APPLIED IMAGING AND MODELLING

2020 - 2021

by Simon Fristed Eskildsen

The applied imaging and modelling (AIM) group investigates pathological and developmental brain changes by applying both conventional and novel imaging techniques and analysis methods. The AIM group is involved in several studies on neurodegenerative diseases, such as Alzheimer's disease (AD), Parkinson's disease (PD), and multiple sclerosis (MS).

In 2020 and 2021, we continued our research on the involvement of the microvasculature in AD with special emphasis on the prodromal phase. Similarly, we explored microvascular mechanisms in prodromal PD by applying the methods we have developed for the AD research. At the other end of the human life spectrum, we have been looking at the effect of congenital heart defects on brain development in both infants and young adults.

Capillary function progressively deteriorates in prodromal Alzheimer's disease

In continuation of our collaboration study with the PET-Centre at Aarhus University Hospital and following up on the work done by former PhD student Rune Bæksager Nielsen[1,2], PhD student Lasse Stensvig Madsen looked at longitudinal changes in brain perfusion in prodromal Alzheimer's disease. Using MRI, Lasse investigated the two-year changes of the cerebral microvascular blood flow in 11 mild cognitively impaired (MCI) patients with brain amyloid deposits (prodromal AD) compared to 12 MCI patients without evidence of amyloid, thus being suspected of non-AD pathology (SNAP). The MCI groups were additionally compared to the changes in 10 cognitively intact age-matched controls. The prodromal AD MCI patients displayed widespread deterioration in microvascular cerebral perfusion associated with capillary dysfunction (see Figure 1). No such changes were observed in the other two groups, suggesting that the dysfunction in capillary perfusion is linked to the AD pathophysiology. The observations fit with the capillary dysfunction hypothesis of AD[4], which suggests that increasing heterogeneity of capillary blood flow is a primary pathological event in AD. Capillary dysfunction may limit local oxygenation leading to downstream β-amyloid aggregation, tau hyperphosphorylation, neuroinflammation and neuronal dysfunction. These important findings of progressive deterioration of capillary function were published in Aging Brain[3]. Lasse will continue his research on microvascular perfusion by looking at associations with amyloid aggregates and possibly linking impaired perfusion to genetic risk factors for AD.

