Advanced MR image analysis in sporadic and Dutch-type hereditary Cerebral Amyloid Angiopathy

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Portfolio

PhD trajectory – an overview

During my PhD, I engaged in a variety of activities and efforts beyond those presented in the scientific chapters of this thesis, a selection is highlighted in this chapter.

The first year of my PhD started during the COVID pandemic, however, the LUMC's (Dutch-type) Cerebral Amyloid Angiopathy ((D-)CAA) studies I was involved in quickly resumed their research visits, provided that participants and investigators had no COVID symptoms. I learned how to perform or assist with every aspect of the research visits as presented in Chapter 1, Table 1.2, under the supervision of fellow PhD-students Thijs van Harten, Sabine Voigt, Kanishk Kaushik, Emma Koemans, and Ingeborg Rasing. Together with fellow PhD-students Reinier van der Zwet, Rosemarie van Dort, and Sanne Schriemer, we later took over these visits for all CAA studies. I obtained scan brevets for 3 Tesla (T) and 7T magnetic resonance imaging (MRI) and was responsible for assessing participants' MRI safety profiles, under the guidance of medical physicist Nick de Jong and senior scientist Wouter Teeuwisse. My contribution to the research visits focused on MRI data acquisition and curation and MRI post-processing, as I took this over from Thijs van Harten. Thijs also introduced me to and mentored me in various post-processing steps and software, including functional (f)MRI post-processing and MeVisLab.

During my first year, I worked on a side project assessing the robustness of fMRI measures across two 3T MR systems and visual stimulation setups. This project was published as conference abstract and demonstrated limited bias in longitudinal and cross-sectional comparisons. This was of importance as the TRACK (AURORA-PLUS) study was planned to be performed on a different MR system than the already running AURORA study. The first main project I worked on is presented in Chapter 2, and includes two MRI analyses – diffusion tensor imaging and visually stimulated fMRI analysis – revealing the association between microstructural white matter integrity and vasoreactivity in (D-)CAA. Also, the project presented in Chapter 7, identifying the occurrence of acute cerebral microbleeds (CMBs) on 7T MRI in (D-)CAA, was initiated.

A project that I focused on during the second year, involved development and validation of a pipeline to quantify perivascular spaces (PVS) in the presence of large, disruptive pathology, as observed in (D-)CAA (Chapter 4). With this project we identified PVS volume fraction as early marker in (D-)CAA. Later this year, I presented the project at the international CAA conference, where I was awarded the prize for best oral presentation.

During the third year, my role in checking MRI participant safety profiles transitioned into a supervisory role, as research assistants (Yasmine Alladin, Nikki Hengeveld and Isabel Kohlmann) took over this task. In this year, I was awarded best poster and best oral presentation prizes at the LUMC Neuroscience Symposium and the CAA early career researchers conference, respectively. Also, I performed the fMRI baseline and one-year follow-up analysis in the (D-)CAA cohorts, revealing variation in vasoreactivity over time, which was included in van der Plas et al., 2025 (https://doi.org/10.1212/WNL.0000000000213546) and resulted in Chapter 3. In addition, the project presented in Chapter 5 was initiated, showing sulcal predominance of CMBs. Lastly, together with Ellen Stijl – 't Hart, Rosemarie van Dort, and Sanne Schriemer, I co-organized a (D-)CAA information day for patients, families, and caregivers, which was attended by over 250 participants. This also included an item and follow-up session on early discussions regarding potential inclusion of D-CAA as a disease subgroup in the cAPPricorn clinical trial.

During the later stages of my PhD, the project presented in Chapter 6 was initiated. Here we identified interindividual CMB clustering in (D-)CAA using a flow territory-based analysis.

Over the course of my PhD, as a team we have acquired roughly 900 MRI scans, reflecting the substantial time investment and coordination required for large-scale data collection. In parallel, I have supervised five students; Arie-Tjerk Razoux-Schultz (bachelor's internship), Lex Otto and Roelof Schraa (BSc gap-year students), Abel Thissen (master's student), and Maria Andrikopoulou (master's student who worked as research assistant). Also, I was involved in the organization and management of four recurring meetings, of which two meetings were new initiatives. One was established for focused sessions and workshops for clinical neuro-focused researchers and the other was a radiology-wide initiative to promote interdisciplinary contact and collaboration. Furthermore, I contributed to annually distributed (D-)CAA newsletters, which communicate research and recent publications to people with (D-)CAA, family members, research participants, and health care professionals.

