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RESEARCH ARTICLE

Cognitive markers for the distinction between asymptomatic and prodromal Alzheimer's disease in Down syndrome: Correlations with volumetric brain changes

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Abstract

INTRODUCTION: Motivated by the difficulties in detecting cognitive deterioration in the context of Down syndrome (DS), we aimed to identify markers of prodromal Alzheimer's disease (AD) in this population.

METHODS: Sixty-two participants with DS (age > 45) distributed in three groups (asymptomatic [A_{DS}], prodromal [P_{DS}], and dementia [D_{DS}]) completed the Cambridge Examination for Mental Disorders of Older People with Down's Syndrome and Others with Intellectual Disabilities, Cambridge Cognitive Examination for older adults with Down's Syndrome, and Barcelona Test for Intellectual Disability tests and a magnetic resonance imaging scan.

RESULTS: Although temporal orientation showed significant differences among groups, only a predictive diagnostic model based on verbal short-term memory tasks (relying on "cued" recall) allowed the correct classification of 88.5% of A_{DS}, 75.0% of P_{DS}, and 95% of D_{DS} individuals. Cognitive decline strongly correlated with brain volume reductions in orbitofrontal, medial-temporal, and bilateral thalamus within the D_{DS} group.

DISCUSSION: Neuropsychological results showed that P_{DS} cases were characterized by a significant deterioration of verbal memory and temporal orientation, compared to A_{DS}. This pattern might be crucial to support diagnosis in clinical settings.

KEYWORDS
Alzheimer's disease, cognitive impairment, Down syndrome, magnetic resonance imaging, neuropsychological assessment, prodromal Alzheimer's disease

Highlights

- Detecting signs of prodromal dementia is a major challenge in Down syndrome.
- Such challenge is due to a poor definition of the early cognitive manifestations.
- Memory tasks relying on "cued" recall allowed the detection of prodromal cases.
- A pattern of temporal disorientation was also evident in the prodromal phase.
- These cognitive deficits preceded volumetric brain changes only present in dementia.

1 | INTRODUCTION

Down syndrome (DS) is the most common form of genetically determined Alzheimer's disease (AD).[1] The complete trisomy of chromosome 21 produces an overexpression of the *APP* gene that generates a progressive accumulation of amyloid protein in DS patients' brains.[2,3] In this vein, the very recent proposal of new diagnostic and staging criteria considers AD as a "biological process" that begins with the presence of AD neuropathology.[4] By the age of 40, all individuals with DS show AD neuropathology,[5] and new criteria suggest it should be assumed that they "have" the disease.

Such an "abnormal" accumulation of AD neuropathology[6,7] is not always accompanied by manifestations of cognitive impairment—that is, exceeding the inherent cognitive issues linked to the intellectual development disability (IDD) that characterizes DS.[1,8,9] Even at older ages (≥ 60 years), there is a reduced but still considerable number of DS patients that remain free of remarkable symptoms of cognitive impairment.[10] Importantly, the new staging criteria assume a stage of "cognitive impairment with early functional impact" that corresponds with the classical mild cognitive impairment (MCI) concept[4] or phase of prodromal AD. Clinical criteria for that prodromal phase have been extensively discussed within the general population, and a consensus exists on the need for a visible/measurable change in cognition compared to a preexisting level of performance.[11] Notably, the distinction between "asymptomatic" and "prodromal" AD cases in DS is not straightforward, because cognitive changes should be evaluated within the context of premorbid IDD, and availability of population norms is currently limited. Therefore, determining cognitive markers of early deterioration is a crucial goal within this field of investigation.[12]

Such potential markers could be obtained by systematically analyzing DS patients' cognitive performance on comprehensive neuropsychological evaluations. Along these lines, the very recent meta-analysis performed by Nadeau et al.[13] identified a series of cognitive batteries and tests that showed a reasonable sensitivity/specificity to detect the prodromal phase of AD in the DS population. According to these authors' considerations, cued recall tests[14,15] demonstrated very promising results, and tasks such as selective recall, verbal fluency, or some praxis tests could also be useful and discriminative enough.[16–18]

An additional confounding factor in the search for optimal cognitive markers is the debate on the "nature" of very early clinical manifestations of dementia in the DS population. Because neuropathological signs observed in DS individuals resemble those present in the AD population with typical development, a similar clinical phenotype might also be expected.[19,20] A clinical phenotype predominantly showing memory deficits and disorientation has been reported in numerous investigations.[14,21,22] An alternative profile characterized by behavioral changes (i.e., agitation, stubbornness, or apathy)[16] has also been proposed. However, cases starting with remarkable behavioral changes might be mostly explained by the frequent psychiatric comorbidities accompanying DS.[23]

With all these controversies in mind, we planned a longitudinal study to detect the potential factors contributing to the progression from asymptomatic DS to prodromal and dementia stages. Here, we present baseline data on early cognitive and volumetric changes indicating prodromal AD in the cohort participating in our longitudinal study.

2 | METHODS

2.1 | Participants

Our sample consisted of 62 participants > 45 years of age with DS. Participants were classified into three diagnostic groups: (1) asymptomatic (A_{DS}); (2) prodromal (P_{DS}); and (3) dementia (D_{DS}). Demographic information is displayed in Table 1.