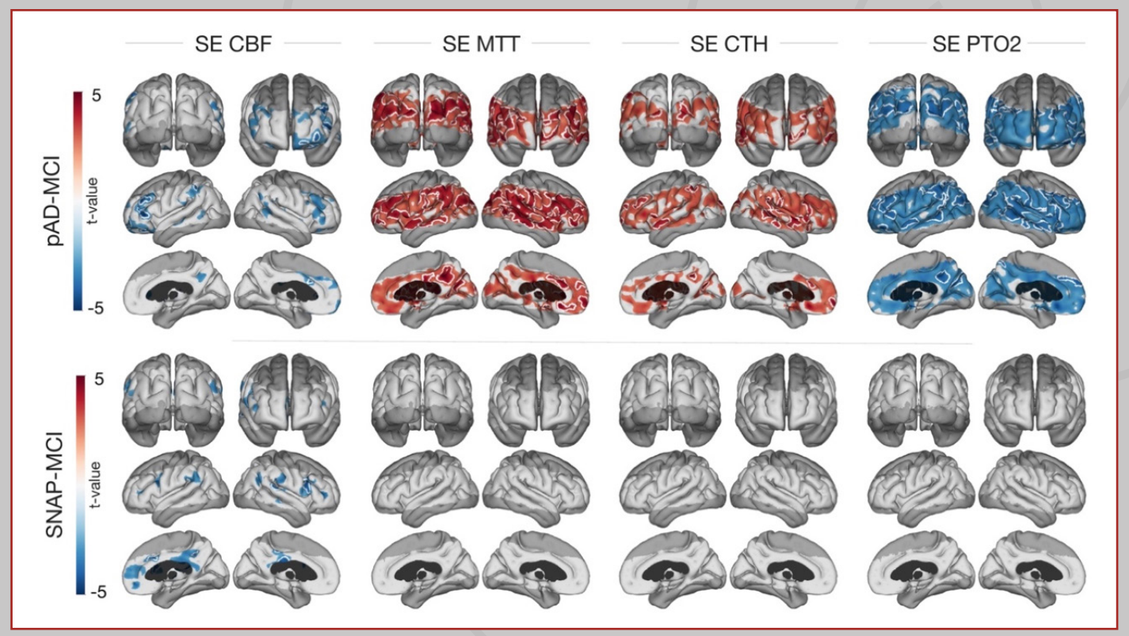


Figure 1
Two-year changes in spin echo-based perfusion weighted magnetic resonance imaging (MRI) of 11 prodromal Alzheimer's disease subjects (pAD-MCI) and 12 suspected non-Alzheimer's pathophysiology subjects (SNAP-MCI). Statistical t-value maps were adjusted for sex and ApoE4 status. Positive t-values (red colours) indicate significant increases in the parameter over two years while negative t-values (blue colours) indicate significant decreases in the parameter over two years. Widespread increase in microvascular mean transit time and capillary transit time heterogeneity accompanied by decrease in tissue oxygen tension and smaller areas of decrease in cerebral blood flow in pAD-MCI subjects compared to SNAP-MCI. Statistical maps were family-wise error rate corrected ($\alpha = 0.05$) using cluster-extent-based thresholding with two levels of primary cluster-defining threshold: $p < 0.01$ and $p < 0.001$. Areas surrounded by a white line indicate clusters surviving $p < 0.001$. Dark grey areas indicate areas outside the MRI field of view. Abbreviations: SE, spin echo; CBF, cerebral blood flow; MTT, mean transit time; CTH, capillary transit time heterogeneity; P_tO_2, tissue oxygen tension. From Madsen et al.[3]

Impaired cerebral microcirculation in presymptomatic Parkinson's disease

Parkinson's disease is the second most common neurodegenerative disease after AD. The primary pathology in PD consists of abnormal aggregation of proteins inside the neurons, which become so-called Lewy bodies named after the German neurologist Fritz Heinrich Lewy who discovered them in 1910. The protein aggregations consists primarily of alpha-synuclein and causes cell death. Lewy bodies are typically found in the midbrain causing degeneration of the dopamine producing cells in substantia nigra, which lead to the commonly seen motor symptoms of PD. Other neurotransmitters, such as serotonin, noradrenaline and acetylcholine are also reduced in PD and causes non-motor symptoms, such as sleep disturbances, cognitive impairment, mood changes, and constipation. In some patients, REM sleep behavior disorder (RBD) are the first symptom of synucleinopathy. Ninety percent of RBD patients develop synucleinopathy and most of these are eventually diagnosed with PD. Brain stem nuclei are affected in the early stages with locus coeruleus (LC) as one of the first to degenerate. LC is involved in sleep/wake homeostasis and noradrenergic fibres innervate intraparenchymal microvessels throughout the brain. Noradrenaline is central in the regulation of blood supply by controlling vasodilation of the microvessels. Disrupting LC's function will most likely lead to a change in brain perfusion and alter tissue oxygenation. To investigate this, we measured the microvascular perfusion in 20 RBD patients compared with 25 healthy controls. The results showed widespread reduced cortical perfusion of the RBD patients. All patients, except one, had a combination of low cerebral blood flow (CBF) and high capillary transit time heterogeneity (CTH). This was the

FACTS

Core group members:

- Simon Fristed Eskildsen, Associate Professor, Head of Group
- Rune Bæksager Nielsen, Postdoc (2018-2020)
- Robert Dahnke, Postdoc (2019-2021)
- Lasse Stensvig Madsen, PhD student (2019-)
- Mikkel Karl Emil Nygaard, PhD student (2020-)

Affiliated group members:

- Martin Langeskov-Christensen, postdoc (2019-)
- Laura Virginie Toussaint, postdoc (2019-)
- Rola Ismail, PhD student (2016-2020)
- Benjamin Asschenfeldt, PhD student (2017-2020)
- Maja Bendtsen Sharma, PhD student (2017-2021)
- Morten Riemenschneider, PhD student (2018-2021)
- Linda Sundvall, PhD student (2018-)
- Pernille Louise Kjeldsen, PhD student (2019-)
- Malene Kaasing Thomsen, PhD student (2020-)
- Tobias Gæmelke, PhD student (2021-)

Internal collaborators:

- Leif Østergaard, Professor
- Sune Nørhøj Jespersen, Professor
- Jakob Udby Blicher, Professor
- Torben Ellegaard Lund, Associate Professor
- Brian Hansen, Associate Professor
- Irene Klærke Mikkelsen, Senior Researcher
- Rikke Dalby, MD, Radiologist

National collaborators:

- Professor David J. Brooks, Positron Emission Tomography Centre, Aarhus University Hospital
- Professor Ulrik Dalgas, Exercise Biology, Department of Public Health, Aarhus University
- 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 Tim Dyrby, Diffusion Imaging Group, Danish Research Centre for Magnetic Resonance
- Associate Professor Erhard Næss-Schmidt, Hammel Neurorehabilitation and Research Center
- 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
- Dr. Sepehr Mamoei, Department of Regional Health Research, IRS - Hospital Sønderjylland, Research Unit of Neurology

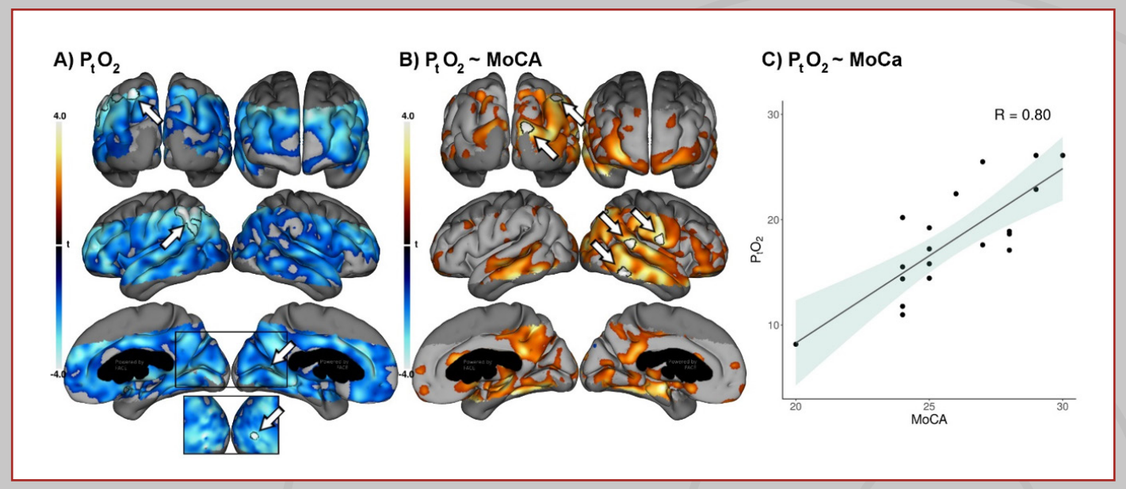
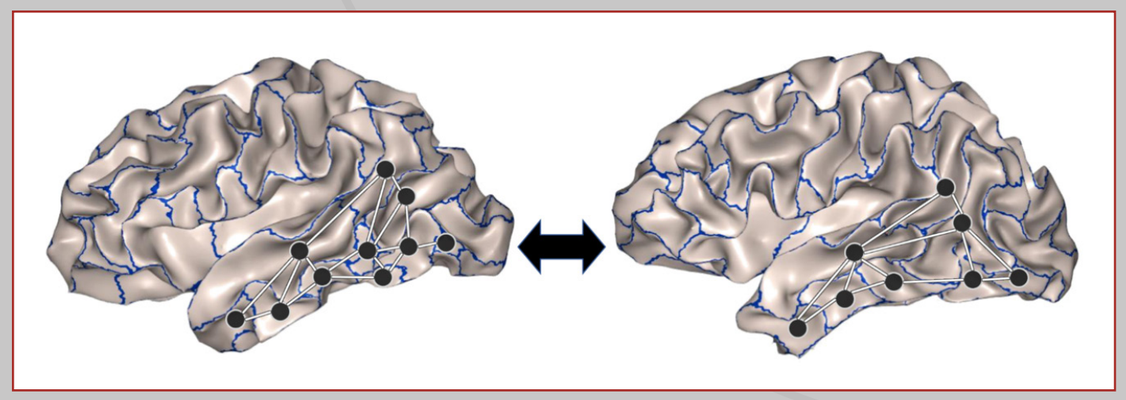