Characterizing for my PhD has been its collaborative nature. A major study I worked on was the multicenter TRACK study; a collaboration between researchers from Leiden, Perth, and Boston. Furthermore, working within the C.J. Gorter MRI Center and closely collaborating with the neurology department, fostered a multidisciplinary team and research environment – facilitating further collaborations for post-processing support of the headache and neurovascular (non-CAA) subgroups of the neurology department.

CRediT statement for the chapters in this thesis

CRediT table for the thesis of Manon R. Schipper

Ch.	Type*	Short Title	Conceptualization	Data Curation	Formal Analysis	Funding Acquisition	Investigation	Methodology	Project Administration	Resources	Software	Supervision	Validation	Visualization	Writing – Original Draft	Writing – Review & Editing	Preregistered	Preprinted	Published with Peer Review
1	Introduction																☐	☐	☐
2	PhD project chapter	DTI vs. fMRI in D-CAA															☐	☐	☑
3	PhD project chapter	fMRI follow-up in (D-)CAA															☐	☐	☐
4	PhD project chapter	PVS in D-CAA															☐	☐	☑
5	PhD project chapter	CMB sulcus vs. gyrus															☐	☐	☐
6	PhD project chapter	CMB flow territories															☐	☐	☐
7	PhD project chapter	Acute CMB on 7T MRI															☐	☐	☑
8	Discussion																☐	☐	☐

*PhD project chapters are the direct result of the PhD project of the PhD candidate.
Some theses also include Collaboration Chapters, to which the PhD candidate has contributed but fall outside the PhD project.

