High Field MRI Lab

2020 - 2021

by Brian Hansen

CFIN's preclinical facility is a vibrant research environment where many scientific backgrounds and viewpoints meet. Consequently, projects cross-pollinate in a fruitful manner which we believe is a strong example of "integrative neuroscience". In the high field MRI lab we count ourselves lucky to be part of and contribute to this exciting environment. As a general imaging resource we become involved in many interesting imaging studies involving samples from many species (human, pig, rat, mouse, the occasional whale) and many organ types (heart, kidney, liver, eyes, teeth, bone) but mostly of course brain.

Core activities in CFIN's high field MRI lab revolve around two major themes: awake mouse MRI and studies of the Locus Coeruleus. This research program requires constant development and refinement of experimental methods. When successfully implemented these methods are then also made available to the many other projects that benefit from the MR lab. In the following, we present project status within selected core areas as well as new colleagues who have joined the lab.

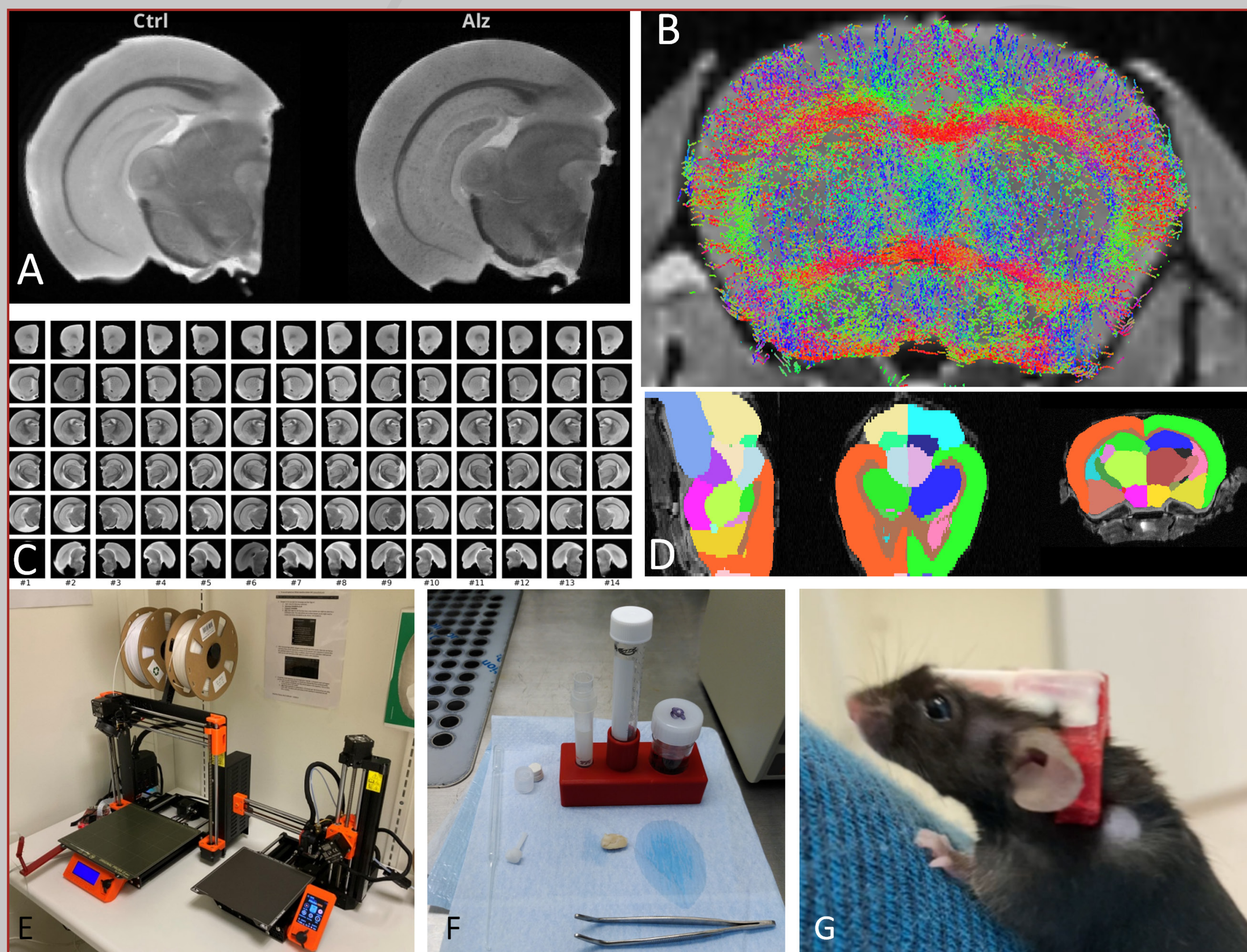

Figure 1
An overview of new and improved tools for preclinical data analysis currently being used and developed in the lab. In many studies, we compare animal models of disease to normal control animals. One example is seen in (A) where a hemisphere from a control animal (left) can be compared to the plaque-riddled brain from an animal model of Alzheimer's Disease (A, right). In panels (B-D) various tools for data analysis are shown. In (B) multishell diffusion MRI data is used to map fiber tracts in mouse brain. Panel (C) shows the result of alignment of several data sets to the same geometry. In (D) artificial intelligence is used to parcellate the mouse brain. These tools make it possible for us to perform sensitive analysis of large data sets in a streamlined manner. The lab makes extensive use of 3D printing (E shows two of our printers). The custom solutions made possible by 3D printing benefits both our *ex vivo* work (F, sample holders) and *in vivo* studies (G, 3D printed surgically implanted head holder on a mouse).

Awake mouse MRI

At the time of writing this report Thomas Beck Lindhardt is completing his PhD on awake mouse MRI in the context of studying the glymphatic system. The impact of Thomas' work is, however, much broader as the habituation method he has developed will be used in many future projects in our group. During his PhD Thomas has shown how mice can be habituated to the MR-scanner environment so that imaging can be performed in the awake animal. We believe this work to be part of a paradigm shift in preclinical neuroimaging. For decades, measurements performed in anesthetized animals have formed the experimental foundation for basic neuroimaging research. While physiological perturbations due to anesthesia are expected and have been investigated recent studies have