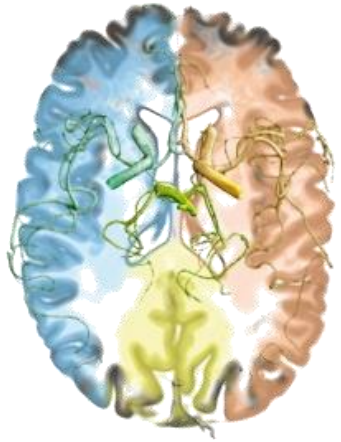
DEBBIE

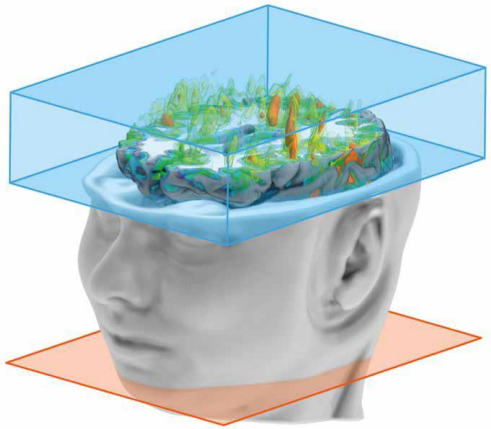
Developing BBB-ASL as non-invasive early biomarker of Alzheimer's disease



EU Joint Programme – Neurodegenerative Disease Research (JPND)
Final Symposium, Brussels, Belgium, 27th - 28th November 2024

Matthias Günther
Physics of medical imaging

Fraunhofer-Institut MEVIS, Bremen
Faculty 1 - Physics / Electrical Engineering, Universität Bremen
mediri GmbH, Heidelberg



DEBBIE project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No. 825664. It is supported through the following funding organisations under the aegis of the EU Joint Program for Neurodegenerative Disease Research (JPND2020-568-106)

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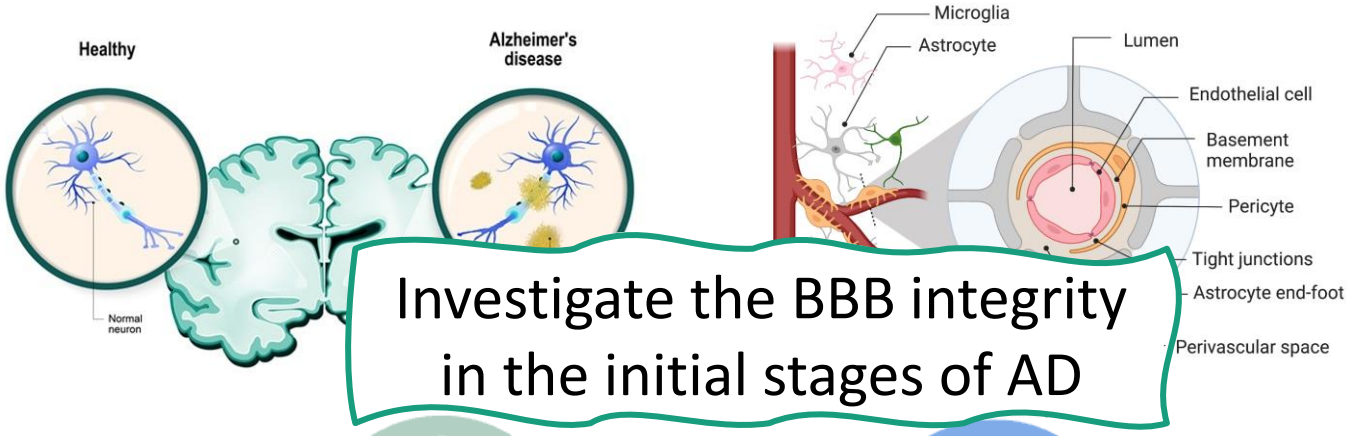
DEBBIE-project

goal and objectives

Alzheimer’s Disease (AD) and Blood-brain barrier (BBB) integrity



Investigate the BBB integrity in the initial stages of AD

CALIBRARION

1

Develop a clinically ready non-invasive MRI biomarker for BBB integrity mapping adpated to physiological variability

STANDARDIZATION

2

Create a standardized pipeline for multi-center processing and quantification of BBB-ASL data

VALIDATION

3

Determine the sensitivity of BBB-ASL by comparing ASL to PET measures of BBB integrity.

