

Neuroimaging

By Markus Nilsson, Danielle van Westen

1. Short description of the infrastructure

Neuroimaging in humans is performed using two types of equipment: magnetic resonance imaging (MRI) and positron emission tomography (PET). MRI is made available through the clinical department of Image and Function at Skåne University Hospital (SUS). Research within the Multipark environment is mainly conducted using three MRI systems with the field strength of 3 Tesla as well as the 7 Tesla MRI scanner at the national 7T MRI facility. For PET imaging, five state-of-the-art scanners have been installed in Lund and Malmö during 2017-2018. In addition to this equipment for human imaging, Lund University also hosts preclinical small-animal equipment for both MRI and PET. This equipment is managed by Lund University BioImaging Center (LBIC; https://www.med.lu.se/bioimaging_center), but is not part of this platform.

The platform supports ongoing MRI and PET acquisitions in multiple cohorts related to Multipark. These cohorts comprise subjects with early dementia with focus on Alzheimer's disease, as well as Parkinson's disease and parkinsonian syndromes. The cohorts have been the basis for multiple publications as shown below. Besides the clinical cohorts, the platform supports basic research on optimization and novel techniques for data acquisition as well as data analysis performed by Multipark-members and associated members from the Department of Diagnostic Radiology and Medical Radiation Physics at Lund University. Further, the platform will be used in clinical treatment trials like STEM-PD.

A physicist with focus on image analysis of MRI and PET data is supported by 50 %; this resource is crucial for making imaging data and results available to researchers in MultiPark. In addition, there was a smaller support for data analysis (level PhD student), as of 2020. The overarching aim is to develop pipelines for image analysis that enables researchers of MultiPark to obtain data necessary for specific projects from larger databases.

For setting up the development and production of novel PET ligands (for instance for PET imaging of dopaminetransporters, synapse density, alpha-synuclein etc), a smaller sum is earmarked for support of a part-time radiochemist at SUS.

After a lengthy recruitment procedure, Laura Wisse PhD, was appointed Associate Senior Lecturer (Assistant Professor) in medicine with focus on neuroimaging in neurodegenerative diseases at the end of 2018. Laura Wisse is a neuropsychologist whose PhD project at the University of Utrecht as well post doc at the University of Pennsylvania, were focused on volumetry of hippocampal subfields. Within the context of the MP budget, she is provided with her salary during a four year period as well as a starting package that has enabled her to hire a PhD student, Anika Wüstefeld (project start October 2020).

2. Is this infrastructure receiving support also from other Strategic Research Areas (SRAs) or organizations at Lund University (e.g. Medical faculty, LBIC). If yes, please specify the type of support and its amount.

Regarding the equipment that is owned by the Skane County (Region Skåne), there is no need for additional financing; operation including technicians, maintenance, upgrading and in due time replacement will be handled by SC. The 7T was funded as a national infrastructure by VR, and its operation is financed through LBIC.

Laura Wisse has funding for an additional, fifth year at Lund University.

For the research assistants for data analysis and the biomedical technologist there is supplementary funding up to 100% employment.

3. Number and names of MultiPark senior researchers using the infrastructure in the period 2018-2020¹.

Research groups using the platform include people from the Departments of Neurology, Neurosurgery, Diagnostic radiology, Clinical physiology and neurophysiology as well as the Clinical memory research group. Senior researchers from MultiPark are denoted in bold.

- *Diagnostic radiology:* **Danielle van Westen, Markus Nilsson**, Pia Sundgren, Johan Wassélius, Geraline Vis, **Laura Wisse**.
- *Clinical Physiology and clinical neurophysiology:* Jonas Jögi, Douglas Hägerström
- *Medical Radiation Physics:* Tomas Ohlsson.
- *Neurology:* **Håkan Widner, Ruben Smith**, Maria Strandberg.
- *Neurosurgery:* **Niklas Marklund**, Mattis Jalakas
- *Neuropathology:* **Elisabet Englund**
- *Clinical memory research group:* **Oskar Hansson, Niklas Mattsson-Carlgrén, Sebastian Palmqvist**, David Berron, Nicola Spotorno, Erik Stomrud, Anna-Märta Gustavsson, Rik Ossenkoppele, Shorena Janelidze, Maria Landqvist Waldö
- *Psychiatry:* Alexander Santillo
- *MRI Physics:* Linda Knutsson, Olof Strandberg, Björn Lampinen, Jonas Svensson, Karin Markenroth Bloch, Filip Szczepankiewicz, Jimmy Lätt, Peter Mannfolk, Gunther Helms.

4. Number and names of senior researchers outside of Multipark and/or non-academic partners using the infrastructure 2018-2020.