shown anesthesia to perturb brain biology in subtle yet profound ways. This realization questions the generality of results from many years of physiologically oriented preclinical neuroimaging. Preclinical research therefore needs to transition to 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 skewed by the influence of anesthetics and 2) experiments are performed with less animal stress (another source of physiological disturbance) and discomfort. The translatability of preclinical research to a large extent hinges on the generality of methodology and results from animal studies to patients. The transition from anesthetized animal MRI to awake animal MRI, therefore, is essential but far from trivial. As part of his PhD Thomas Beck Lindhardt has designed the hardware and protocol needed for successful mouse habituation. The efficiency of his method is documented in a recent publication which interestingly shows that female mice respond differently to habituation than male mice. Our study shows however that both male and female mice can be successfully habituated. This is important because preclinical research must do away with the potential bias imposed by only using male mice for research. In his work, Thomas has contributed to these important developments. By sharing his designs through online repositories the transition to awake mouse MRI has been made much easier for many labs across the globe. Our next

FACTS

Group members:

- Brian Hansen
- Christian Stald Skoven
- Thomas Bech Lindhardt
- Rasmus West Knopper
- Saba Molhemi
- Nanna Bertin Markussen (2020-2021)

goal is to implement awake mouse phosphorous spectroscopy as part of Saba Molhemi's PhD-project.

Studies of Locus Coeruleus

We study the Locus Coeruleus (LC) because its dysfunction and degeneration is linked to a range of brain disorders including psychiatric illness and neurodegenerative diseases. In short, when LC breaks the brain goes haywire. We are only slowly beginning to understand, why this is, as accumulating evidence suggests that LC is a crucial, although historically overlooked physiological hub for the brain as a whole. For this reason, interest in LC has increased recently, and advances in this area are a timely contribution to current neuroscience. Our LC research program investigates what happens, when LC breaks down and loses control over the brain's intricate clockwork. Due to LC's widespread involvement in most aspects of brain physiology our investigations need to cover multiple levels of organization from cellular connectivity to behavior as well as development of related imaging technology. As a foundation for our studies our group have established a mouse model of LC dysfunction. In order to serve as a basis for future work this animal model needs to very well-documented have documented validity both on the cellular and behavioural levels. This tremendous effort has been undertaken by Nanna Bertin Markussen and Rasmus West Knopper and is nearing completion.

