

 <p>UniSR Università Vita-Salute San Raffaele</p>	<p>APPLICATION TO ACT AS SUPERVISOR AND RESEARCH PROJECT PROPOSAL</p>	<p>MO 20-5 ed. 02 of 16/01/2026 PO 20 Page 5 of 12</p>
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PROJECT

Supervisor: Maria Salsone

Title: From detection to stratification: a digital-based patient-specific operating model for Alzheimer’s Disease

Curriculum: Cognitive and behavioural Science

Link to the personal page of the University or relevant hospital site website: <https://www.unisr.it/docenti/s/salsone-maria> -----

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

Background/gap of knowledge

Anti-amyloid antibodies (AAAs) have recently been approved as the first disease-modifying therapies (DMTs) for Alzheimer’s disease (AD)¹. This represents a historic milestone but also introduces major challenges. First, DMTs appear to provide the greatest clinical benefit when administered during the earliest pathological phases of the disease, requiring tools for early diagnosis². Second, not all patients with AD are suitable candidates for AAA therapy due to eligibility criteria and the risk of treatment-related adverse events.

Although biological tools are available to diagnose AD, their availability remains limited, costly, and difficult to scale for population-level implementation^{3,4}. Moreover, no established strategies currently exist to identify individuals who are most likely to benefit from AAAs.

In this context, electroencephalography (EEG) represents a potentially scalable biomarker due to its low cost, non-invasiveness, and widespread availability in clinical settings⁵. However, the clinical translation of EEG biomarkers has been limited by methodological constraints, including reduced spatial resolution and the effects of volume conduction.

Computational approaches based on personalized brain models have recently emerged as a promising strategy to overcome these limitations^{6,7}. These models integrate multimodal data to simulate the impact of structural and functional brain alterations on large-scale neural dynamics at the individual level. Recent studies have demonstrated that computational models can accurately predict cerebrospinal (CSF) biomarkers of AD and the risk of progression to clinical cognitive decline⁸, serving as potential digital biomarkers.



Rationale and hypothesis

The clinical implementation of AAAs requires scalable strategies capable of identifying individuals with a high probability of underlying AD pathology and prioritizing them for confirmatory biomarker testing and treatment eligibility assessment. We hypothesize that EEG-based personalized brain modeling can generate digital biomarkers capable of detecting early AD-related alterations in brain network dynamics and stratifying individuals according to their probability of AD pathology and treatment eligibility.

Objectives and specific aims

- 1- to develop EEG-based personalized computational models, to generate robust digital biomarkers capable of predicting AD pathology and the progression of cognitive decline.
- 2- to apply these models to estimate the probability of eligibility for AAAs treatment and to stratify individuals according to priority for advanced diagnostic assessment, thereby supporting more efficient patient selection for disease-modifying therapies.

Expected outcomes

By integrating EEG-based digital biomarkers with multidimensional clinical data, the proposed approach aims to support precision-medicine strategies and improve the identification of individuals most likely to benefit from DTMs.

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

The student will acquire skills in integrating and analyzing complex clinical, cognitive, and biological data. The student will learn to extract multimodal features, developing predictive models using advanced statistical and machine learning techniques, and translating computational results into practical clinical frameworks.

References (max. 15)

- ¹Van Dyck, C. H., Swanson, C. J., Aisen, P., Bateman, R. J., Chen, C., Gee & Iwatsubo, T. (2023). Lecanemab in early Alzheimer's disease. *New England Journal of Medicine*, 388(1), 9-21.
- ²Jack, C. R., Jr, Bennett, D. A., Blennow, K., Carrillo, M. C., Dunn, B., Haeberlein, S. B., Holtzman, D. M., Jagust, W., Jessen, F., Karlawish, J., Liu, E., Molinuevo, J. L., Montine, T., Phelps, C., Rankin, K. P., Rowe, C. C., Scheltens, P., Siemers, E., Snyder, H. M., Sperling, R., ... Contributors (2018). NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. *Alzheimer's & dementia : the journal of the Alzheimer's Association*, 14(4), 535-562. <https://doi.org/10.1016/j.jalz.2018.02.018>



³Mazzeo, S., Lassi, M., Padiglioni, S., Vergani, A. A., Moschini, V., Scarpino, M., Giacomucci, G., Burali, R., Morinelli, C., Fabbiani, C., Galdo, G., Amato, L. G., Bagnoli, S., Emiliani, F., Ingannato, A., Nacmias, B., Sorbi, S., Grippo, A., Mazzoni, A., & Bessi, V. (2026). Towards the development of a management protocol for subjective cognitive decline: Insights from a cross-sectional and longitudinal analysis of multimodal data from a memory clinic. *Journal of Alzheimer's disease : JAD*, 13872877261416117. Advance online publication. <https://doi.org/10.1177/13872877261416117>

⁴Mazzeo, S., Boveri, S., Bortolin, E., Bruschi, G., Girani, E., Bombaci, A., Pozzi, F. E., Corbari, M. V., Ambroggi, F., Agosta, F., Filippi, M., Salsone, M., & Alzheimer's Disease Neuroimaging Initiative (2025). Data-driven subtypes of subjective cognitive decline: neuropsychological profiles, Alzheimer's disease biomarkers, and clinical trajectories. *Journal of neurology*, 272(10), 669. <https://doi.org/10.1007/s00415-025-13418-0>

⁵Lassi, M., Fabbiani, C., Mazzeo, S., Burali, R., Vergani, A. A., Giacomucci, G., Moschini, V., Morinelli, C., Emiliani, F., Scarpino, M., Bagnoli, S., Ingannato, A., Nacmias, B., Padiglioni, S., Micera, S., Sorbi, S., Grippo, A., Bessi, V., & Mazzoni, A. (2023). Degradation of EEG microstates patterns in subjective cognitive decline and mild cognitive impairment: Early biomarkers along the Alzheimer's Disease continuum?. *NeuroImage. Clinical*, 38, 103407. <https://doi.org/10.1016/j.nicl.2023.103407>

⁶Amato, L. G., Vergani, A. A., Lassi, M., Fabbiani, C., Mazzeo, S., Burali, R., Nacmias, B., Sorbi, S., Mannella, R., Grippo, A., Bessi, V., & Mazzoni, A. (2024). Personalized modeling of Alzheimer's disease progression estimates neurodegeneration severity from EEG recordings. *Alzheimer's & dementia (Amsterdam, Netherlands)*, 16(1), e12526. <https://doi.org/10.1002/dad2.12526>

⁷Amato, L. G., Lassi, M., Vergani, A. A., Carpaneto, J., Mazzeo, S., Moschini, V., Burali, R., Salvestrini, G., Fabbiani, C., Giacomucci, G., Galdo, G., Morinelli, C., Emiliani, F., Scarpino, M., Padiglioni, S., Nacmias, B., Sorbi, S., Grippo, A., Bessi, V., & Mazzoni, A. (2025). Digital twins and non-invasive recordings enable early diagnosis of Alzheimer's disease. *Alzheimer's research & therapy*, 17(1), 125. <https://doi.org/10.1186/s13195-025-01765-z>