Figure 2
Tissue oxygenation is impaired in RBD patients and oxygenation levels correlate with cognitive scores. P_tO_2 predicted by the biophysical model. Panel A: statistical t map showing significantly reduced values in RBD patients compared to controls thresholded at p=0.05 (uncorrected). Panel B: statistical t map showing significant correlations between P_tO_2 and MoCA scores in iRBD patients. Clusters surviving family-wise error correction at p_{FWE}=0.05 are white with black borders (white arrows). Panel C: scatter plot of MoCA scores and mean P_tO_2 within FWE clusters. From Eskildsen et al.[5]

case for only one healthy control indicating almost perfect separation of patients and controls based on the perfusion parameters. Our biophysical model of tissue oxygenation showed significant reduced cortical oxygenation (see Figure 2A). The reduced oxygenation correlated with lower general cognitive performance (see Figure 2B-C). The RBD patients had no sign of brain atrophy, thus the altered small-vessel perfusion may be a result of impaired neurogenic control caused by degeneration of the noradrenalinergic neurons in the LC. It is possible that pharmacological restoration of perivascular neurotransmitter levels could help maintain cognitive function in patients with this prodromal phenotype of parkinsonism. The study was carried out in collaboration with the PET Centre at AUH and Hospital Clínic de Barcelona and published in Brain[5].



Adults with simple congenital heart disease have abnormal brain sulcal patterns

PhD student Benjamin Asschenfeldt, co-supervised by Simon Eskildsen, studied brain abnormalities in adults who are born with a heart defect. Benjamin recruited a relatively large cohort of 66 individual with simple congenital heart defect (CHD), which all had surgical defect closure as infants. Approximately half of the cohort had atrial septal defect (ASD), while the other half had ventricular septal defect (VSD). Benjamin has previously shown that his cohort has impaired cognitive functions[6] and he is looking for brain alterations, which may explain this impairment and link the symptoms to the CHD. As part of his PhD, Benjamin did a research stay at Professor Ellen Grant's group at Boston Children's Hospital. In collaboration with Professor Grant's group, we investigated the sulcal patterns in the brains of the CHD cohort and compared these to the patterns of 37 healthy controls matched on age, sex and educational attainment. Using structural MRI, geometrical surfaces of the brain's white matter were generated from which graphs of the sulcal patterns could be constructed (see Figure 3). These graphs can be compared between individuals and the similarity quantified. In the CHD cohort, we found a decreased sulcal pattern similarity in the left hemisphere, but not in the right hemisphere, compared to the controls. The pattern varied slightly between ASD and VSD, with abnormalities primarily found in the left temporal lobe for the ASD group, while the VSD group was abnormal at the hemispheric level. The cause of these abnormalities in simple CHD may be found during end gestation, where the fetal brain has high metabolic demand. Within the fetal brain, tissue oxygen levels play a key role in the proliferation and differentiation of nerve cells and the formation of the microvasculature needed to support their

Figure 3
Example of the sulcal graph pattern matching and similarity measure (value from 0 to 1) in the temporal lobe between two subjects. The black nodes in the graph structure represent sulcal pits and the corresponding sulcal basins (blue boundaries) that are automatically extracted on the white matter surface. When sulcal basins meet, sulcal pits in those basins are connected with an edge. The two sulcal graph patterns are optimally matched and their similarity is measured by using the geometric features of the nodes (3D position, depth and area of sulcal basin), their relationship, and sulcal graph topology. A pair having high similarity shows more similar geometric features of nodes and their interrelationship and sulcal arrangement than the pair having low similarity. From Asschenfeldt et al.[8]