All participants were recruited at the Down Syndrome Adult Unit of the Internal Medicine Service at La Princesa University Hospital (Madrid, Spain) and presented a mild or moderate level of IDD according to Diagnostic and Statistical Manual of Mental Disorders Fifth Edition Text Revision criteria (see more information in Supplementary material).

Participants were not receiving any drug treatment that could interfere with assessments. Individuals showing clinical hypo-/hyperthyroidism, uncontrolled B9/B12 vitamin deficiency, delirium, severe uncorrected sensory impairment (auditory or visual), or any disorders that may be confused with cognitive impairment (i.e., depression) were excluded.

Our study was conducted in accordance with the International Code of Medical Ethics of the World Medical Association (Declaration of Helsinki), and the protocol was approved by the clinical research ethical committee of La Princesa University Hospital. Written informed consent was obtained from parents or legal guardians, and additional verbal or written assent was obtained from DS patients.

RESEARCH IN CONTEXT

1. **Systematic review**: The authors reviewed published literature on neuropsychological markers of prodromal and dementia stages in Down syndrome (DS), and evidence of brain atrophy at both stages. Because a large percentage of people with DS will present signs of cognitive impairment due to Alzheimer's disease (AD), this article focuses on the cognitive markers that might differentiate the asymptomatic and prodromal phases, as well as on their correspondence with neuroanatomical changes.
2. **Interpretation**: Findings suggest that declines in verbal short-term memory tasks, prospective memory, and temporal disorientation appear as the first symptoms of prodromal AD in DS. In the dementia phase, these symptoms increase and show a strong relationship with brain volume reductions in certain regions.
3. **Future directions**: Considering the longitudinal nature of our investigation, new information on cognitive changes, brain volumetry, and additional data on electroencephalogram and plasma biomarkers in this population will be considered.

2.2 | Clinical and neuropsychological assessment

All participants and informants (family members/legal guardians) completed a comprehensive clinical and neuropsychological protocol. This protocol has been designed/adapted and validated for the DS/IDD population in the Spanish population and has been used in numerous studies in DS population assessing cognitive impairment due to AD.[24–29]

The protocol included the following evaluation tools: (1) the Spanish version of the Cambridge Cognitive Examination for older adults with Down's Syndrome (CAMCOG-DS) subtest of the Cambridge Examination for Mental Disorders of Older People with Down's Syndrome and Others with Intellectual Disabilities (CAMDEX-DS)[30] and (2) The Barcelona Test-Intellectual Developmental Disorder (BT-IDD).[31] Only the most discriminative domains of the BT-ID, identified in previous studies as relevant for assessing cognitive impairment in people with DS, were used.[24–29,32]

Diagnosis of prodromal AD and dementia in our participants was based on expert clinical judgment, as it is the standard recommendation for DS.[26,28,32] This was informed by results from the clinical (CAMDEX-DS) and neuropsychological (BT-ID and CAMCOG-DS) examination (for further exhaustive description, see the Supplementary material).

2.3 | Magnetic resonance imaging acquisition

Magnetic resonance imaging (MRI) data were acquired on a General Electric Signa 3T MR HDxt (GEHC). The scanner was equipped with an 8-channel phased array coil. Anatomical data were obtained by applying a sagittal spoiled gradient recalled echo (a rapid 3D T1-weighted acquisition) sequence with: repetition time: 6.5, echo time: 2.78 ms, inversion time: 400 ms, field of view: 260 mm, matrix: 256 × 256, slice thickness: 1.2 mm, 31.25 bandwidth, ASSET: Phase Acceleration Factor 1.00.

2.3.1 | MRI processing and volumetric analysis

Morphometric analysis of T1-weighted images was carried out using CAT12[33] and Statistical Parametric Mapping software (SPM12; The Welcome Department of Imaging Neuroscience) under

TABLE 1 Descriptive statistical summary of sociodemographic information.

	A_{DS} ($n = 26$)	P_{DS} ($n = 16$)	D_{DS} ($n = 20$)	*p* value
Age	51.27 (4.19) 51.00 (49.00–53.50) 45, 62	52.94 (4.68) 52.50 (50.00–55.50) 45, 62	53.50 (5.06) 53.00 (50.00–57.25) 45, 63	0.241
Sex: f/m	15/11	9/7	11/9	0.983

Note: For age: mean (standard deviation); median (Q1–Q3); min, max; *P* value of one-way analysis of variance test. For sex: absolute counts; *P* value of chi-squared test.
Abbreviations: A_{DS}, asymptomatic group; D_{DS}, dementia group; P_{DS}, prodromal group.

MATLAB R2020b (The MathWorks, Inc.), using standard segmentation protocols.[34] A detailed description of the MRI processing and procedure for volume estimation is available in Supplementary material.

2.4 | Statistical analysis

Patient characteristics were summarized using frequencies for categorical variables, and mean, standard deviation (SD), and other measures for continuous variables. Listwise deletion was used to handle missing data. The comparison among the three diagnostic groups was carried out using the chi-squared test for categorical variables and the Kruskal–Wallis test for continuous variables (followed by pairwise comparisons based on the Mann–Whitney–Wilcoxon test with Holm correction for multiple testing). Non-parametric tests were chosen due to the small sample size available in each diagnostic group and the lack of normality (Shapiro–Wilk test).