Publication and dissemination table

1. Schipper, M. R.*, van Harten, T. W., van Bronkhorst, M., van der Plas, M. C. E., Wermer, M. J. H., van Walderveen, M. A. A., and van Osch, M. J. P. (2022). Vascular reactivity measurements are insensitive to changes in visual stimulus presentation method. Conference abstract – poster presentation at ISMRM Benelux 2022. Not part of this thesis.
2. Schipper, M. R.*, Vlegels, N.*, Voigt, S., van Harten, T. W., de Luca, A., Rasing, I., Biessels, G.J., van Osch, M.J.P., van Walderveen, M.A.A., and Wermer M.J.H. (2022). The relationship between vascular reactivity and microstructural white matter integrity in (pre-)symptomatic Dutch-type cerebral amyloid angiopathy. Conference abstract – power pitch at World Stroke Conference 2022. Not part of this thesis.
3. Schipper, M. R.*, Vlegels, N.*, van Harten, T. W., Voigt, S., Koemans, E. A., Rasing, I., de Luca, A., Kaushik, K., van Etten, E.S., van Buchem, M.A., Terwindt, G.M., Biessels, G.J., van Osch, M.J.P., van Walderveen, M.A.A., and Wermer, M.J.H. (2022). The relationship between vascular reactivity and microstructural white matter integrity in (pre-)symptomatic Dutch-type cerebral amyloid angiopathy. Conference abstract – poster presentation at International CAA conference 2022. Not part of this thesis.
4. Schipper, M. R., Razoux-Schultz, A., van Harten, T. W., van der Grond, J., van Buchem, M. A., Greenberg, S. M., Wermer, M.J.H., van Osch, M.J.P., van Walderveen, M.A.A., and van Rooden, S. (2022). Total white matter perivascular space volume: An early marker for Dutch-type Cerebral Amyloid Angiopathy. Conference abstract – oral presentation at International CAA conference 2022. Not part of this thesis.
5. Schipper, M. R., Razoux-Schultz, A., van Harten, T. W., van der Grond, J., van Buchem, M. A., Greenberg, S. M., Wermer, M.J.H., van Osch, M.J.P., van Walderveen, M.A.A., and van Rooden, S. (2023). Total white matter perivascular space volume: An early marker for Dutch-type Cerebral Amyloid Angiopathy. Conference abstract – poster presentation at ISMRM Benelux 2023. Not part of this thesis.
6. Schipper, M. R., Razoux-Schultz, A., van Harten, T. W., van der Grond, J., van Buchem, M. A., Greenberg, S. M., Wermer, M.J.H., van Osch, M.J.P., van Walderveen, M.A.A., and van Rooden, S. (2023). Total white matter perivascular space volume: An early marker for Dutch-type Cerebral Amyloid Angiopathy. Conference abstract – oral presentation at ISMRM 2023. Not part of this thesis.
7. Schipper, M.R., Vlegels, N., Voigt, S., van Harten, T.W., de Luca, A., Rasing, I., Biessels, G.J., van Osch, M.J.P., van Walderveen, M.A.A., and Wermer, M.J.H. (2023). The relationship between vascular reactivity and microstructural white matter integrity in Dutch-type Cerebral Amyloid Angiopathy. Conference abstract – poster presentation at ISMRM 2023. Not part of this thesis.
8. Schipper, M. R., Razoux-Schultz, A., van Harten, T. W., Wermer, M. J. H., van Osch, M. J. P., van Walderveen, M. A. A., and van Rooden, S. (2023). Does a manual determined threshold bias quantitative perivascular spaces measurements based on the Frangi vesselness filter? Meeting abstract – oral presentation at ICP 2023. Not part of this thesis.
9. Schipper, M. R., van der Plas, M. C., Koemans, E. A., Kaushik, K.,, van Dort, R., van der Zwet, R. G. J., Schriemer, S.E., van Harten, T.W., Voigt, S., Rasing, I., van Walderveen, M.A.A., van Osch, M.J.P., and Wermer, M.J.H. (2024). One-year follow-up of visually stimulated task-based fMRI in Dutch-type and sporadic Cerebral Amyloid Angiopathy. Meeting abstract – poster presentation at ISMRM Benelux 2024. Part of this thesis (Chapter 3).
10. van der Zwet, R. G. J., Koemans, E. A., Voigt, S., van Dort, R., Rasing, I., Kaushik, K., van Harten T. W., Schipper, M. R., Terwindt, G.M., van Osch, M.J.P., van Walderveen, M.A.A., van Etten, E.S., and Wermer, M.J.H. (2024). Sensitivity of the Boston Criteria Version 2.0 in Dutch-Type Hereditary Cerebral Amyloid Angiopathy. https://doi.org/10.1177/17474930241239801. Not part of this thesis.

