PROJECT

Supervisor: FEDERICA AGOSTA

Title: Multimodal Brain MRI Signatures of Anti-Amyloid Therapy in Alzheimer's Disease

Curriculum: Neuroscience and Experimental Neurology

Link to the personal page of the University or relevant hospital site website: **https://www.unisr.it/docenti/a/agosta-federica**

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

Alzheimer's disease (AD) is the leading cause of dementia worldwide and represents a major unmet therapeutic challenge (1). The recent introduction of anti-amyloid therapies (AATs) has opened a new therapeutic era for patients with early AD (2-6). However, despite their increasing clinical use, apart from amyloid removal, the central biological effects of these therapies on brain structure and function remain only partially understood.

Magnetic resonance imaging (MRI) plays a central role in the clinical management of patients undergoing AATs, primarily for monitoring treatment-related adverse events such as amyloid-related imaging abnormalities (ARIA). Beyond safety monitoring, MRI provides a unique opportunity to investigate how AAT influence brain organization at multiple biological levels. Advanced MRI techniques capture complementary aspects of brain architecture and function. Structural MRI allows the assessment of regional atrophy (7, 8), diffusion MRI characterizes white-matter microstructure and structural connectivity and resting-state functional MRI provides insights into large-scale brain network organization (9). Integrating these modalities may reveal measurable neuroimaging signatures reflecting AAT-related changes in tissue integrity, microstructural organization, and functional network dynamics.

Despite the rapid implementation of AATs in clinical practice, little is known about the longitudinal neuroimaging trajectories associated with treatment in real-world populations. Moreover, it remains unclear whether baseline neuroimaging features may identify patients who are more susceptible to ARIA or who exhibit different patterns of therapeutic response.

We hypothesize that AAT is associated with measurable longitudinal changes in multimodal MRI markers reflecting structural, microstructural, and network-level brain reorganization. Baseline neuroimaging characteristics may also be associated with clinical trajectories, biomarker evolution, and susceptibility to ARIA during treatment.

In this project we propose to characterize longitudinal multimodal MRI changes associated with AAT in early AD, evaluate the relationship between longitudinal neuroimaging changes and clinical or biomarker trajectories and explore whether multimodal MRI markers can identify distinct imaging phenotypes associated with differential disease trajectories, treatment response and ARIA risk.

Finally, we aim to explore the feasibility of applying multimodal neuroimaging analyses to accelerated MRI acquisitions, including ultra-fast MRI protocols that may be implemented following dedicated training (10, 11).

By integrating structural and functional MRI, this project aims to identify multimodal MRI signatures reflecting the central brain effects of AATs and to support the development of imaging biomarkers for monitoring therapeutic response and guiding personalized treatment strategies in AD.

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

Diagnosis, treatment and monitoring of AD patients. Management and coordination of AAT programs (patient selection, imaging, biomarker assessments, longitudinal monitoring integrating MRI, PET, clinical and neuropsychological data). Active collection and

analysis of clinical data and biological material (blood and cerebrospinal fluid). Analysis of neuropsychological data. MRI acquisition. Advanced MRI analysis, knowledge of MRI techniques and sequences and skill in the use of software for voxel-wise analysis. Amyloid-PET analysis. Drafting of research reports and articles.

References (max. 15)

1. Frisoni GB, Hansson O, Nichols E, Garibotto V, Schindler SE, van der Flier WM, et al. New landscape of the diagnosis of Alzheimer's disease. Lancet. 2025;406(10510):1389-407.

2. Agosta F, Cecchetti G, Spinelli EG, Ghirelli A, Rugarli G, Pisano S, et al. Real-world implementation of lecanemab and donanemab in an Italian memory center: a 1-year experience. Alzheimer's Research & Therapy. 2026.

3. Filippi M, Cecchetti G, Spinelli EG, Ghirelli A, Rugarli G, Pisano S, et al. Anti-amyloid therapies and the transformation of Alzheimer's care pathways: early lessons from the frontline. Lancet Reg Health Eur. 2026;64:101609.

4. Fox NC, Belder C, Ballard C, Kales HC, Mummery C, Caramelli P, et al. Treatment for Alzheimer's disease. Lancet. 2025;406(10510):1408-23.

5. Sims JR, Zimmer JA, Evans CD, Lu M, Ardayfio P, Sparks J, et al. Donanemab in Early Symptomatic Alzheimer Disease: The TRAILBLAZER-ALZ 2 Randomized Clinical Trial. Jama. 2023;330(6):512-27.

6. van Dyck CH, Swanson CJ, Aisen P, Bateman RJ, Chen C, Gee M, et al. Lecanemab in Early Alzheimer's Disease. N Engl J Med. 2023;388(1):9-21.

7. 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. Current Opinion in Neurology. 2025;38(4).

8. Hampel H, Elhage A, Cho M, Apostolova LG, Nicoll JAR, Atri A. Amyloid-related imaging abnormalities (ARIA): radiological, biological and clinical characteristics. Brain. 2023;146(11):4414-24.

9. Zimmer JA, Ardayfio P, Wang H, Khanna R, Evans CD, Lu M, et al. Amyloid-Related Imaging Abnormalities With Donanemab in Early Symptomatic Alzheimer Disease: Secondary Analysis of the TRAILBLAZER-ALZ and ALZ 2 Randomized Clinical Trials. JAMA Neurology. 2025;82(5):461-9.

10. Alves F, Kalinowski P, Ayton S. Accelerated Brain Volume Loss Caused by Anti-β-Amyloid Drugs: A Systematic Review and Meta-analysis. Neurology. 2023;100(20):e2114-e24.

11. Belder CRS, Boche D, Nicoll JAR, Jaunmuktane Z, Zetterberg H, Schott JM, et al. Brain volume change following anti-amyloid β immunotherapy for Alzheimer's disease: amyloid-removal-related pseudo-atrophy. Lancet Neurol. 2024;23(10):1025-34.

12. Spotorno N, Strandberg O, Vis G, Stomrud E, Nilsson M, Hansson O. Measures of cortical microstructure are linked to amyloid pathology in Alzheimer's disease. Brain. 2023;146(4):1602-14.

13. Arani A, Borowski B, Felmlee J, Reid RI, Thomas DL, Gunter JL, et al. Design and validation of the ADNI MR protocol. Alzheimer's & Dementia. 2024;20(9):6615-21.

14. Rosa-Grilo M, Chughtai HR, Thomas DL, Alexander DC, Beament M, Belder CRS, et al. Ultra-fast MRI for dementia diagnosis and treatment eligibility: A prospective study. Alzheimers Dement. 2025;21(6):e70341.