The association between the scores of neuropsychological variables and the diagnostic group was assessed using univariate and multivariate multinomial logistic regressions (MLR), considering the A_{DS} group as the reference category. Possible multicollinearity was addressed based on condition indices and each of their variance partition proportions for the predictor variables. The goodness of fit of the final predictive diagnostic model (PDM) was measured in terms of Nagelkerke R^2 (pseudo R squared). The diagnostic classification capacity was assessed in terms of the number of patients correctly classified per group and the pairwise receiver operating characteristic (ROC) curves with their corresponding area under the ROC curve (AUC) values. The closer the ROC curve is to the northwest corner and the closer the AUC is to 1, the greater the predictive power of the model.

For each diagnostic group, the Spearman rank correlation coefficient ρ was calculated to measure the association between each one of the best predictive neuropsychological variables (those included in the PDM) and each one of the cluster-based variables derived from the volumetric analyses. For ease of graphical visualization, this association analysis was carried out at the level of the principal components obtained from a principal component analysis (PCA) carried out separately over the two sets of variables (i.e., neuropsychological vs. volumetric) using the SPSS Regression method, providing component scores in z score form.

Statistical analysis was performed using SPSS 27, RStudio "Ocean Storm," and JASP 0.18.3. A two-tailed P value < 0.05 was considered statistically significant.

3 | RESULTS

3.1 | Summary of changes in the cognitive profile

The sociodemographic characteristics of the study sample are shown in Table 1. First, it is important to note that the three diagnostic groups were balanced according to age ($p = 0.241$) and sex ($p = 0.983$).

Results derived from CAMCOG-DS scores showed a decline in orientation, new learning (memory domain), abstract thinking, and total score in the P_{DS} group compared to the A_{DS} group. Notably, orientation, new learning, and total score also showed significant differences between the P_{DS} and D_{DS} groups. The decline was even more evident when reaching the dementia stage, and significant differences were observed between the A_{DS} and D_{DS} groups in virtually all domains, except for attention, praxis, and perception. P_{DS} showed a significant decline in BT-ID measurements compared to the A_{DS} group, specifically in: time orientation; verbal memory texts free immediate recall and verbal memory texts immediate key recall (henceforth denoted VMT_{IK} = verbal memory texts immediate key); new serial learning immediate recall (henceforth denominated NSL_I = new serial learning immediate); and prospective memory. NSL_I reflects the ability to learn, retain, and perform an immediate recall of simple verbal material (words). VMT_{IK} represents similar capabilities (retention and recall), but with greater demands as the material is more complex (recall of a short text) and the recall is supported by keys or "cues." On the other hand, comparing the P_{DS} and D_{DS} groups, dementia cases showed a worse performance in time and spatial orientation, automatic language (reverse order within working memory domain), planning and organization, verbal memory texts free immediate recall (free delayed and delayed cues), NSL_I, and postural and constructive praxis (clock order). Finally, mirroring the CAMCOG-DS results, the D_{DS} group showed a significant decrease in the performance of most of the tasks related to orientation, executive functions, memory, and praxis execution compared to the A_{DS} group (Table 2).

3.2 | Predictive diagnostic model

First, univariate MLR models were fitted for each of the neuropsychological variables, identifying the most significant ones per each cognitive domain and function (see Table 2). Second, with the variables identified as significant in the univariate analysis, a multivariate MLR model was fitted using a forward stepwise procedure. The multivariate MLR analysis showed that VMT_{IK} and NSL_I (both derived from the BT-ID), were statistically significant in predicting the diagnostic group (Nagelkerke $R^2 = 0.843$). It is interesting to highlight that both variables were significant in distinguishing between D_{DS} and A_{DS} groups, but only NSL_I emerged as significant in distinguishing between A_{DS} and P_{DS} groups. Specifically:

1. An increase of one unit in VMT_{IK} yielded a reduction of 82.5% in the odds of belonging to the D_{DS} group versus A_{DS} group (odds ratio $[OR]_{DDS\ vs.\ ADS} = 0.175$, P value = 0.041, 95% confidence interval [CI]: 0.033–0.932).
2. An increase of one unit in NSL_I yielded a reduction of 21.2% in the odds of belonging to the P_{DS} group versus A_{DS} group ($OR_{PDS\ vs.\ ADS} = 0.788$, P value = 0.003, 95% CI: 0.673–0.923).
3. An increase of one unit in NSL_I yielded a reduction of 91.5% in the odds of belonging to the D_{DS} group versus A_{DS} group ($OR_{DDS\ vs.\ ADS} = 0.085$, P value = 0.044, 95% CI: 0.008–0.941).

TABLE 2 Descriptive statistical summary of neuropsychological assessments variables.