11. Schipper, M. R.*, Vlegels, N.*, van Harten, T. W., Rasing, I., Koemans, E. A., Voigt, S., de Luca, A., Kaushik, K., van Etten, E.S., van Zwet, E.W., Terwindt, G.M., Biessels, G.J., van Osch, M.J.P., van Walderveen, M.A.A., and Wermer, M.J.P. (2023). Microstructural white matter integrity in relation to vascular reactivity in Dutch-type hereditary cerebral amyloid angiopathy. https://doi.org/10.1177/0271678X231200425. Part of this thesis (Chapter 2)
12. van Dort, R., Kaushik, K., Rasing, I. van der Zwet, R. G. J., Schipper, M. R., van der Grond, J., van Rooden, S., van Zwet, E.W., Terwindt, G.M., Middelkoop, H.A.M., Hart, E.P., van Osch, M.J.P., van Walderveen, M.A.A., and Wermer, M.J.H. (2024). Cognition in (pre)symptomatic Dutch-type hereditary and sporadic cerebral amyloid angiopathy. https://doi.org/10.1002/alz.14171. Not part of this thesis.
13. Rasing, I., Vlegels, N., Schipper, M. R., Voigt, S., Koemans, E. A., Kaushik, K., van Dort, R., van Harten, T.W., de Luca, A., van Etten, E.S., van Zwet, E.W., van Buchem, M.A., Middelkoop, H.A.M., Biessels, G.J., Terwindt, G.M., van Osch, M.J.P., van Walderveen, M.A.A., and Wermer, M.J.H. (2024). Microstructural white matter damage on MRI is associated with disease severity in Dutch-type cerebral amyloid angiopathy. https://doi.org/10.1177/0271678X241261771. Not part of this thesis.
14. Koemans, E. A., Rasing I., Voigt, S., van Harten, T. W., van der Zwet, R. G. J., Kaushik, K., Schipper, M. R., van der Weerd, N., van Zwet, E.W., van Etten, E.S., van Osch, M.J.P., Kuiperij, B., Verbeek, M.M., Terwindt, G.M., Greenberg, S.M., van Walderveen, M.A.A., and Wermer, M.J.H. (2024). Temporal ordering of biomarkers in Dutch-type hereditary cerebral amyloid angiopathy. https://doi.org/10.1161/STROKEAHA.123.044688. Not part of this thesis.
15. Schipper, M. R., van Harten, T. W., Razoux-Schultz, A., Otto, A. L. D., Kaushik, K., Hirschler, L., Voigt, S., Rasing, I., Koemans, E.A., van Dort, R., van der Zwet, R.G.J., Schriemer, S.E., van Zwet, E.W., van der Grond, J., van Buchem, M.A., Greenberg, S.M., Wermer, M.J.H., van Osch, M.J.P., van Walderveen, M.A.A., and van Rooden, S. (2025). Quantification of Total White Matter Perivascular Space Volume: Follow-up in Dutch-type Hereditary Cerebral Amyloid Angiopathy. Meeting abstract – poster presentation at ISMRM 2025. Not part of this thesis.
16. Schipper, M. R., van Harten, T. W., Razoux-Schultz, A., Kaushik, K., Hirschler, L., Voigt, S., Rasing, I., Koemans, E.A., van Dort, R., van der Zwet, R.G.J., Schriemer, S.E., van Zwet, E.W., van der Grond, J., van Buchem, M.A., Greenberg, S.M., Wermer, M.J.H., van Osch, M.J.P., van Walderveen, M.A.A., and van Rooden, S. (2025). Cross-sectional and longitudinal quantification of Total white matter perivascular space volume fraction in Dutch-type Cerebral Amyloid Angiopathy. https://doi.org/10.1016/j.nicl.2025.103778. Part of this thesis (Chapter 4).
17. van der Plas, M. C., Koemans, E. A., Schipper, M. R., Voigt, S., Rasing, I., van der Zwet, R. G. J., Kaushik, K., van Dort, R., Schriemer, S.E., van Harten, T.W., van Zwet, E.W., van Etten, E.S., van Osch, M.J.P., Terwindt, G.M., van Walderveen, M.A.A., and Wermer, M.J.H. (2025). One-Year Radiologic Progression in Sporadic and Hereditary Cerebral Amyloid Angiopathy. https://doi.org/10.12.12/WNL.0000000000213546. Not part of this thesis.
18. de Bruin, O. F.*, Schipper, M. R*, Koemans, E. A., van Harten, T. W., Rasing, I., Kaushik, K., Hirschler, L., van Dort, R., van der Zwet, R.G.J., van Osch, M.J.P., van Walderveen, M.A.A., Wermer, M.J.H., and Voigt, S. (2025). Hyperintense lesions suspect for acute cerebral microbleeds on ultra-high field T1 weighted 7 Tesla MRI in patients with cerebral amyloid angiopathy. https://doi.org/10.1016/j.ejrad.2025.112428. Part of this thesis (Chapter 7)
19. Schipper, M. R.*, van der Zwet, R. G. J.*, Goeman, J. J., van Harten, T. W., Koemans, E. A., Wermer, M. J. H., Walderveen, M.A.A., and van Osch, M.J.P. (in submission). Clustering of Cerebral Microbleeds in Cerebral Amyloid Angiopathy: A Flow Territory-Based Analysis. Part of this thesis (Chapter 6). Open code is available: R-code for statistical analysis is added as supplementary materials to the submission
20. Schipper, M. R.*, van Harten, T. W., Koemans, E. A., Goeman, J. J., Wermer, M. J. H., van Osch, M.J.P., and van Walderveen M.A.A. (in submission). Following the curvature: sulcal versus gyral cortical localization of cerebral microbleeds in Cerebral Amyloid Angiopathy. Part of this thesis (Chapter 5).