In addition to the two examples above the MRI lab also provides data to many projects, some within CFIN, some at AU/AUH, and some in Europe. A key person in these collaborative efforts is Christian Stald Skoven who has recently joined the lab as a postdoc. Christian is rapidly evolving into an MRI expert, and his programming skills and brilliant solutions and 3D designs already benefit a wide range of users and projects.

Activities in the MRI lab generally suffered some setbacks during the pandemic. Nevertheless, we have remained productive and by keeping the scanners as active as possible during lockdown we now possess rich data sets that we are busy processing. With the team we have assembled and the excellent laboratory facilities at Skejby we are optimistic that the next few years will be very productive.

NEW FACE at CFIN

Rasmus West Knopper joined CFIN in December 2020 as a PhD student at the High Field MRI Lab headed by Brian Hansen.

He studied for a Master's degree at the Sino-Danish Center in Beijing and received his degrees in Neuroscience and Neuroimaging from Aarhus University and Neurobiology from the University of Chinese Academy of Sciences in 2020. While working on his Master's thesis, he studied the brain network related to olfactory working memory in mice using awake mouse fMRI at the Institute of Neuroscience in Shanghai.

Rasmus is now working on the project titled "Locus coeruleus: The master switch for brain health?". In a locus coeruleus ablated mouse model, the project aims to elucidate the role of locus coeruleus in cerebral microvasculature regulation, brain development, and cognition using different MRI modalities, behavioral tests, and two-photon microscopy.

NEW FACE at CFIN

Christian Stald Skoven, PhD, M.Sc.Pharm., joined CFIN in March 2022 as a Post Doc with Brian Hansen in the High Field MRI Lab.

Christian defended his Ph.D. thesis in August 2022, based on work carried out at the DRCMR (Hvidovre Hospital). His thesis work investigated neurobiological mechanisms of optogenetic stimulation of the transcallosal pathways - using an electrophysiology, light and transmission electron microscopy, and diffusion-weighted MRI.

Christian is now assisting different existing projects with acquistion and processing of both in vivo and ex vivo MRI data on the 9.4 T Bruker system. This includes optimization and standardization of workflows (using e.g. custom designed and 3D-printed utensils) – as well as establishing data processing piplines for the acquried data sets. Examples of foci are dw-MRI tracography, atlas-based extraction of dw-MRI metrics from regions of interest and comparison of tissue states with histology and diffusion kurtosis imaging. In the future this will be accompanied by investigation of behavior and sleep of mice.

NEW FACE at CFIN

Saba Molhemi joined CFIN in April 2022 as a research assistant at the High Field MRI Laboratory supervised by Brian Hansen.

He received a double Master's degree from Sino-Danish Center with a degree in Neuroscience and Neuroimaging from Aarhus University and a degree in Neurobiology and Biophysics from the University of Chinese Academy of Sciences. His Master's thesis was conducted at the department of Drug Design and Pharmacology at Copenhagen University in collaboration with CFIN, aiming to investigate diffusion kurtosis imaging's potential at detecting early amyloid pathological alterations on an Alzheimer's disease mouse model, the 5xfAD.

After his master's he was employed as a research assistant, undergoing preparatory work for the PhD project funded by Lundbeck. The project aims to access a metabolic window into the brain tissue's high-energy metabolites linked to bioenergetics and lipid membrane metabolism by Phosphorus Magnetic Resonance Spectroscopy (31P-MRS). 31P-MRS permits the understanding of normal and pathological conditions associated with mitochondrial dysfunction and lipid membrane alterations and will be performed on awake and anaesthetized healthy and disease-modelling mouse models.