Neuropsychological Tests **Cambridge Cognitive Examination for older adults with Down's Syndrome (CAMCOG-DS)**							
Cognitive domain	**Cognitive function/ variable name**	**A_{DS} ($n = 26$)**	**P_{DS} ($n = 16$)**	**D_{DS} ($n = 20$)**	**A_{DS} vs. $_{DS}$**	**P_{DS} vs. D_{DS}**	**A_{DS} vs. D_{DS}**
Orientation	Orientation H2 = 0.465 *P* = 1.83E-9	11.54 (0.76) 12.00 (11.00–12.00) 0.18, -1.32	8.75 (4.16) 11.00 (4.75–;12.00) −1.11, −0.86	5.40 (2.91) 5.50 (2.75–7.00) −0.10, 0.41	*	*	***
Language	Comprehension H2 = 0.130 *P* = 0.006	7.12 (1.48) 8.00 (7.00–8.00) 1.46, −1.34	7.31 (1.45) 7.00 (7.00–8.25) 0.49, −0.77	5.65 (2.06) 5.50 (4.00–7.00) −0.54, 0.12		*	*
	Expression H2 = 0.177 *P* = 2.87E-4	14.62 (2.32) 15.00 (13.00–16.75) −0.67, −0.57	13.56 (2.42) 13.50 (11.75–15.25) −1.05, 0.29	10.70 (4.35) 12.00 (9.75–14.00) 0.32, −0.89		•	**
Memory	New learning H2 = 0.585 *P* = 1.25E-11	13.96 (2.34) 14.00 (12.00–15.75) −0.07, −0.03	9.63 (4.19) 11.50 (6.00–12.25) −0.02, −0.75	5.25 (3.49) 5.00 (2.50–7.50) −1.14, 0.14	**	**	***
	Delayed memory H2 = 0.137 *P* = 0.003	2.54 (0.90) 2.00 (2.00–3.50) −0.85, 1.10	1.94 (1.48) 2.00 (0.75-2.50) −1.03, 0.12	1.25 (1.41) 1.00 (0.00–2.00) −0.78, 0.63			**
	Recent memory H2 = 0.124 *P* = 0.002	2.69 (0.93) 2.00 (2.00–3.75) −1.22, 0.36	2.25 (1.57) 2.00 (1.50–4.00) −1.25, −0.35	1.20 (1.64) 0.00 (0.00–3.00) −1.14, 0.83			**
Attention	Attention H2 < 0.01 *P* = 0.200	7.43 (1.07) 8.00 (7.00–8.00) −0.35, −0.64	7.13 (1.71) 8.00 (6.75–8.00) 1.27, 1.50	6.50 (2.50) 8.00 (5.00–8.00) −0.31, −1.17			
Praxis	Praxis (drawing) H2 = 0.190 *P* = 6.317E-4	5.12 (1.88) 5.50 (3.25–6.75) −1.08, −0.29	3.94 (2.24) 3.00 (2.00–6.00) −1.24, 0.13	2.65 (2.01) 2.50 (1.00–4.25) −1.04, 0.23			***
	Praxis (motor action) H2 = 0.043 *P* = 0.023	7.77 (1.56) 8.00 (6.25–9.00) −0.98, −0.20	7.31 (2.18) 7.50 (5.75–9.00) −0.75, −0.59	5.90 (2.95) 7.00 (2.75–8.00) −1.27, −0.34			
Abstract thinking	Abstract thinking H2 = 0.238 *P* = 2.88E-4	3.42 (1.45) 3.50 (2.00–4.00) −0.62, 0.20	2.06 (2.41) 1.50 (0.00–3.50) −0.96, 0.80	1.20 (1.54) 0.00 (0.00–2.00) −0.73, 0.87	*		***
Perception	Perception H2 = 0.050 *P* = 0.023	4.96 (1.08) 5.00 (4.00–6.00) −0.47, 0.08	5.13 (1.59) 5.00 (4.75–6.25) 0.13, −0.69	4.05 (1.96) 4.00 (3.00–5.00) 0.39, −0.45			
CAMCOG-DS total score	H2 = 0.405 *P* = 7.56E-8	81.19 (8.81) 81.50 (75.00–87.75) −0.45, −0.10	69.00 (18.29) 75.50 (53.50–83.25) −1.07, −0.73	49.75 (21.50) 52.50 (35.50–67.00) −0.80,−0.39	*	*	***

Barcelona Test for Intellectual Disability (BT-ID)								
Cognitive domain	**Cognitive function**	**Variable name**	**A_{DS} ($n = 26$)**	**P_{DS} ($n = 16$)**	**ATD_{DS} ($n = 20$)**	**A_{DS} vs. P_{DS}**	**P_{DS} vs. D_{DS}**	**A_{DS} vs. D_{DS}**
Orientation	**Personal**	Personal orientation H2 = 0.125 *P* = 0.004	22.62 (4.10) 25.00 (24.00–25.00) 0.72, −1.51	20.38 (4.46) 19.50 (17.75–25.00) −1.08, −0.38	17.45 (6.11) 17.50 (11.00–24.25) −1.77, 0.07			**
	Spatial	Spatial orientation H2 = 0.421 *P* = 1.07E-8	17.50 (5.62) 19.50 (12.25–22.75) −1.25, −0.51	13.25 (9.33) 11.00 (5.75–23.00) −1.64, −0.19	3.95 (3.91) 4.00 (00.00–6.00) −0.21, 0.82		*	***

(Continues)

TABLE 2 (Continued)