FACTS

International collaborators:

- 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

Research projects:

Alzheimer's disease

- Magnetic resonance imaging biomarkers in Alzheimer's disease: investigating capillary dysfunction and neurodegeneration for diagnosis and prediction. Rune Nielsen, Simon 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 Kjeldsen, Lasse Madsen, Malene Damholdt, Joel Aanerud, Simon Eskildsen, David 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 Madsen, Pernille Kjeldsen, David Brooks, Leif Østergaard, Simon Eskildsen.
- Capillary function, oxygen uptake, and amyloid load in healthy APOE-ε3 and APOE-ε4 carriers. Malene Kaasing Thomsen, Joel Aanerud, Jakob Blicher, David Brooks, Simon Eskildsen, Leif Østergaard.

Multiple sclerosis

- Magnetic resonance imaging biomarkers of disease severity and impact of exercise training in neurodegenerative diseases. Mikkel Nygaard, Martin Christensen, Ulrik Dalgas, Louis Collins, Simon Eskildsen.
- Integrating immunological responses with clinical and neuroimaging for identifying early MS disease mechanisms. Linda Sundvall, Irene Mikkelsen, Simon Eskildsen, Thor Petersen, Kristina Svendsen, Peter Rasmussen.
- Effects of aerobic exercise on brain health in multiple sclerosis. Martin Christensen, Mikkel Nygaard, Simon Eskildsen, Ulrik Dalgas.
- Early Exercise Efforts in Multiple Sclerosis. Morten Riemenschneider, Lars Hvid, Steffen Ringgaard, Mikkel Nygaard, Simon Eskildsen, Thor Petersen, Egon Stenager, Ulrik Dalgas.
- Exercise and Neuroprotection in Older Persons With Multiple Sclerosis. Tobias Gemælke, Mikkel Nygaard, Simon Eskildsen, Ulrik Dalgas.
- Central and Peripheral Nervous System Changes as markers of Disease Progression in Multiple Sclerosis. Sepehr Mamoei, Mikkel Nygaard, Simon Eskildsen, Ulrik Dalgas, Egon Stenager

metabolic demands. In fetuses with CHD, blood oxygenation measurements suggest that brain tissue oxygen tension is lower than in the normal fetus. This may explain their altered brain development, which manifest as altered sulcal pattern and cognitive impairment. In an independent cohort we did indeed find smaller brain volumes in infants with CHD[7]. However, in the adult cohort, no difference in brain volume was observed[6], suggesting a gradual correction of volume during development. Since the formation of sulcal patterns are established in the fetal brain and remain unaltered throughout the lifespan, our findings of abnormal sulcal patterns in these adult CHD individuals is a sign of neurodevelopmental disturbances in early life. The results of the collaborative study was published in Journal of the American Heart Association[8].

References

1. Nielsen, R. B. et al. Capillary dysfunction is associated with symptom severity and neurodegeneration in Alzheimer's disease. Alzheimers Dement 13, 1143-1153, doi:10.1016/j.jalz.2017.02.007 (2017).
2. Nielsen, R. B. et al. Impaired perfusion and capillary dysfunction in prodromal Alzheimer's disease. Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring 12, e12032, doi:10.1002/dad2.12032 (2020).
3. Madsen, L. S. et al. Capillary function progressively deteriorates in prodromal Alzheimer's disease: A longitudinal MRI perfusion study. Aging Brain 2, 100035, doi:https://doi.org/10.1016/j.nbas.2022.100035 (2022).
4. Ostergaard, L. et al. The capillary dysfunction hypothesis of Alzheimer's disease. Neurobiol Aging 34, 1018-1031, doi:10.1016/j.neurobiolaging.2012.09.011 (2013).
5. Eskildsen, S. F. et al. Impaired cerebral microcirculation in isolated REM sleep behaviour disorder. Brain 144, 1498-1508, doi:10.1093/brain/awab054 (2021).
6. Asschenfeldt, B. et al. Neuropsychological Status and Structural Brain Imaging in Adults With Simple Congenital Heart Defects Closed in Childhood. Journal of the American Heart Association 9, e015843, doi:doi:10.1161/JAHA.120.015843 (2020).
7. Skotting, M. B. et al. Infants with congenital heart defects have reduced brain volumes. Scientific Reports 11, 4191, doi:10.1038/s41598-021-83690-3 (2021).
8. Asschenfeldt, B. et al. Abnormal Left‐Hemispheric Sulcal Patterns in Adults With Simple Congenital Heart Defects Repaired in Childhood. Journal of the American Heart Association 10, e018580, doi:doi:10.1161/JAHA.120.018580 (2021).