Completed courses and other training

Mandatory activities

Year	Title (+ description if needed)	Hours
2021	Leiden University Onboarding Program Inform & Connect (2 activities), LUMC	5
2021	Basic Methods and Reasoning in Biostatistics, LUMC	42
2021	Responsible Research (2 activities), LUMC	42

Scientific courses, workshops, and other training activities

Year	Title (+ description if needed)	Hours
2021	European Stroke Organization Conference (ESOC) conference, online	27
2022	International Society for Magnetic Resonance in Medicine (ISMRM) Benelux conference, Maastricht	9
2022	ISMRM conference, London	36
2022	Getting a @Handle on Big Neuroimaging Datasets, educational ISMRM 2022	4
2022	Microstructure: Relaxation, Magnetization Transfer & Susceptibility, educational ISMRM 2022	4
2022	The Circadian Clock & Its Effect on the Human Brain, educational ISMRM 2022	4
2022	MRI Artifacts & Corrections, educational ISMRM 2022	4
2022	Physics for Clinicians I and II, educational ISMRM 2022	4
2022	World Stroke Conference (WSC), Singapore	34
2022	International CAA conference (ICAA), Perth	25.5
2022-2025	Organization of multiple meeting (LUMC)	36
2023	ISMRM Benelux conference, Brussel	9
2023	School of MRI (organized by ESMRM-B)	18
2023	ISMRM conference, Toronto	36
2023	MR Physics I, educational ISMRM 2023	4
2023	MR Physics II, educational ISMRM 2023	4
2023	Key Contrast Mechanisms for Imaging Neuroinflammation, educational ISMRM 2023	4
2023	International CAA ECR conference, online	4
2023	Imaging Cerebral Physiology (ICP), Utrecht	27
2023	LUMC Neuroscience Symposium with presentation	6
2024	ISMRM Benelux, ‘s Hertogenbosch	11
2024	7T Philips User meeting with presentation, Amsterdam	16
2024	ICAA conference, München	25
2024	Leducq Consortium meeting, München	16
2025	Leducq Consortium meeting, Seattle	24
2025	ISMRM Benelux, Hilversum	9
2025	ISMRM conference, Honolulu	48

Transferable skills courses, workshops, and other training activities		
Year	Title (+ description if needed)	Hours
2022	Teaching – Bachelor's internship supervision	28
2022	Committee member of Teaching Radiology Exchange (T-REx)	52
2023	Teaching – gap-year internship supervision	28
2023	7 Tesla MRI tour assistance during Leiden International (Bio)Medical Student Conference (LIMSC)	5
2023	Teaching – one-day psychology BSc student supervision	4
2023	Organizing team (D-)CAA information day	58
2023	Teaching – supervising research assistant	40.5
2023	Careers outside academia, educational ISMRM 2023	4
2023	More success with less stress, Leiden University	28
2024	Career orientation - LAP day focused with meetings focused on career opportunities	8
2024	Teaching – Master's internship supervision	16
2024	Teaching – gap-year internship supervision	16
2021-2025	Total of mandatory activities, scientific skills and transferable skills	825

Dissemination, acknowledgement, esteem and other relevant scientific activities table

Presentations at conferences and different type of meetings		
Year	Description	Linked to chapter(s)
2022	Poster presentation at ISMRM Benelux 2022, titled "Vascular reactivity measurements are insensitive to changes in visual stimulus presentation method."	-
2022	Power pitch at World Stroke Conference 2022, titled "The relationship between vascular reactivity and microstructural white matter integrity in (pre-)symptomatic Dutch-type cerebral amyloid angiopathy."	Chapter 2
2022	Poster presentation at International CAA conference 2022 "The relationship between vascular reactivity and microstructural white matter integrity in (pre-) symptomatic Dutch-type cerebral amyloid angiopathy."	Chapter 2
2022	Oral presentation at International CAA conference 2022, titled "Total white matter perivascular space volume: An early marker for Dutch-type Cerebral Amyloid Angiopathy."	Chapter 4
2023	Poster presentation at ISMRM Benelux 2023, titled "Total white matter perivascular space volume: An early marker for Dutch-type Cerebral Amyloid Angiopathy."	Chapter 4
2023	Oral presentation at ISMRM 2023, titled "Total white matter perivascular space volume: An early marker for Dutch-type Cerebral Amyloid Angiopathy."	Chapter 4