Barcelona Test for Intellectual Disability (BT-ID)								
Cognitive domain	**Cognitive function**	**Variable name**	**A_{DS} ($n = 26$)**	**P_{DS} ($n = 16$)**	**ATD_{DS} ($n = 20$)**	**A_{DS} vs. P_{DS}**	**P_{DS} vs. D_{DS}**	**A_{DS} vs. D_{DS}**
	Time	Time orientation H2 = 0.349 *P* = 3.91E-7	54.73 (15.47) 61.50 (54.25–67.00) 0.05, −1.18	34.06 (28.30) 33.00 (2.75–63.00) −1.83, −0.06	13.50 (22.00) 3.00 (00.00–17.00) 1.28, 1.63	• .054	• .054	***
Attention		Direct digits H2 < 0.01 *P* = 0.584	2.88 (0.86) 3.00 (2.00–3.00) 0.54, 0.23	2.75 (0.77) 3.00 (2.00–3.00) −1.06, 0.49	2.60 (1.14) 2.50 (2.00–3.00) 0.62, −0.03			
Executive functions	**Working memory**	Inverse digits H2 = 0.131 *P* = 0.020	1.42 (1.24) 2.00 (0.00–2.00) −1.68, −0.08	0.75 (1.06) 0.00 (0.00–2.00) −0.71, 0.94	0.45 (1.23) 0.00 (0.00–0.00) 10.17, 3.11			**
		Automatic language (reverse order) H2 = 0.079 *P* = 0.064	3.50 (4.24) 1.50 (0.00–5.00) −0.78, 0.85	3.13 (2.56) 3.00 (2.00–4.00) 6.59, 2.04	1.35 (2.56) 0.00 (0.00–0.75) 1.49, 1.67		*	
	Planning and organization	Planning and organization H2 = 0.388 *P* = 3.97E-8	3.96 (2.09) 3.50 (3.00–4.00) 1.75, 1.25	2.94 (1.84) 3.00 (2.00–4.00) 2.93, 1.12	1.20 (1.15) 1.00 (0.00–2.00) 0.11, 0.71	•	**	***
Oral language	**Automatic language**	Automatic language (direct order) H2 < 0.01 *P* = 0.203	8.50 (3.31) 9.50 (7.00–10.00) 0.73, −0.85	7.63 (2.58) 8.50 (6.75–9.00) 0.03, −0.77	6.55 (4.75) 7.50 (2.50–11.00) −1.55, −0.21			
	Visuoverbal naming	Visuoverbal naming H2 = 0.151 *P* = 0.001	15.73 (2.44) 16.00 (15.00–18.00) −0.60, −0.78	14.94 (2.02) 16.00 (13.50–16.00) −0.61, −1.02	11.80 (5.22) 13.50 (10.50–15.25) 0.24, −1.20		•	**
	Verbal comprehension	Verbal comprehension H2 = 0.034 *P* = 0.031	7.88 (2.45) 8.00 (6.25–9.00) −0.54, 0.00	7.63 (2.25) 7.50 (6.00–10.00) −0.60, −0.26	5.80 (3.32) 7.00 (2.50–8.00) −1.16, −0.42			
Memory	**Verbal memory**	Verbal memory texts (free immediate) H2 = 0.239 *P* = 7.00E-5	5.31 (2.98) 5.50 (3.00-8.00) −0.84, −0.32	2.75 (2.35) 2.00 (1.00-4.00) 0.01, 0.90	1.90 (1.94) 2.00 (0.00-3.00) 0.72, 0.87	*		***
		Verbal memory texts (immediate key) H2 = 0.469 *P* = 6.74E-8	7.85 (2.27) 7.50 (7.00–9.75) −0.56, −0.06	6.38 (4.21) 5.00 (5.00–6.50) 2.35, 1.47	2.95 (1.93) 2.50 (2.00–4.25) −0.45, 0.41	*	**	***
		Verbal memory texts (free delayed) H2 = 0.300 *P* = 7.43E-7	3.88 (2.69) 3.50 (3.00–5.00) −0.21, 0.52	2.38 (2.25) 2.00 (0.00–5.00) −1.85, 0.18	0.55 (0.60) 0.50 (0.00–1.00) −0.45, 0.58		*	***
		Verbal memory texts (delayed cues) H2 = 0.359 *P* = 3.00E-6	9.69 (5.10) 9.50 (7.00–13.50) −0.26, 0.22	6.75 (4.39) 7.00 (3.00–10.25) −0.45, 0.34	2.55 (3.85) 2.00 (0.00–3.25) 11.02, 3.01	•	**	***
	New learning	**New serial learning (immediate)** H2 = 0.682 *P* = 3.94E-16	23.85 (5.58) 24.00 (22.00–27.00) 0.58, −0.27	17.25 (4.55) 16.50 (14.00–17.75) 1.31, 1.24	8.25 (3.67) 8.00 (6.00–11.25) −0.02, −0.22	***	***	***

(Continues)

TABLE 2 (Continued)

