Emotion

Professor Morten L. Kringelbach

**Schematic of strategy for forcing transition between source and target brain states.**

A fundamental question in neuroscience is how to force a transition from one brain state to another. We used whole-brain modelling to discover how to wake up the sleeping brain and vice versa (Deco et al 2019, PNAS). A) This was achieved by creating a whole-brain model of each brain state and systematically perturbing each brain region. B) More specifically, we changed the stimulation intensity, i.e. the strength of the perturbation, by changing the local bifurcation parameter for each brain region (right panel). The matrix shows the results of stimulating the whole-brain model bilaterally with the KL-distance obtained for brain state transition fitting when perturbing separately each of the 45 regions (using bilateral stimulation) with different stimulation intensities in source state (deep sleep). To illustrate the procedure, we have highlighted one region (in grey), which is being stimulated while the other regions are kept at their normal bifurcation parameter.

The colour scale for the results shows the level of fitting with the target state (wakefulness), ie. lower values (deep blue) correspond to the most effective transitions. The results show that stimulation in most regions will lead to an awakening.

## Learning

Professor Elvira Brattico

**From Denmark to the world**

Learning to predict the environment is not restricted to a specific place and culture. It is a mechanism that allows us humans to adapt to any new situation and to form new meanings and ultimately to build new cultures and transmit them among humans and across generations. We strive to understand how these processes, when related to music, manifest in the behavior and brains across the lifespan and in the world. Further, we simulate learning and transmitting musical codes across generations in the lab with a 2-player signalling game, finding the underlying auditory-cortex intraconnectivity as reported in a paper published in eLife.

A. Bringing mobile EEG in a primary school, we study instrument learning by measuring the brain responses to piano, flute and violin sounds in 9-years old children.

B. For investigating learning across world cultures, we measured in Aarhus with MEG around 40 Danish and Chinese participants. Profiting from Professor M. Pearce's expertise in modelling the local expectancy of melody pitches based on a Chinese or a German corpus, we found that long-term knowledge of a musical culture does not affect the auditory-cortex responses to each sound.

# Highlights in 2018 & 2019

### Early Career Prize by The British Association for Cognitive Neuroscience (BACN)

The 'Early Career Prize' is awarded to young researchers who have contributed their high-standard and pioneering work to the field of cognitive neuroscience. In 2019, the prize was awarded to Micah G. Allen, Associate Professor at CFIN, Aarhus University and Cambridge University, and AIAS Fellow at AU. The aim of the prize is to reward and to recognize distinguished scholarship and research excellence undertaken over a period by a cognitive neuroscientist who is currently active in research, and who has made a substantial contribution to Cognitive Neuroscience in the UK.

'The Early Career Prize' was awarded to Micah on 2 September 2019 at the Annual Meeting of the British Association for Cognitive Neuroscience (BACN), where he gave an 'Early Career lecture' entitled 'Interoceptive Self-Inference: An Embodied Approach to Computational Psychiatry'.

### Leif Østergaard awarded a Lundbeck Professorship

In December 2019 Professor and head of CFIN, Leif Østergaard was awarded DKK 40 mio. from the Lundbeck Foundation's Professorship program. Over the next 6 years, the Lundbeck Professorship grant will allow him to examine the role of capillaries – the brain's smallest blood vessels – in healthy aging and in the development of dementia.

The grant will allow Leif Østergaard's research team to develop and validate methods to detect capillary dysfunction and examine the importance of this overlooked vascular disease phenomenon in aging and dementia. The team hopes their research will ultimately result in new strategies to prevent, diagnose, and treat some of the disease changes that contribute to age-related cognitive decline, reducing the number of citizens who develop dementia.

The new research program is called BRAIN COMET.





### CFIN South and MIB housewarming, 27 June 2019

After a long and strenuous moving process during the spring of 2019, CFIN South and MIB researchers and administration settled in building 1A at the old hospital grounds.

A grand housewarming was organized and resulted in a lovely, warm day in the old garden in front of the building, where fun and games celebrated our new home at Nørrebrogade.

We were blessed with fabulous weather and had a great day both inside and outside the old hospital building.

All photos: Vibeke Sauer Panyella





## Two new Doctors of Medicine at CFIN

During 2018 and 2019 two CFIN researchers defended their Higher Doctoral Dissertations and received the Doctor of Medicine (Dr.Med.Sc.) degree.

