

Exploring Phenotypic Heterogeneity of Early- And Late-Onset Alzheimer's Disease: A Neuropsychological Data-Driven Approach

Jaume Torres-Coll¹, Agnès Perez-Millán^{1,2}, Axel Rigol¹, Magdalena Castellví¹, Bea Bosch^{1,3}, Marta M. Sánchez¹, Víctor Patricio-Toribio¹, Jordi Juncà-Parella^{1,3}, Georgina Rubio¹, Claudia Morante-Serra¹, Laura Mir¹, Neus Falgàs^{1,3}, Sergi Borrego-Écija^{1,3}, Núria Guillen^{1,3}, Diana Esteller¹, Isabel Martín¹, Miquel Massons¹, Paula Canasto¹, Raquel Sánchez-Valle^{1,3}, Mircea Balasa^{1,3}, Albert Lladó^{1,3}, Adrià Tort-Merino^{1,3}.

¹ Alzheimer's Disease and other Cognitive Disorders unit, Hospital Clínic de Barcelona, Fundació de Recerca Clínic Barcelona – Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Universitat de Barcelona, Barcelona, Spain

² eHealth Center, Faculty of Computer Science, Multimedia and Telecommunications, Universitat Oberta de Catalunya, 08016 Barcelona, Spain

³ Centro de Investigación Biomédica en Red en Enfermedades Neurodegenerativas (CIBERNED), Madrid, Spain

BACKGROUND

Alzheimer's disease (AD) encompasses a broad spectrum of clinical presentations. Early-onset AD (EOAD) is often associated with greater clinical heterogeneity when compared to late-onset presentations (LOAD). Data-driven neuropsychological approaches can complement clinical judgment and uncover a broader spectrum of clinical presentations. Based on previously published work, we aimed to apply a neuropsychological data-driven method to identify the phenotypic heterogeneity of AD in a well-characterized cohort of patients with sporadic EOAD and LOAD.

METHODS

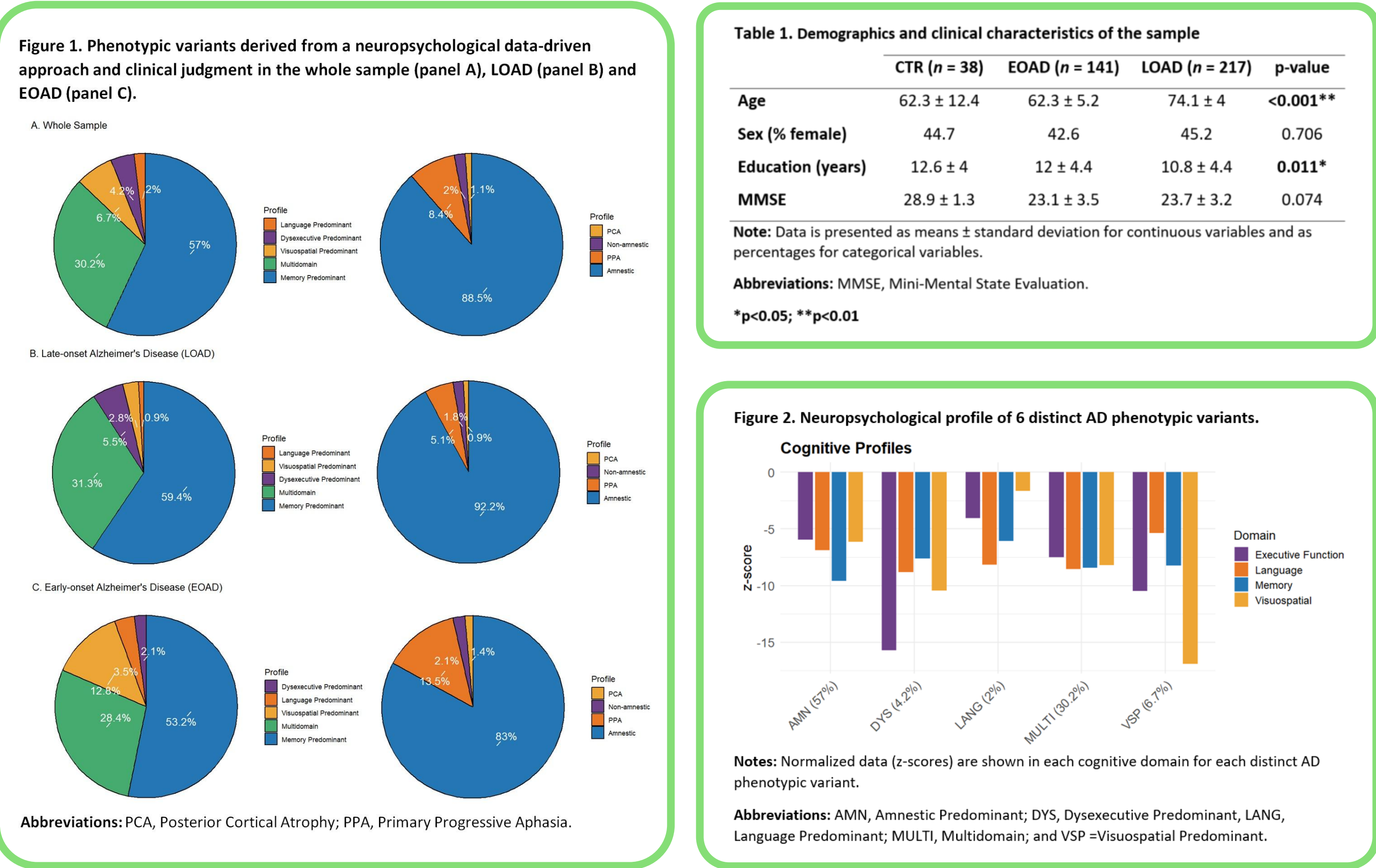
Neuropsychological data from 358 AD patients were analysed, including 141 EOAD cases and 217 LOAD. Education-corrected normative comparisons were obtained using a reference sample of 38 cognitively unimpaired individuals. Phenotypic profiles of cognitive impairment were delineated by comparing the relative severity of deficits across various cognitive domains. A threshold of 1.5 standard deviations below the normative mean was applied to identify "predominant" impairment within each domain. Participants who did not meet this criterion were classified as having multidomain impairment, indicating that cognitive deficits were distributed across multiple domains without a clearly predominant area of impairment. Longitudinal analyses are ongoing to evaluate the ability of this data-driven model to predict patients' cognitive trajectories over time.