Barcelona Test for Intellectual Disability (BT-ID)								
Cognitive domain	**Cognitive function**	**Variable name**	**A_{DS} ($n = 26$)**	**P_{DS} ($n = 16$)**	**ATD_{DS} ($n = 20$)**	**A_{DS} vs. P_{DS}**	**P_{DS} vs. D_{DS}**	**A_{DS} vs. D_{DS}**
		New serial learning (delayed) H2 = 0.144 $p = 0.002$	4.58 (3.13) 4.00 (3.00–7.00) −1.06, −0.03	2.88 (2.58) 3.00 (0.75–4.25) 0.44, 0.77	1.60 (2.23) 0.50 (0.00–3.00) 0.30, 1.25			**
		New serial learning (delayed recognition) H2 = 0.044 $P = 0.248$	11.31 (1.78) 12.00 (11.00–12.00) 3.85, 0.50	10.73 (1.16) 11.00 (10.00–12.00) −1.31, −0.34	10.70 (0.92) 11.00 (10.00–11.00) −0.59, −0.21			
	Visual memory	Visual memory (delayed recall) H2 = 0.263 $P = 7.40E\text{-}5$	2.81 (1.13) 3.00 (2.00–4.00) 1.04, −1.02	1.88 (1.59) 2.00 (0.00–3.00) −1.65, 0.00	1.00 (1.21) 1.00 (0.00–1.25) 5.37, 1.96			***
		Visual memory (delayed recognition) H2 < 0.01 $P = 0.591$	7.65 (3.27) 8.00 (5.00–10.75) −1.38, −0.21	7.75 (3.26) 8.50 (5.50–10.00) −0.57, −0.55	6.75 (3.80) 5.00 (3.00–10.00) −1.80, 0.29			
	Prospective memory	Prospective memory H2 = 0.332 $P = 2.00E\text{-}6$	2.96 (1.75) 3.50 (2.00–4.00) −1.01, −0.27	1.56 (2.00) 1.00 (0.00–2.00) 1.42, 1.44	0.45 (0.60) 0.00 (0.00–1.00) 0.18, 1.00	*	•	***
Praxis	**Gesture praxis**	Symbolic gesture (dominant hand) H2 = 0.070 $P = 0.979$	13.76 (3.71) 15.00 (15.00–15.00) 9.47, −3.25	13.75 (1.24) 13.50 (13.00–15.00) −1.72, −0.18	13.60 (2.33) 14.00 (13.00–15.00) 10.17, −2.94	•		•
		Symbolic gesture (non-dominant hand) H2 = 0.071 $P = 0.322$	13.40 (3.72) 15.00 (14.00–15.00) 6.61, −2.69	13.38 (1.50) 13.00 (12.00–15.00) −1.41, −0.19	11.85 (4.65) 13.50 (12.00–15.00) 3.00, −1.99			• .051
	Postural praxis	Postural sequences H2 = 0.102 $P = 0.007$	6.62 (4.07) 6.00 (3.25–10.00) −0.86, 0.19	6.19 (3.67) 7.00 (3.75–8.00) −0.86, −0.04	3.60 (1.85) 3.50 (2.00–5.00) 0.40, 0.38		• .057	*
	Constructive praxis	Constructive praxis (2D+3D) H2 = 0.057 $P = 0.036$	15.42 (7.75) 13.50 (10.25–21.50) −0.73, 0.12	13.40 (7.95) 12.00 (6.00–19.50) −1.00, 0.56	9.55 (7.34) 8.00 (2.75–17.00) −1.37, 0.09			•
		Graphic constructive praxis (clock order) H2 = 0.220 $P = 3.83E\text{-}4$	8.00 (3.03) 7.50 (6.00–10.75) 0.13, −0.57	6.31 (2.63) 6.00 (5.00–8.00) 1.73, −0.18	4.15 (3.54) 4.50 (1.50–5.25) 1.71, 0.95	•	*	***
		Graphic constructive praxis (clock copy) H2 < 0.01 $P = 0.457$	9.42 (3.99) 10.00 (8.25–11.75) 0.21, −0.66	9.13 (3.03) 9.50 (8.75–10.00) 6.00, −1.48	8.10 (3.67) 8.50 (7.00–10.00) 0.59, −0.82			

Note: Mean (standard deviation); median (Q1–Q3); kurtosis and skewness coefficients; H2: effect size "eta squared" for the Kruskal–Wallis *H* test (< 0.01 very small effect; [0.01, 0.06) small effect; [0.06, 0.14) moderate effect; ≥ 0.14 large effect) and pairwise comparisons based on Mann–Whitney-Wilcoxon test with Holm correction for multiple testing. Statistical significance. $p < .10$, * $p < .05$, ** $p < .01$, *** $p < .001$; *p*: *p* values in univariate multinomial logistic regression models.

Abbreviations: A_{DS}, asymptomatic group; D_{DS}, dementia group; P_{DS}, prodromal group.

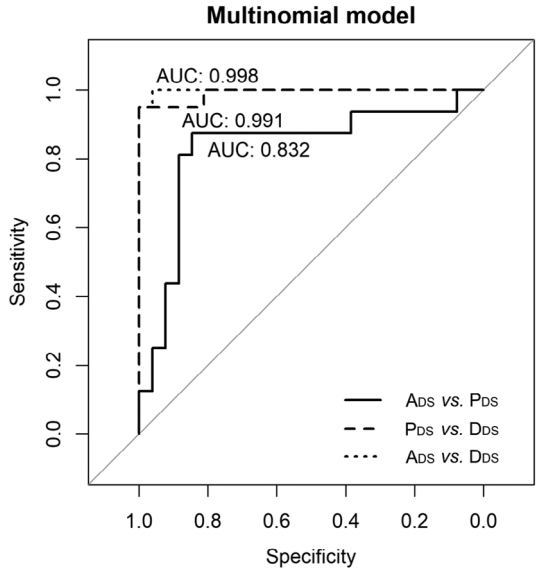

FIGURE 1 Pairwise ROC curves and AUC values derived from the multinomial model-based fit. A_{DS}, asymptomatic group; AUC, area under the receiver operating characteristic curve; D_{DS}, dementia group; P_{DS}, prodromal group; ROC, receiver operating characteristic.