APPLICATION

4

Assess the clinical value of the BBB-ASL measurement as novel biomarker of AD, by adding the sequence to ongoing AD studies

Courtesy: Beatriz Padrela

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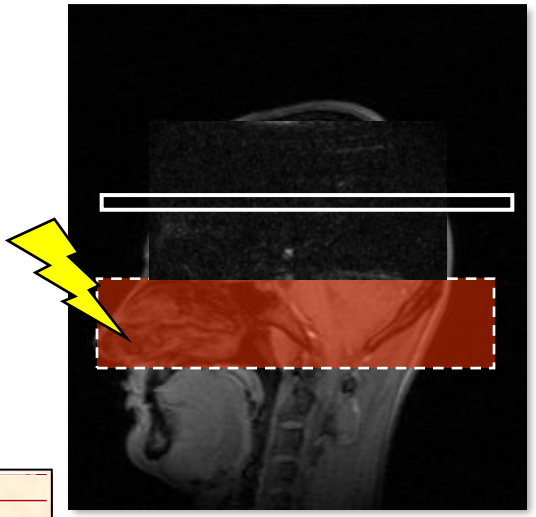
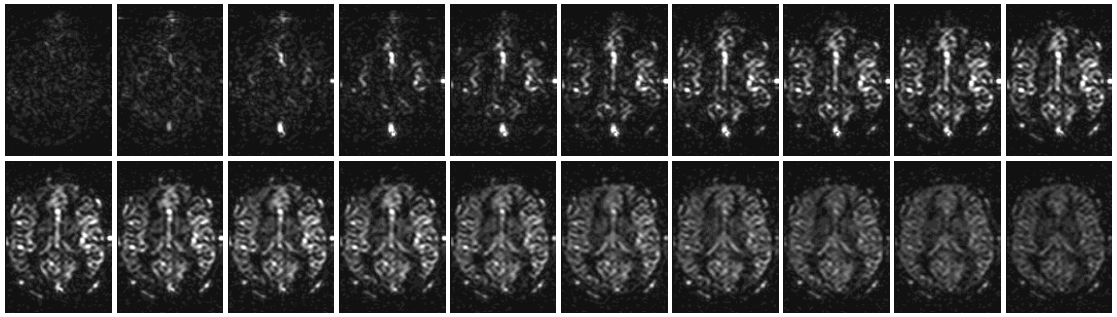
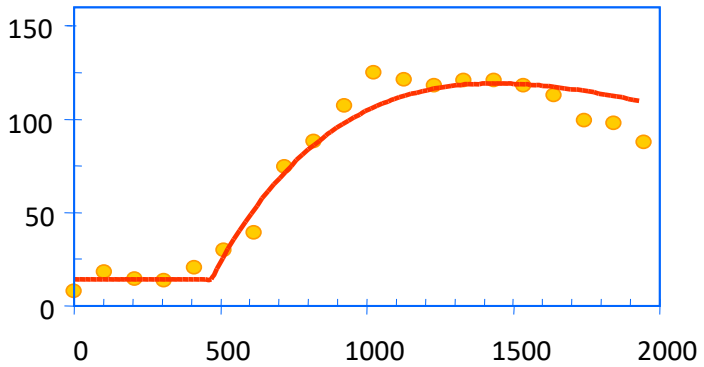
Physiological imaging: perfusion

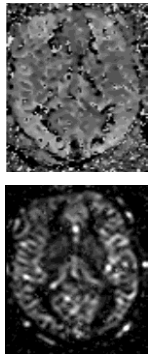
Arterial Spin Labeling (ASL)

