PROJECT

Supervisor: Edoardo Gioele Spinelli

Title: Quantitative MRI biomarkers of cerebral amyloid angiopathy–related vascular injury across the Alzheimer's disease spectrum

Curriculum: Cognitive and Behavioural Sciences

Link to the personal page of the University or relevant hospital site website: https://unifind.unisr.it/get/person/spinelli-edoardogioele

Description of the Project (max 3,000 characters including spaces)

Background/gap of knowledge

Cerebral amyloid angiopathy (CAA) is a small vessel disease characterized by deposition of amyloid-β in the walls of cortical and leptomeningeal vessels. CAA frequently coexists with Alzheimer's disease (AD) and contributes to vascular brain injury, cognitive decline, and increased risk of intracerebral hemorrhage. Currently, the diagnosis of CAA relies largely on conventional MRI markers such as cerebral microbleeds and cortical superficial siderosis. However, these imaging features usually reflect relatively advanced vascular damage.

The development of disease-modifying therapies targeting amyloid pathology has highlighted the clinical importance of vascular vulnerability in patients with AD, as anti-amyloid monoclonal antibodies may induce amyloid-related imaging abnormalities (ARIA). The presence of underlying CAA is considered a major risk factor for ARIA, yet current imaging markers are insufficient to reliably identify patients at higher risk before treatment initiation.

Advanced MRI techniques provide the opportunity to detect subtle and quantitative signatures of vascular injury beyond conventional markers. However, the potential of multimodal MRI approaches to identify early CAA-related damage and to differentiate pure AD and mixed AD+CAA pathology remains insufficiently explored.

Rationale and hypothesis

The central rationale of this project is that advanced multimodal MRI at 3T can identify subtle and quantitative imaging signatures of vascular amyloid-related injury that are not captured by conventional radiological markers. Techniques such as diffusion tensor imaging (DTI), susceptibility-weighted imaging (SWI), and resting-state functional MRI may detect

microstructural white matter alterations, susceptibility-related cortical changes, and network-level dysfunction associated with CAA pathology.
We hypothesize that specific quantitative MRI patterns reflecting CAA-like vascular damage exist across the AD spectrum. These biomarkers may help identify individuals with increased vascular vulnerability who are more likely to develop ARIA during anti-amyloid treatment.

Objectives and specific aims

Aim 1: To identify quantitative MRI markers of CAA-related vascular injury using multimodal imaging approaches.
Aim 2: To characterize imaging patterns that distinguish patients with pure AD and mixed AD+CAA pathology.
Aim 3: To investigate whether these MRI biomarkers are associated with the occurrence of amyloid-related imaging abnormalities in patients with AD treated with anti-amyloid drugs.

Expected outcomes

The project is expected to identify novel quantitative MRI biomarkers reflecting subtle vascular injury associated with CAA, improving the characterization of vascular pathology across the AD spectrum. Furthermore, the identification of imaging signatures associated with increased vascular vulnerability may contribute to improved risk stratification for ARIA in patients receiving anti-amyloid therapies.

Skills that the student should acquire (max. 600 characters including spaces):

During the project, the student will acquire expertise in the clinical and cognitive assessment of AD and CAA, advanced MRI acquisition and preprocessing, and quantitative neuroimaging analysis. The student will learn to analyze DTI, SWI, and functional MRI data, perform clinico-imaging correlation analyses, apply advanced statistical methods, and develop skills in scientific writing and presentation of research findings.

References (max. 15)

1. Greenberg SM, Bacskai BJ, Hernandez-Guillamon M, Pruzin J, Sperling R, van Veluw SJ. Cerebral amyloid angiopathy and Alzheimer disease - one peptide, two pathways. Nat Rev Neurol. 2020 Jan;16(1):30-42. doi: 10.1038/s41582-019-0281-2. Epub 2019 Dec 11. PMID: 31827267; PMCID: PMC7268202.
2. Salloway S, Wojtowicz J, Voyle N, Lane CA, Klein G, Lyons M, Rossomanno S, Mazzo F, Bullain S, Barkhof F, Bittner T, Schneider A, Grundman M, Aldea R, Boada M, Smith J, Doody R. Amyloid-Related Imaging Abnormalities (ARIA) in Clinical Trials of Gantenerumab in Early

Alzheimer Disease. JAMA Neurol. 2025 Jan 1;82(1):19-29. doi: 10.1001/jamaneurol.2024.3937. Erratum in: JAMA Neurol. 2025 Feb 24. doi: 10.1001/jamaneurol.2025.0076. PMID: 39556389; PMCID: PMC11574721.

3. Filippi M, Cecchetti G, Spinelli EG, Vezzulli P, Falini A, Agosta F. Amyloid-Related Imaging Abnormalities and β-Amyloid-Targeting Antibodies: A Systematic Review. JAMA Neurol. 2022 Mar 1;79(3):291-304. doi: 10.1001/jamaneurol.2021.5205. PMID: 35099507.
4. Agosta F, Cecchetti G, Spinelli EG, Ghirelli A, Rugarli G, Filippi M. MRI protocols and sequences for amyloid-related imaging abnormalities monitoring in Alzheimer's disease patients treated with monoclonal antibodies. Curr Opin Neurol. 2025 Aug 1;38(4):289-297. doi: 10.1097/WCO.0000000000001388. Epub 2025 Jun 4. PMID: 40466018.
5. Santos A, Almeida FC, Gauthreaux K, Mock CN, Kukull WA, Crary JF, Oliveira TG. White matter microstructure is differentially impacted by cerebral amyloid angiopathy, neurofibrillary tangles, and neuritic plaque co-pathology. Alzheimers Dement. 2025 Oct;21(10):e70637. doi: 10.1002/alz.70637. PMID: 41085201; PMCID: PMC12519507.