Based on this MLR fit, 23 A_{DS} patients (88.5%), 12 P_{DS} patients (75.0%), and 19 D_{DS} patients (95.0%) were correctly classified. The patients wrongly classified are assigned to a contiguous group: three A_{DS} patients to the P_{DS} group (11.5%), four P_{DS} patients to the A_{DS} group (25.0%), and only one D_{DS} patient to the P_{DS} group (5.0%). Figure 1 shows the associated pairwise ROC curves with their corresponding AUC values (AUC = 0.832, 0.991, 0.998 for distinguishing A_{DS} vs. P_{DS}, P_{DS} vs. D_{DS}, and A_{DS} vs. D_{DS}, respectively).

3.3 | Volumetric changes

The one-way whole-brain analysis of covariance showed a significant main effect of group in four clusters covering mainly (1) left ("L OFC-PHPC") and (2) right orbitofrontal ("R OFC-Temporal") and para-hippocampal gyri (including regions of the hippocampus and the amygdala), (3) left fusiform gyrus (including some basal ganglia, hippocampal and para-hippocampal, and temporal regions, "L Fusiform-BG"), and (4) bilateral thalamus (also including some cingulate gyrus regions, "Bilateral Thalamus-CG"). The subsequent *t* tests evidenced that this main effect of group was driven by the significant differences between both the A_{DS} and the P_{DS} compared to the D_{DS}, such as that A_{DS} and P_{DS} showed greater gray matter volume (GMV) in those four regions. No significant differences were found between A_{DS} and P_{DS}, and there were no brain regions showing greater GMV in D_{DS} compared to the other two groups (see Table S1 in Supplementary material and Figure 2). The average volume values of each significant cluster were submitted for further (i.e., correlation) statistical analyses.

3.4 | Volumetric changes versus predictive diagnostic model

GMV values in the four clusters were significantly correlated with NSL_I in the D_{DS} group, with moderate to strong positive correlations: 0.682, 0.674, 0.644, and 0.594 (all *P* values < 0.05; Figure 3). However, no significant correlations were observed between these volumetric variables and NSL_I in any of the other two groups. As for VMT_{IK}, no significant correlations with the volumetric variables were found in any of the three diagnostic groups. Albeit not reaching statistical significance, moderate positive correlations were observed in the D_{DS} group ranging from 0.307 to 0.454 (Figure 3).

To visualize the association between the two main neuropsychological variables and the four volumetric clusters through a single linear regression, we performed two PCAs. On the one hand, to summarize the information given by the two predictive neuropsychological variables, a principal component including both variables (VMT_{IK} and NSL_I) called $PC1_N$ was obtained, and turned out to explain 76.2% of the original variability. On the other hand, another principal component, called $PC2_V$, was gathered, including the four volumetric clusters and explaining 86.0% of the original variability presented in the cluster-based variables. When studying the association between $PC1_N$ and $PC2_V$, a statistically significant positive correlation of moderate to strong magnitude was obtained only in the D_{DS} group: 0.602 (*P* value < 0.05, Figure 4).

4 | DISCUSSION

Overall, our findings demonstrated that an adequate and exhaustive neuropsychological assessment can discriminate and help categorize the three main stages (asymptomatic, prodromal, and dementia) within the AD continuum of DS. This is of crucial importance for clinical practice, in which it is essential to differentiate those patients who may present early cognitive signs of deterioration from those who are showing signs of the IDD itself, without further cognitive impairment. Moreover, the observed cognitive decline correlated with reductions in brain GMVs in broad regions, including orbitofrontal and medial-temporal (i.e., hippocampus, para-hippocampus, amygdala, etc.) cortices, and bilateral thalamus.

According to our results, the P_{DS} group showed a decline in orientation, verbal short-term memory, prospective memory, and abstract thinking with respect to the A_{DS} group. The P_{DS} group also showed significantly lower values in the CAMCOG-DS total score, indicating that the prodromal phase is characterized by a generalized decline in most domains assessed by this tool. As expected, such decline was even more evident and generalized in the D_{DS} group. In line with these findings, Rodríguez-Hidalgo et al.[29] previously indicated that scores < 82 on the CAMCOG-DS total score corresponded to a status 3 (mild cognitive and/or behavioral impairment) on the Global Deterioration Scale for people with DS (see also Garcia-Alba et al.[24] and Ramírez-Toraño et al.[25]). Nevertheless, it is also worthwhile to point out that some