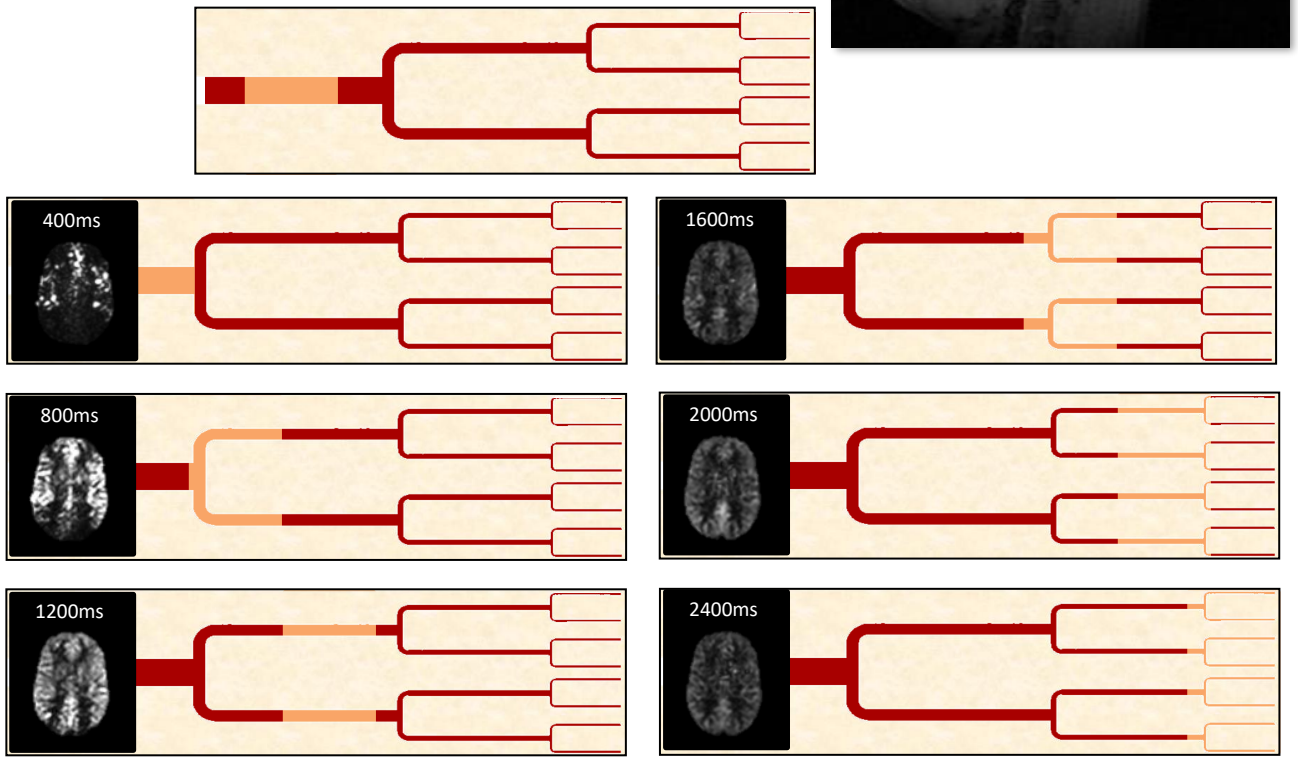


Principle:
- preparation of blood upstream
- imaging downstream after inflow time TI
- control image without preparation to cancel out tissue signal