**Brian Hansen**, Associate Professor and head of the High Field MRI Lab defended his Higher Doctoral Dissertation, entitled *Experimental diffusion MRI from cellular-level microscopy to in vivo application* on 7 September 2018.

Read more at page 8-10

**Kristian Sandberg**, Associate Professor and head of the Perception and Neuroarchitectural Mapping Group (PNM) defended his Higher Doctoral Dissertation, entitled *On the role of the posterior cortex in human conscious perception* on 6 September 2019.

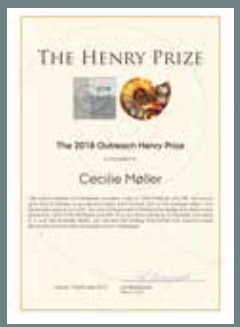
Read more at page 60-61

## 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 2018 The Henry Prize was split between CFIN research radiographer Dora Grauballe and MIB researcher, postdoc Cecilie Møller.
In 2019 The Henry Prize was split between CFINs head of technical staff, Associate Professor Torben Ellegaard Lund and MIB researcher, postdoc Jan Alexander Stupacher.
They were all nominated for the prize by their fellow researchers as worthy of the 2018/2019 prize for their research contributions, initiative, helpfullness and overall admirable efforts to communicate 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)
Diego Vidaurre
Elvira Brattico (MIB)
Eugenio Gutiérrez Jiménez
Jakob Udby Blicher
Kim Mouridsen
Kim Ryun Drasbek
Kristian Sandberg
Leif Østergaard
Micah Allen
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

## Technical Staff

Anna Bay Nielsen, Laboratory Technician
Christopher Bailey, MEG Physicist
Dora Grauballe, Research Radiographer
Irene Klærke Mikkelsen, Data manager
Lisa Ann Hald, Animal Technician
Mads Sloth Vinding, MR Physicist
Martin Snejbjerg Jensen, Engineer
Michael Geneser, Radiographer
Mikkel Bo Hansen, Software Engineer
Ryan Sangill, MR Physicist
Susanne Smith Christensen, Laboratory Technician
Torben Ellegaard Lund, Head of Technical Staff

## Administrative Staff

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

## High Field MRI Lab

**Group leader: Brian Hansen**
Thomas Beck Lindhardt

## Pre-clinical Optical Group (POG)

**Group leader: Nina Kerting Iversen**
**Optical lab coordinator: Eugenio Gutiérrez Jiménez**
Anders Dyhr Sandgaard
Anete Dudele
Brian Hansen
Christian Damsgaard
Donato Sardella
Halvor Østerby Guldbrandsen
Ina Maria Schiessl
Katrine Tang Stenz
Kim Ryun Drasbek
Lisa Ann Hald
Luca Bordoni
Mia Skjødt Viuff
Sebastian Frische
Signe Kirk Fruekilde
Susanne Smith Christensen
Thomas Beck Lindhardt
Tingting Gu
Vladimir Matchkov

## Molecular and Cellular Neuroscience Lab

**Group leader: Kim Ryun Drasbek**
Jesper Just
Katrine Tang Stenz
Kristina Christensen
Morten Jenrich Hansen
Signe Kirk Fruekilde
Sun Sha
Tingting Gu

## Applied Imaging and Modelling (AIM)

**Group leader: Simon Fristed Eskildsen**
Lasse Stensvig Madsen
Mikkel Karl Emil Nygaard
Robert Dahnke
Rune Bæksager Nielsen

## Cognitive Neuroscience Research Unit (CNRU)

**Group leader: Morten Overgaard**
Asger Hinrup Kirkeby
Martin Dietz
Peter Fazekas
Thomas Alrik Sørensen
Timo Lehmann Kvamme

## ECG Group
**Group leader: Micah G. Allen**
Camile Costa Correa
Nanna Kildahl
Nicolas Legrand
Niia Nikolova
Malthe Brændgaard Sørensen
Peter Thestrup Waade

## Functional Hemodynamics
**Group leader: Leif Østergaard**
Anete Dudele
Anna Tietze
Eugenio Gutiérrez Jiménez
Hugo Angleys
Irene Klærke Mikkelsen
Jakob Udby Blicher
Kim B. Mouridsen
Kim Ryun Drasbek
Klaus Ulrik Koch
Maryam Anzabi
Maryam Ardalen
Mikkel Bo Hansen
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Peter Mondrup Rasmussen
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emotion
functional hemodynamics
neurotransmission
brain
MEG
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neuroenergetics
subject
stroke


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