FACTS

Research projects:

Parkinson's disease

- Cerebral microcirculation in isolated rapid eye movement sleep behaviour disorder. Kristian Stær, Morten Stokholm, Simon Eskildsen, Arne Møller, David Brooks, Leif Østergaard, Nicola Pavese.
- Effects of aerobic exercise on brain health in people with Parkinson's disease, Martin Christensen, Mikkel Nygaard, Simon Eskildsen, Ulrik Dalgas

Congenital heart disease

- Brain Matters in Heart Matters – from early fetal development. Mette Lauridsen, Mikkel Skotting, Steffen Ringgaard, Simon Eskildsen, Vibeke Hjortdal.
- The effect of congenital heart disease on cerebral function and comorbidity in adult-hood. Benjamin Asschenfeldt, Sara Lau-Jensen, Lars Evald, Johan Heiberg, Leif Østergaard, Simon Eskildsen, Vibeke Hjortdal

Cancer – radiation thearpy

- Image-based biomarkers for radiation-induced brain damage in pediatric brain tumors. Laura Toussaint, Oscar Casares-Magaz, Simon Eskildsen, Ludvig Muren.
- Cross Sectional Study of Late Toxicity after Intensity-Modulated Radiotherapy for Sinonasal Cancer. Maja Sharma, Kenneth Jensen, Ali Amid, Simon Eskildsen, Cai Grau

Other projects

- 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 Eskildsen, Leif Østergaard, Line Underbjerg, Lars Rejnmark.
- Cerebral perfusion in patients with late-onset major depression. Rikke Dalby, Simon Eskildsen, Poul Videbech, Leif Østergaard.
- The implication of the schizophrenia-associated gene, BRD1, in behavior, cognition and brain development in genetically modified mice. Per Qvist, Steffen Ringgaard, Simon Eskildsen, Jens Nyengaard, Gregers Wegener, Jane Christensen, Anders Børglum.
- Cortical thickness and structural connectivity in the Vervet monkey brain. Simon Eskildsen, Henrik Lundell, Tim Dyrby.
- Quantification of cerebral gyrification in the primate brain. Robert Dahnke, Christian Gaser, Simon Eskildsen.
- Bioactive formula to improve gut, immunity and brain development in preterm pigs. Karina Obelitz-Ryom, Steffen Ringgaard, Sune Jespersen, Anders Brunse, Simon Eskildsen, Thomas Thymann

Events

- PhD Day, January 2020, Lasse Madsen, Mikkel Nygaard and Simon Eskildsen (Chair)
- PhD defense, Rola Ismail, January 2020
- OHBM virtual conference, June 2020, Simon Eskildsen
- PhD defense, Benjamin Asschenfeldt, December 2020
- PhD Day, January 2021, Lasse Madsen, Mikkel Nygaard and Simon Eskildsen (Chair)
- PhD defense, Sepehr Mamoei, January 2021
- Neuroscience Day, May 2021, Lasse Madsen, Mikkel Nygaard and Simon Eskildsen
- PhD defense, Morten Riemenschneider, June 2021
- PhD defense, Nick Yin Larsen, June 2021, Simon Eskildsen (Chair)
- PhD defense, Maja Bendtsen Sharma, December 2021