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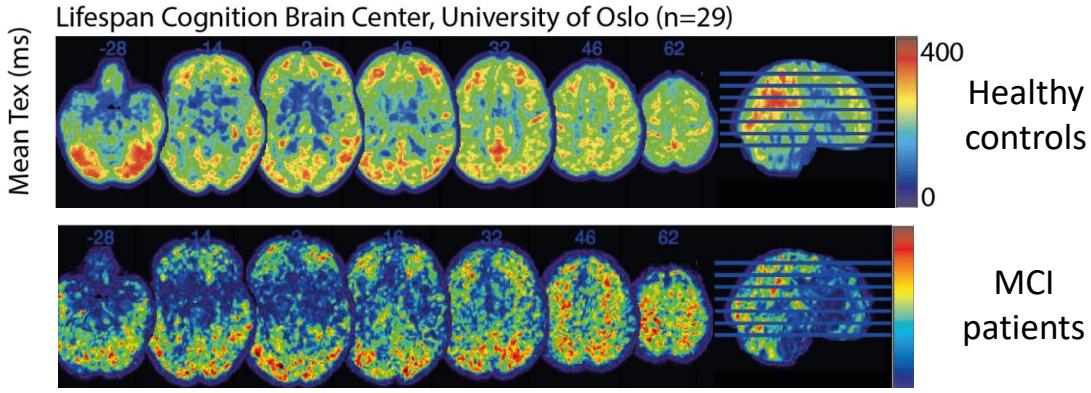
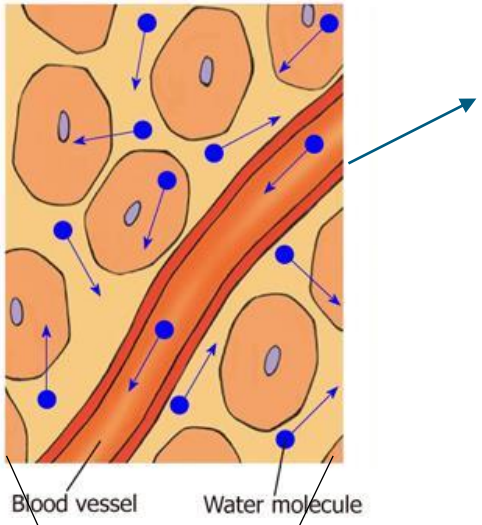
BBB-assessment with ASL

Separate intra and extra-vascular compartments

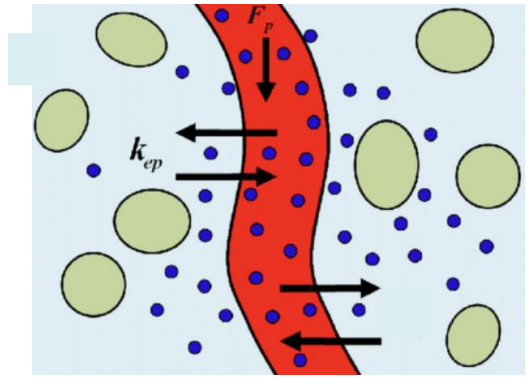
Intra- and extravascular components separated based on their T2 relaxation time

Quantification based on 2-3 compartment model



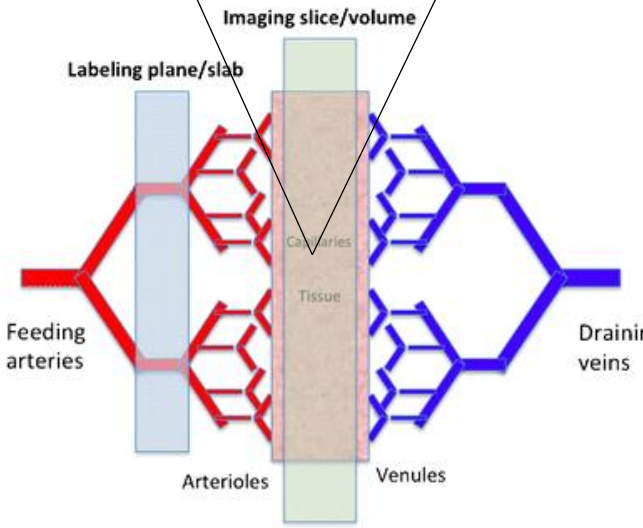


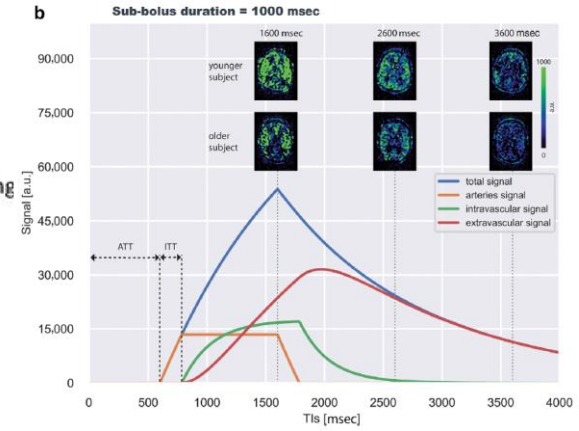
Differences in the T2 relaxation times



Multi-echo ASL

T2 (blood) > T2 (tissue)