As mentioned above, data acquired the platform are analyzed in collaboration with a number of groups in Sweden and internationally.

5. Does the infrastructure have a steering document accessible to the users? If yes, when was it last updated?²

¹ If the infrastructure was first established in 2020, please include this information.

² Note that the Multipark leadership may ask to see this document with a very short notice.

For both the clinical equipment (3 T MRI and PET) as well as for the 7T there is a research board to which researchers direct an application in order to obtain scanner time. In the case of the large cohorts with longitudinal follow-up, there are meetings regularly in order to ensure smooth logistics as well as adjust and coordinate the participant flow. There is no steering document and may not be necessary for infrastructure not supported by MP.

6. Is the infrastructure charging user fees? If yes, state the amount and what is covered by the user fees.

For the hardware part there are user fees collected by the department of Image and Function, as agreed upon with each separate researcher/research group that acquires data using its machines. For the human assets, there are no user fees; research projects are conducted in agreement with the researcher/asset.

7. List publications generated with the help of this infrastructure during the past 3 years (2018-2020). Do not include manuscripts in preparation and please give the full reference (i.e., complete author list, complete title, journal name with year, volume, pages)³.

Deep learning from MRI-derived labels enables automatic brain tissue classification on human brain CT. Srikrishna M, Pereira JB, Heckemann RA, Volpe G, van Westen D, Zettergren A, Kern S, Wahlund LO, Westman E, Skoog I, Schöll M. *Neuroimage*. 2021 Sep 25;244:118606. doi: 10.1016/j.neuroimage.2021.118606. Online ahead of print.

Inter-modality assessment of medial temporal lobe atrophy in a non-demented population: application of a visual rating scale template across radiologists with varying clinical experience. Håkansson C, Tamaddon A, Andersson H, Torisson G, Mårtensson G, Truong M, Annertz M, Londos E, Björkman-Burtscher IM, Hansson O, van Westen D. *Eur Radiol*. 2021 Jul 30. doi: 10.1007/s00330-021-08177-1. Online ahead of print. PMID: 34328536

Plasma markers predict changes in amyloid, tau, atrophy and cognition in non-demented subjects. Pereira JB, Janelidze S, Stomrud E, Palmqvist S, van Westen D, Dage JL, Mattsson-Carlsson N, Hansson O. *Brain*. 2021 Jun 2:awab163. doi: 10.1093/brain/awab163. Online ahead of print. PMID: 34077494

Structural and functional neuroimaging changes associated with cognitive impairment and dementia in Parkinson's disease. Owens-Walton C, Jakabek D, Power BD, Walterfang M, Hall S, van Westen D, Looi JCL, Shaw M, Hansson O. *Psychiatry Res Neuroimaging*. 2021 Jun 30;312:111273. doi: 10.1016/j.psychres.2021.111273. Epub 2021 Apr 8. PMID: 33892387

Plasma neurofilament light protein correlates with diffusion tensor imaging metrics in frontotemporal dementia. Spotorno N, Lindberg O, Nilsson C, Landqvist Waldö M, van Westen D, Nilsson K, Vestberg S, Englund E, Zetterberg H, Blennow K, Lätt J, Markus N, Lars-Olof W, Alexander S. *PLoS One*. 2020 Oct 27;15(10):e0236384. doi: 10.1371/journal.pone.0236384. eCollection 2020. PMID: 33108404

³ If the infrastructure was first established in 2020, please include this information here too.

Association of Enlarged Perivascular Spaces and Measures of Small Vessel and Alzheimer Disease. Gertje EC, van Westen D, Panizo C, Mattsson-Carlgrén N, Hansson O. *Neurology*. 2021 Jan 12;96(2):e193-e202. doi: 10.1212/WNL.0000000000011046. Epub 2020 Oct 12. PMID: 33046608

Reporting frequency of radiology findings increases after introducing visual rating scales in the primary care diagnostic work up of subjective and mild cognitive impairment. Håkansson C, Torisson G, Londos E, Hansson O, Björkman-Burtscher IM, van Westen D. *Eur Radiol*. 2021 Feb;31(2):666-673. doi: 10.1007/s00330-020-07180-2. Epub 2020 Aug 26. PMID: 32851442

Plasma GFAP is an early marker of amyloid- β but not tau pathology in Alzheimer's disease. Pereira JB, Janelidze S, Smith R, Mattsson-Carlgrén N, Palmqvist S, Teunissen CE, Zetterberg H, Stomrud E, Ashton NJ, Blennow K, Hansson O. *Brain*. 2021 Jul 14:awab223. doi: 10.1093/brain/awab223. Online ahead of print. PMID: 34259835

