

 <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 14</p>
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PROJECT

Supervisor: Salvatore Mazzeo

Title: A novel integrative lifespan approach to brain vulnerability:
capturing neurodevelopmental differences in neurodegenerative
diseases

Curriculum: Cognitive and behavioural Science

Link to the personal page of the University or relevant hospital site website: <https://www.unisr.it/en/docenti/m/mazzeo-salvatore>

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

Background/gap of knowledge

Neurodegenerative dementias include diseases characterized by pathological and clinical heterogeneity. Alzheimer’s disease may present with typical amnesic phenotype or atypical variants, including language-predominant presentations¹. Frontotemporal lobar degeneration may manifest with behavioral or language variants of frontotemporal dementia as well as other nosological entities². Linguistic variants are grouped under primary progressive aphasia, a syndrome characterized by isolated and progressive language impairment³. The factors explaining why individuals develop specific clinical variants rather than typical presentations remain poorly understood.

Growing evidence suggests that neurodevelopmental differences may contribute to this variability^{4,5}. Language difficulties or specific learning disorders during childhood may influence trajectories toward neurodegenerative diseases⁶. However, research in this field is limited by the lack of instruments to retrospectively assess neurodevelopmental history in older adults. Additionally, the native language spoken by an individual may influence both brain development and clinical manifestations of neurodegenerative diseases⁷. Therefore, exploring how cultural background interacts with neurodevelopmental differences to shape dementia could provide interesting and useful insights.

Rationale and hypothesis



Exploring the relationship between early-life vulnerabilities, brain connectivity and neurodegeneration is essential to understand how neurodevelopmental differences affect disease onset and progression.

We hypothesize that:

- neurodevelopmental differences may predispose to different manifestations of neurodegenerative diseases;
- language difficulties and specific learning disorders during development represent markers of selective vulnerability within specific neural networks;
- this effect may be influenced by the native language.

Objectives and specific aims

1. Develop, validate, and administer a structured digital-based retrospective questionnaire to identify neurodevelopmental differences in patients with neurodegenerative diseases.
2. Explore the association between early-life vulnerabilities and neuropsychological, brain connectivity, and fluid biomarkers of neurodegeneration.
3. Investigate whether this relationship is influenced by linguistic features of the Italian and English languages.

Expected outcomes

It is expected that: 1) the digital-based questionnaire can retrospectively capture neurodiversity in patients with neurodegenerative diseases; 2) specific associations will emerge between early-life developmental difficulty and the clinical variant of neurodegenerative disorders; 3) neurodevelopmental profiles may be associated with specific cognitive and connectivity measures, supporting a lifespan model of selective vulnerability; 4) linguistic features of Italian and English may influence the interaction between neurodevelopmental and neurodegenerative disorders.

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

Year 1: systematic literature review; definition of study procedures and methodology of clinical studies; development of a clinical retrospective questionnaire; implementation of digital platforms for questionnaire administration.

Year 2: become familiar with: procedures related to patient recruitment, including informed consent, administration of neuropsychological tasks; training in the analysis of EEG data; data management and analysis; Submission of research abstracts for scientific conferences.

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Year 3: apply classical and advanced statistical methods; data interpretation within a development–degeneration framework; drafting and submission of scientific manuscripts.

References (max. 15)

- ¹Bader I, Groot C, Van Der Flier WM, Pijnenburg YAL, Ossenkoppele R. Survival Differences Between Individuals With Typical and Atypical Phenotypes of Alzheimer Disease. *Neurology*. 2025 May 27;104(10):e213603. doi: 10.1212/WNL.00000000000213603. Epub 2025 Apr 28. PMID: 40294367; PMCID: PMC12042099.
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- ³Gorno-Tempini, M. L., Hillis, A. E., Weintraub, S., Kertesz, A., Mendez, M., Cappa, S. F., Ogar, J. M., Rohrer, J. D., Black, S., Boeve, B. F., Manes, F., Dronkers, N. F., Vandenberghe, R., Rascovsky, K., Patterson, K., Miller, B. L., Knopman, D. S., Hodges, J. R., Mesulam, M. M., & Grossman, M. (2011). Classification of primary progressive aphasia and its variants. *Neurology*, 76(11), 1006–1014. <https://doi.org/10.1212/WNL.0b013e31821103e6>
- ⁴Miller ZA, Mandelli ML, Rankin KP, et al. Handedness and language learning disability differentially distribute in progressive aphasia variants. *Brain*. 2013;136(Pt 11):3461–3473. doi:10.1093/brain/awt242
- ⁵Magnin E. Neurodevelopmental and Neurodegenerative Similarities and Interactions: A Point of View About Lifelong Neurocognitive Trajectories. *J Alzheimers Dis*. 2021;79(4):1397–1407. doi:10.3233/JAD-201207
- ⁶Miller, Z. A., Ossenkoppele, R., Graff-Radford, N. R., Allen, I. E., Shwe, W., Rosenberg, L., Olguin, D. J., Erkinen, M. G., Butler, P. M., Spina, S., Yokoyama, J. S., Desikan, R. S., Scheltens, P., van der Flier, W., Pijnenburg, Y., Wolters, E., Rademakers, R., Geschwind, D. H., Kramer, J. H., ... Gorno-Tempini, M. L.



(2025). Neurodevelopment and neural environment inform Alzheimer's disease age at onset and phenotype. *Alzheimer's and Dementia*, 21(9). <https://doi.org/10.1002/alz.70668>

⁷ Mazzeo S, Hardy CJD, Jiang J, Morinelli C, Moschini V, Brooks E, Johnson JCS, Chokesuwattanaskul A, Giacomucci G, Volkmer A, Rohrer JD, Ingannato A, Bagnoli S, Padiglioni S, Nacmias B, Sorbi S, Bessi V, Warren JD. Primary Progressive Aphasia in Italian and English: A Cross-Linguistic Cohort Study. *Neurology*. 2024 Dec 24;103(12):e210058. doi: 10.1212/WNL.0000000000210058. Epub 2024 Nov 21. PMID: 39571120; PMCID: PMC11587988.