Courtesy: Beatriz Padrela

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Limitations

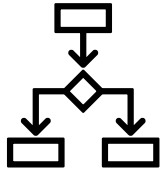
Current clinical Limitations of using ASL for direct BBB integrity mapping

To create a clinically feasible direct BBB integrity biomarker, the following is lacking:

Scan time
(too long)

Calibration
(physiological variation)

Standardization
(data acquisition & image processing)



Interpretation
(“healthy BBB”)

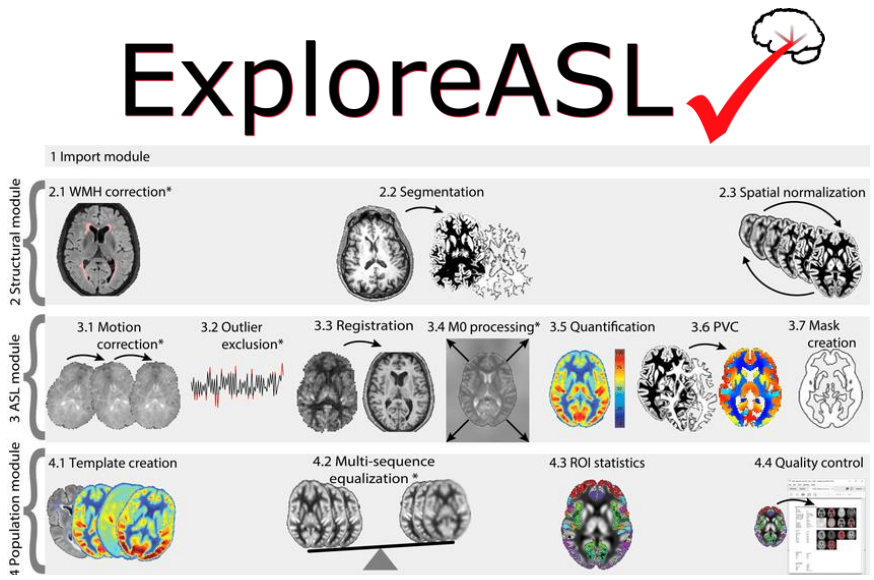
Validation
(ASL-BBB validation)

Application
(in clinical context)