Tau PET correlates with different Alzheimer's disease-related features compared to CSF and plasma p-tau biomarkers. Ossenkoppele R, Reimand J, Smith R, Leuzy A, Strandberg O, Palmqvist S, Stomrud E, Zetterberg H; Alzheimer's Disease Neuroimaging Initiative, Scheltens P, Dage JL, Bouwman F, Blennow K, Mattsson-Carlgrén N, Janelidze S, Hansson O. *EMBO Mol Med*. 2021 Aug 9;13(8):e14398. doi: 10.15252/emmm.202114398. Epub 2021 Jul 13. PMID: 34254442

Accuracy of Tau Positron Emission Tomography as a Prognostic Marker in Preclinical and Prodromal Alzheimer Disease: A Head-to-Head Comparison Against Amyloid Positron Emission Tomography and Magnetic Resonance Imaging. Ossenkoppele R, Smith R, Mattsson-Carlgrén N, Groot C, Leuzy A, Strandberg O, Palmqvist S, Olsson T, Jögi J, Stormrud E, Cho H, Ryu YH, Choi JY, Boxer AL, Gorno-Tempini ML, Miller BL, Soleimani-Meigooni D, Iaccarino L, La Joie R, Baker S, Borroni E, Klein G, Pontecorvo MJ, Devous MD Sr, Jagust WJ, Lyoo CH, Rabinovici GD, Hansson O. *JAMA Neurol*. 2021 Aug 1;78(8):961-971. doi: 10.1001/jamaneurol.2021.1858. PMID: 34180956

Sex differences in off-target binding using tau positron emission tomography. Smith R, Strandberg O, Leuzy A, Betthausen TJ, Johnson SC, Pereira JB, Hansson O. *Neuroimage Clin*. 2021;31:102708. doi: 10.1016/j.nicl.2021.102708. Epub 2021 May 29. PMID: 34091353

The BIN1 rs744373 Alzheimer's disease risk SNP is associated with faster A β -associated tau accumulation and cognitive decline. Franzmeier N, Ossenkoppele R, Brendel M, Rubinski A, Smith R, Kumar A, Mattsson-Carlgrén N, Strandberg O, Duering M, Buerger K, Dichgans M, Hansson O, Ewers M; Alzheimer's Disease Neuroimaging Initiative (ADNI)* and the Swedish BioFINDER study. *Alzheimers Dement*. 2021 Jun 1. doi: 10.1002/alz.12371. Online ahead of print. PMID: 34060233

A multicenter comparison of [(18)F]flortaucipir, [(18)F]RO948, and [(18)F]MK6240 tau PET tracers to detect a common target ROI for differential diagnosis. Leuzy A, Pascoal TA, Strandberg O, Insel P, Smith R, Mattsson-Carlgrén N, Benedet AL, Cho H, Lyoo CH, La Joie R, Rabinovici GD, Ossenkoppele R, Rosa-Neto P, Hansson O. *Eur J Nucl Med Mol Imaging*. 2021 Jul;48(7):2295-2305. doi: 10.1007/s00259-021-05401-4. Epub 2021 May 27. PMID: 34041562

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Mild behavioral impairment and its relation to tau pathology in preclinical Alzheimer's disease. Johansson M, Stomrud E, Insel PS, Leuzy A, Johansson PM, Smith R, Ismail Z, Janelidze S, Palmqvist S, van Westen D, Mattsson-Carlgrén N, Hansson O. *Transl Psychiatry.* 2021 Jan 26;11(1):76. doi: 10.1038/s41398-021-01206-z. PMID: 33500386

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Contribution of mixed pathology to medial temporal lobe atrophy in Alzheimer's disease. de Flores R, Wisse LEM, Das SR, Xie L, McMillan CT, Trojanowski JQ, Robinson JL, Grossman M, Lee E, Irwin DJ, Yushkevich PA, Wolk DA. *Alzheimers Dement*. 2020 Jun;16(6):843-852. doi: 10.1002/alz.12079. Epub 2020 Apr 22. PMID: 32323446 Free PMC article.

Characterization of hippocampal subfields using ex vivo MRI and histology data: Lessons for in vivo segmentation. de Flores R, Berron D, Ding SL, Ittyerah R, Pluta JB, Xie L, Adler DH, Robinson JL, Schuck T, Trojanowski JQ, Grossman M, Liu W, Pickup S, Das SR, Wolk DA, Yushkevich PA, Wisse LEM. *Hippocampus*. 2020 Jun;30(6):545-564. doi: 10.1002/hipo.23172. Epub 2019 Nov 1. PMID: 31675165

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