RESULTS

Our analysis identified 5 distinct phenotypic presentations: Amnestic Predominant, Language Predominant, Visuospatial Predominant, Attention/Dysexecutive Predominant, and Multidomain.

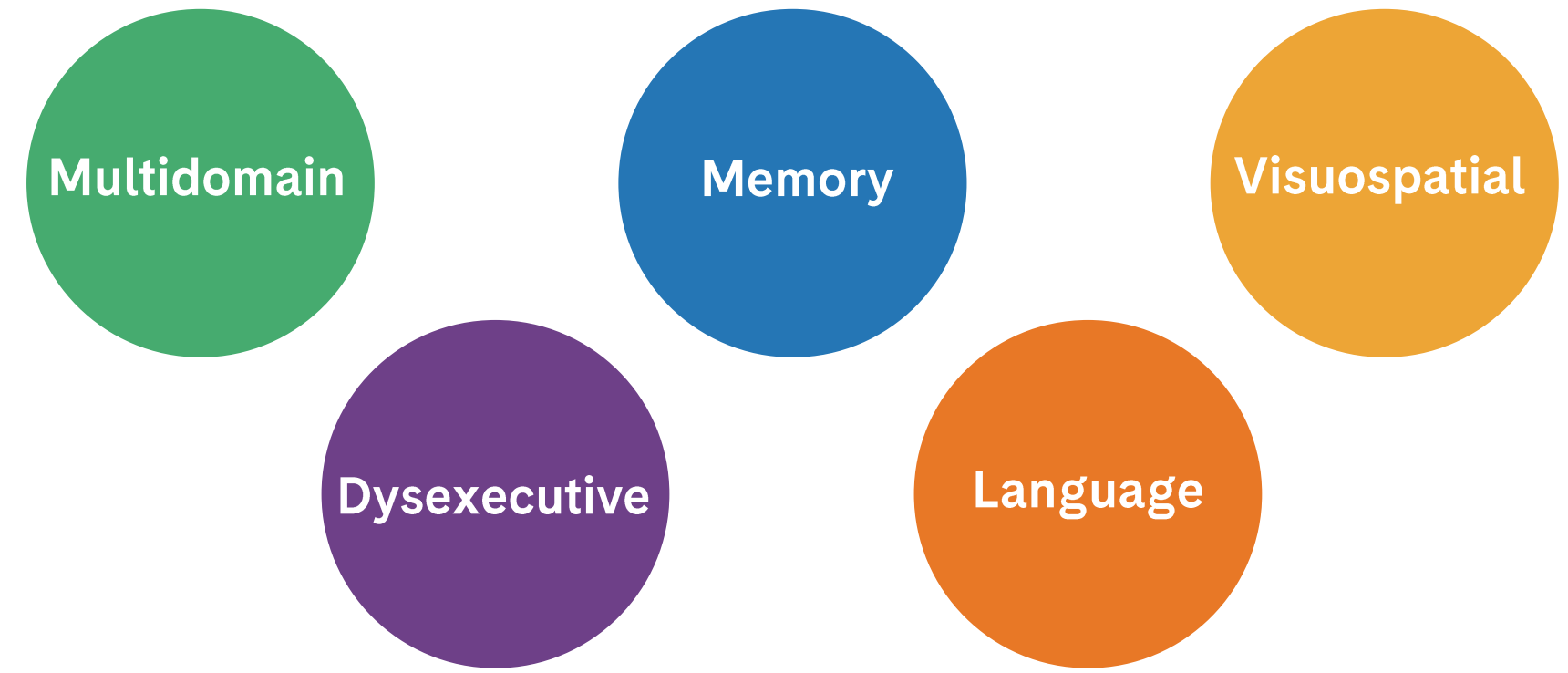
- From this, Amnestic Predominant subtype was the most common (57%), followed by Multidomain (30.2%), Visuospatial (6.7%), Attention/Dysexecutive (4.2%), and Language (2%) [Figure 1A].
- Compared to LOAD, patients with EOAD displayed a higher proportion of predominant impairments in atypical domains [i.e., Visuospatial Predominant (12.8% vs. 2.8%) and Language Predominant (3.5% vs. 0.9%)] and a lower proportion in classically affected domains [i.e., Memory Predominant (53.2% vs. 59.4%) and Attention/Dysexecutive Predominant (2.1% vs. 5.5%)] [Figure 1B-C].

The neuropsychological profiles of the phenotypic variants are shown in Figure 2.



CONCLUSIONS

Our study highlights the heterogeneous nature of AD and demonstrates how neuropsychological data-driven methods can provide a refined understanding of its clinical presentations. By capturing subtle variations in cognitive symptom predominance, data-driven methods could contribute significantly to advancing both diagnostic precision and therapeutic approaches in AD. Longitudinal analyses will further elucidate the prognostic value of this data-driven model.



CONTACT

Jaume Torres Coll

To learn more about this research or for further discussion, kindly reach out through the following e-mail:

jatorres@recerca.clínic.cat