Courtesy: Beatriz Padrela

Standardization

- Hardware-agnostic sequence development
- Data and image processing



NeuroImage 219 (2020) 117031

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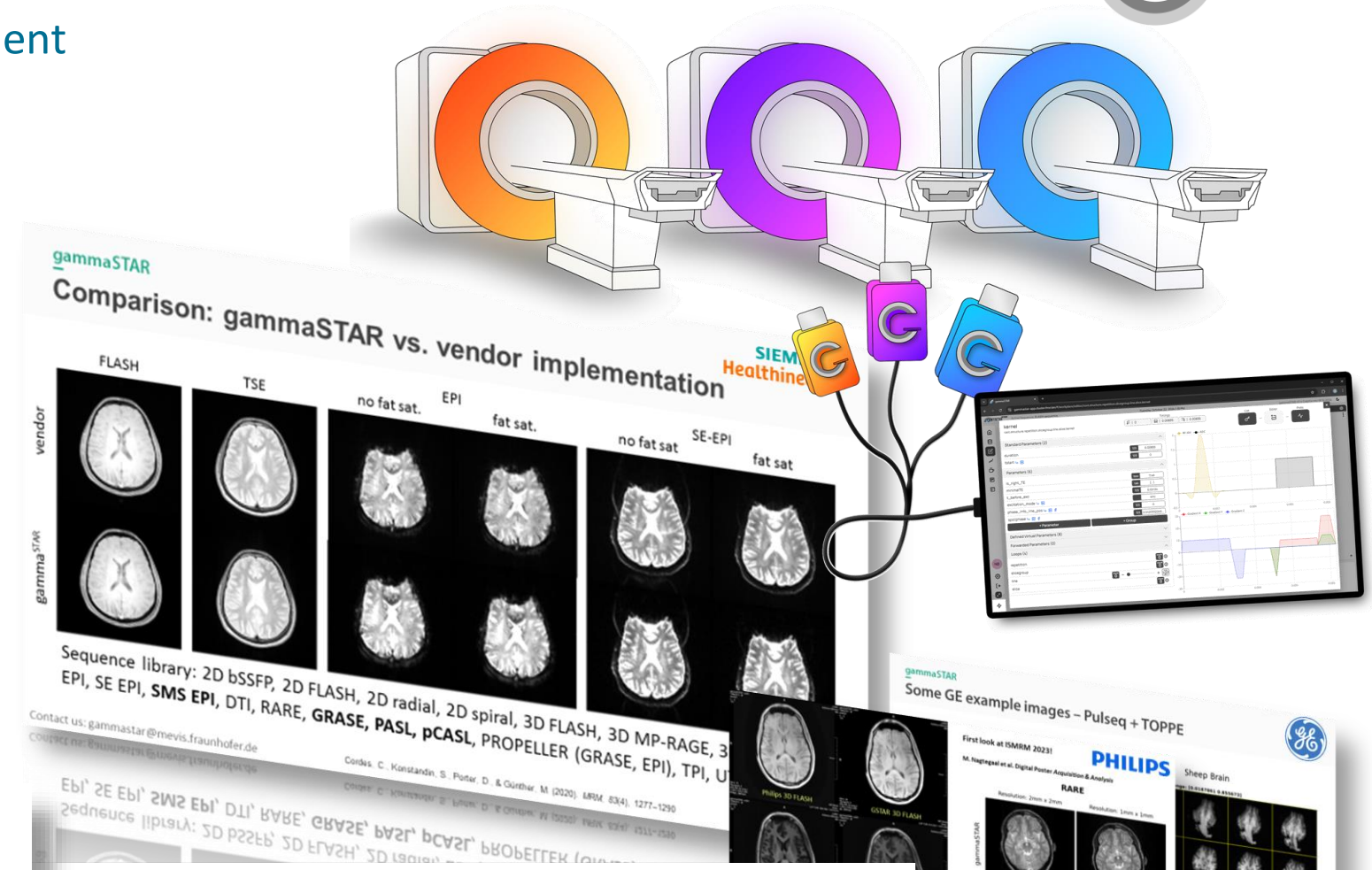
NeuroImage

journal homepage: www.elsevier.com/locate/neuroimage

ExploreASL: An image processing pipeline for multi-center ASL perfusion MRI studies

Henk J.M.M. Mutsaerts [a,b,c,d,e,*,1], Jan Petr [d,f,1], Paul Groot [b], Pieter Vandemaele [e], Silvia Ingala [a], Andrew D. Robertson [g], Lena Václavů [h], Inge Groote [i], Hugo Kuijf [j], Fernando Zelaya [k],