2023	Poster presentation at ISMRM 2023, titled “The relationship between vascular reactivity and microstructural white matter integrity in Dutch-type Cerebral Amyloid Angiopathy”	Chapter 2
2023	Oral presentation at ICP 2023, titled “Does a manual determined threshold bias quantitative perivascular spaces measurements based on the Frangi vesselness filter?”	Chapter 4
2023	Poster presentation at Neuroscience Symposium LUMC 2023, titled “Total white matter perivascular space volume: An early marker for Dutch-type Cerebral Amyloid Angiopathy.”	Chapter 4
2023	Oral presentation at CAA ECR online conference 2023, titled “Quantification of Total White Matter Perivascular Space Volume in Dutch-type Hereditary Cerebral Amyloid Angiopathy: Longitudinal Preliminary Data.”	Chapter 4
2024	Poster presentation at ISMRM Benelux 2024, titled “One-year follow-up of visually stimulated task-based fMRI in Dutch-type and sporadic Cerebral Amyloid Angiopathy.”	Chapter 3
2025	Poster presentation at ISMRM 2025, titled “Quantification of Total White Matter Perivascular Space Volume: Follow-up in Dutch-type Hereditary Cerebral Amyloid Angiopathy.”	Chapter 4

Awards

Year	Description	Linked to chapter(s)
2022	Best oral presentation award at International CAA conference 2022	Chapter 4
2023	Best poster presentation award at Neuroscience Symposium LUMC 2023	Chapter 4
2023	Best oral presentation award at CAA ECR online conference 2023	Chapter 4

Grant applications

Year	Description	Linked to chapter(s)
2025	Alzheimer Nederland travel grant application: Small Grants - Financial support for conference attendance	Chapter 4

Curriculum Vitae

Manon Roxanne Schipper was born on March 11th, 1997, in Hardinxveld-Giessendam, the Netherlands. After graduating from high school in 2015, she started the bachelor in Psychology with the Honours track 'science and society' at the social faculty of Leiden University. She completed her bachelor's internship under supervision of Dr. Laura Steenbergen at Leiden University and wrote a bachelor's thesis titled "The relationship between transcutaneous vagal nerve stimulation, decision-making, happiness, and heart rate variability". In 2018 she started the Cognitive Neuroscience track of the Psychology research master at Leiden University. She completed her master's internship at the Amsterdam UMC under supervision of Dr. Marieke van der Pluijm and Dr. Anne Trutti and wrote a master's thesis titled "The use of neuromelanin-sensitive MRI to assess neuromelanin differences in the substantia nigra between treatment resistant and respondent patients with schizophrenia". She graduated from the master's program in 2020. During her studies, she worked as a care assistant for demented elderly at a restricted psychogeriatric department of caring home 'Rijn en Vliet' in Leiden.

In May 2021 Manon started her PhD research at the C.J. Gorter MRI Center of the Radiology department at the Leiden University Medical Center (LUMC) under the supervision of Dr. Marianne van Walderveen, Prof. Dr. Marieke Wermer, and Prof. dr. ir. Matthias van Osch. She worked in a multidisciplinary team; working closely with the LUMC Neurology department and researchers in both Boston, USA, and Perth, Australia. The focus of her PhD was on advanced MR image analyses in sporadic and Dutch-type Cerebral Amyloid Angiopathy.

Manon is currently continuing her research as a post-doctoral researcher at the C.J. Gorter MRI Center of the Radiology department at the LUMC, further focusing on advanced MR image analyses in sporadic and Dutch-type Cerebral Amyloid Angiopathy.

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