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DOI: 10.1002/mrm.28020

FULL PAPER

Magnetic Resonance in Medicine

Portable and platform-independent MR pulse sequence programs

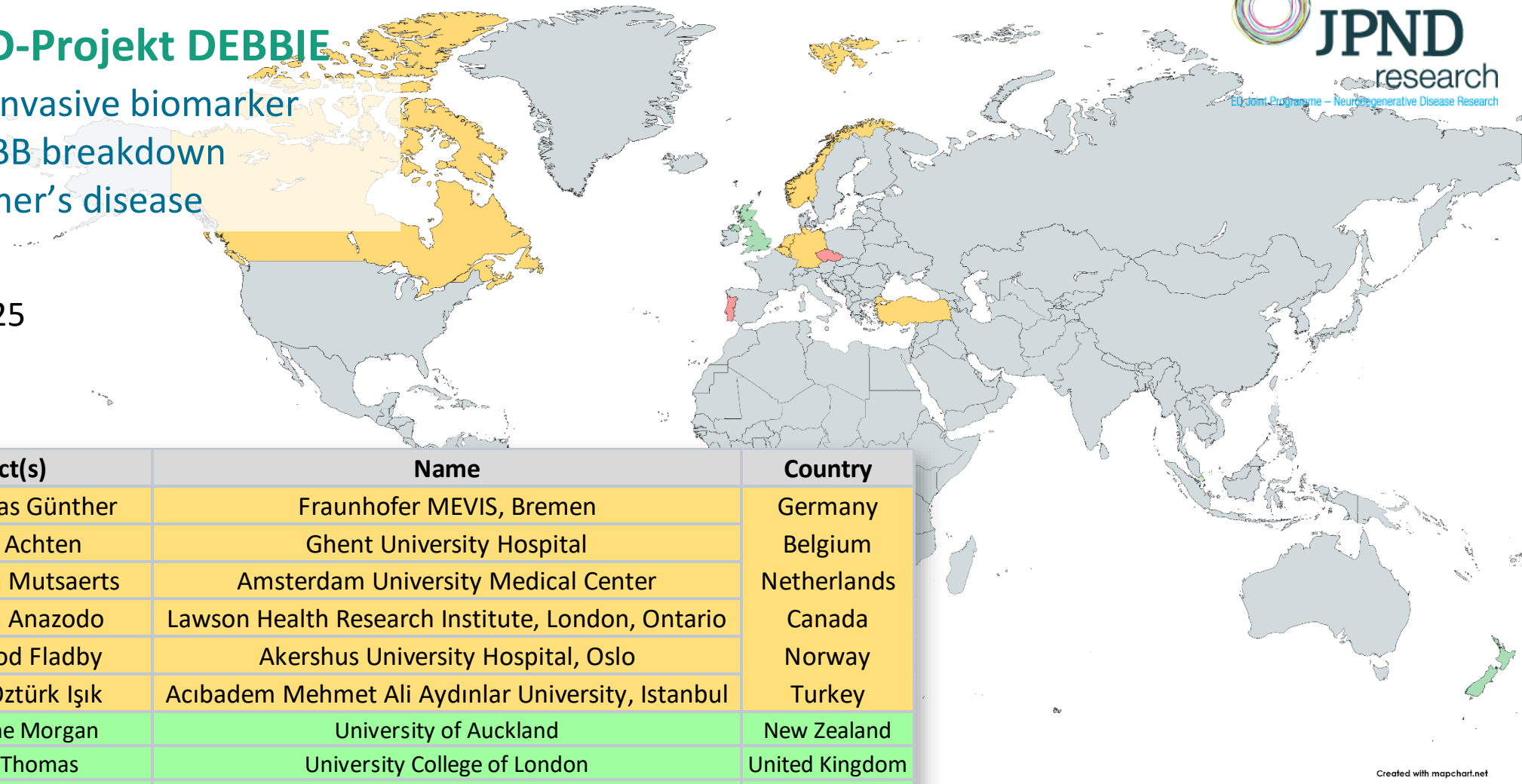
Cristoffer Cordes[1] | Simon Konstandin[1] | David Porter[2] | Matthias Günther[1,3]

Consortium JPND-Projekt DEBBIE

Developing a non-invasive biomarker for early BBB breakdown in Alzheimer's disease

duration: 2021-2024/25

funding: ~2,8M€



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external partner	Prof. Jennifer Linn, Dr. Jan Petr	Technical University Dresden	Germany
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ext. partner cand.		University Hospital Prague	Czech Republic

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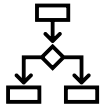
DEBBIE-AD project

(Developing BBB-ASL as non-invasive early biomarker of Alzheimer's disease)

Methodological questions

1.A Reproducibility



1.B Accuracy

1.C Normal variability

Clinical questions

2.A Health vs Disease

2.B BBB-ASL vs established AD biomarkers

2.C BBB-ASL in novel AD pathways

DEBBIE-AD project

(Developing BBB-ASL as non-invasive early biomarker of Alzheimer's disease)

	1.A	1.B	1.C
Methodological questions	Reproducibility	Accuracy	Normal variability
Why	Establish reproducibility in healthy controls	Compare with gold standard water PET	Create a reference atlas of BBB integrity from healthy participants
How	UZ GENT 50 controls Age = 55-75	LAWSON HEALTH RESEARCH INSTITUTE 12 controls + 36 patients (12 stroke, 12 MCI, 12 AD) Age = 50-90	LCBC LIFESPAN CHANGES in brain and cognition 218 controls Age = 20-90

DEBBIE-AD project

(Developing BBB-ASL as non-invasive early biomarker of Alzheimer's disease)

Clinical questions

Why

How

Health vs Disease

Detect BBB-ASL disruption between healthy controls and AD patients

- UZ GENT / UNIVERSITEIT GENT — Memory clinic — 50 controls, 30 MCI, 20 AD (Age = 55-75)
- THE UNIVERSITY OF AUCKLAND NEW ZEALAND — 50 controls, 50 MCI, 25 AD (Age = 55+)

2.B BBB-ASL vs established AD biomarkers

Investigate if BBB-ASL correlate with the current AD biomarkers

- UNIVERSITAS OSLOENSIS — 50 controls, 50 (Aβ+ and WMH) (Age = 40-80)
- NUS National University of Singapore — Memory clinic 200 SCD / MCI (Age = 45-65)
- THE UNIVERSITY OF AUCKLAND NEW ZEALAND — 50 controls, 50 MCI, 25 AD (Age = 55+)

- Fluid — Aβ-38, Aβ-40/42, p-tau, t-tau, NfL, albumin
- MRI — T1, T2, FLAIR
- PET — Amyloid-PET

2.C BBB-ASL in novel AD pathways

Study the relation of BBB-ASL with novel biomarkers of AD

Amsterdam UMC University Medical Centers

- VVI — 55 MCI (Aβ+) → Age >50 — NUS National University of Singapore — Vascular damage and WMH
- InflammAD — 20 controls + 20 MCI (Aβ+) → Age >50 — TECHNISCHE UNIVERSITÄT DRESDEN — Sleep disturbances

- …GFAP, TREM2
- FLAIR, DTI, SWI
- [11C]SMW139

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DEveloping BBB-ASL as non-Invasive Early biomarker of Alzheimer's Disease (DEBBIE-AD): Study design; Beatriz Padrela, Amnah Mahroo, Mervin Tee, Markus Sneve, Paulien Moyaert, Oliver Geier, Joost Kuijer, Soetkin Beun, Wibeke Nordhøy, Yufei David Zhu, Mareike Buck, Daniel Hoinkiss, Simon Konstandin, Jörn Huber, Julia Wiersinga, Roos Rikken, Diederick de Leeuw, Håkon Grydeland, Lynette Tippett, Erin Cawston, Esin Ozturk-Isik, Jennifer Linn, Moritz Brandt, Betty Tijms, Elsmarieke van de Giessen, Majon Muller, Anders Fjell, Kristine Walhovd, Lene Pålhaugen, Per Selnes, Patricia Clement, Eric Achten, Udunna Anazodo, Frederik Barkhof, Saima Hilal, Tormod Fladby, Klaus Eickel, Catherine Morgan, David Thomas, Jan Petr, Matthias Günther, Henk JMM Mutsaerts; 2023; https://doi.org/10.1016/j.cccb.2024.100308; Proceedings; VasCog 2023 Cerebral Circulation - Cognition and Behavior, Vol6, Sup 1

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Thank you!

Have a look at the poster of the DEBBIE project presented by Beatriz E. Padrela as poster 12

DEBBIE project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No. 825664. It is supported through the following funding organisations under the aegis of the EU Joint Program for Neurodegenerative Disease Research (JPND2020-568-106)