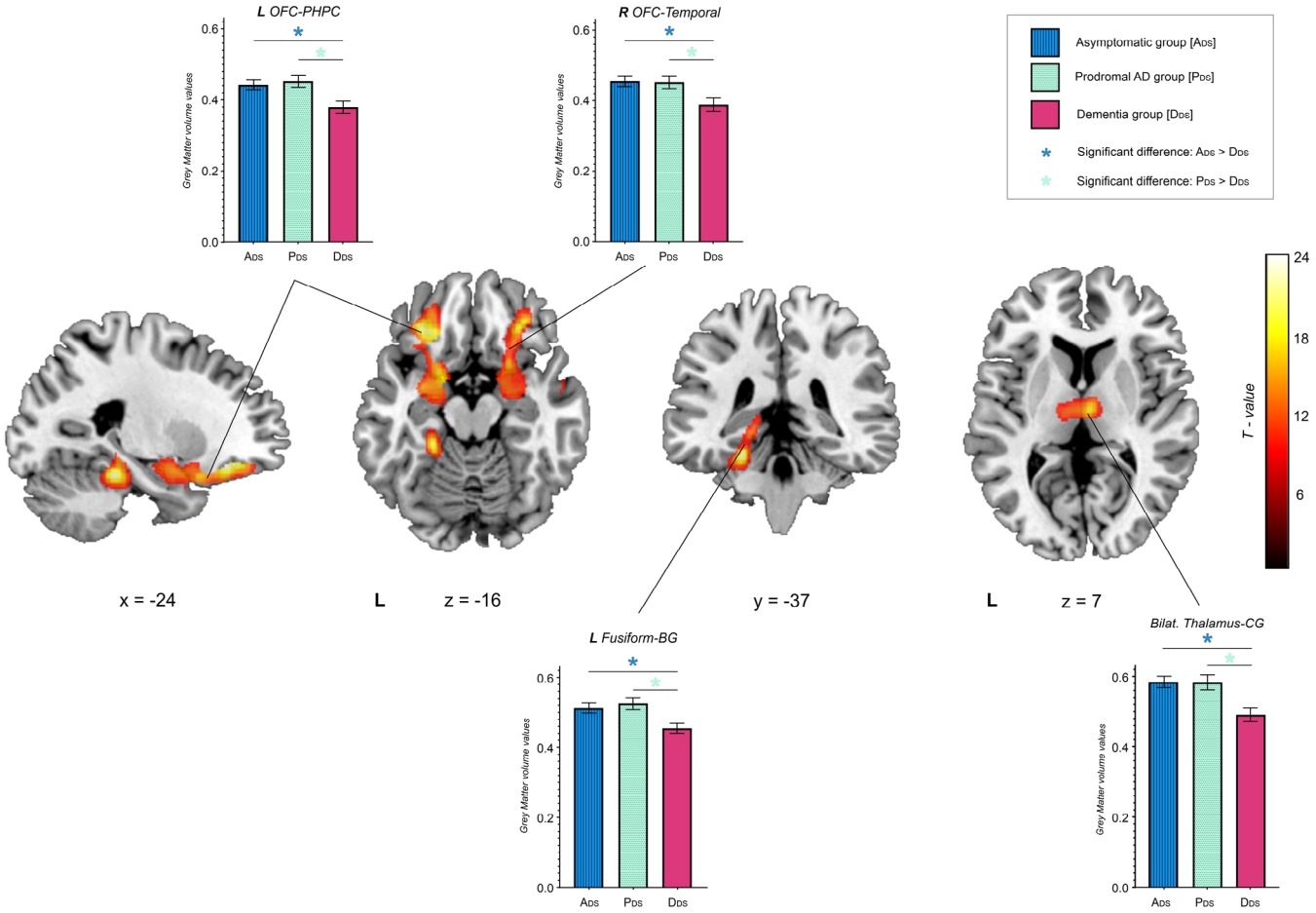

FIGURE 2 Results from the volumetric (VBM) analyses overlayed on standard brain images in MNI space shown at an uncorrected *P* value of 0.001 with a cluster size of 1000 contiguous voxels. The analysis of covariance shows a main effect of group on four clusters: left (L OFC-PHPC) and right (R OFC-Temporal) orbitofrontal and para-hippocampal cortices, left fusiform gyrus (L Fusiform-BG), and bilateral thalamus (Bilat. Thalamus-CG). MNI coordinates are given. Bar graphs depict the pairwise *t* tests, with significant results marked with asterisks. A_{DS}, asymptomatic group; BG, basal ganglia; Bilat., bilateral; CG, cingulate gyrus; D_{DS}, dementia group; L, left; MNI, Montreal Neurological Institute; OFC, orbitofrontal gyrus; PHPC, parahippocampal cortex; P_{DS}, prodromal group; VBM, voxel-based morphometry.

domains evaluated by the CAMCOG-DS did not reflect significant decline even when patients reached the stage of dementia (Table 2). This was also the case for some of the cognitive domains assessed by the BT-ID (Table 2). This indicates that not all cognitive domains are equally affected along the AD continuum, highlighting the importance of properly determining and characterizing cognitive changes in the DS population, especially in the prodromal phase of the disease.

Both the BT-ID and the CAMCOG-DS scores evidenced declines in orientation and verbal short-term memory as early markers of cognitive deterioration. Importantly, the deterioration of temporal orientation has been consistently observed in this context in previous reports.[25,26] However, verbal short-term memory decline, represented by a decrease in the scores of the two key variables selected by the PDM (i.e., NSL_I and VMT_{IK}) seemed to play an even more important role in the current data. The observed deficits in NSL_I are probably indicating failures in encoding and in the capability to learn and perform an immediate recall of verbal information. The clear deterioration in VMT_{IK} demonstrated, in turn, that cues did not facilitate recall in the P_{DS} and D_{DS} groups. This may imply a potential failure in the encoding and consolidation processes[29] during verbal memory tasks, which has been previously reported in prodromal AD cases within the DS population.[26] Notably, encoding and consolidation deficits have been traditionally associated with medial-temporal damage,[35] and might play a crucial role in the detection of prodromal AD.

In their influential publication, Dubois et al.[35] defined prodromal AD symptoms in terms of an "episodic memory loss of the hippocampal type," not sufficiently severe to affect instrumental activities of daily living. Such memory loss was characterized by a free-recall deficit while testing "not normalized with cueing" conditions as those used in the Free and Cued Selective Reminding Test.[36] This observation has been confirmed by previous investigations,[14,15] and to some extent by our current results, indicating that cued recall tests might be of particular relevance to detect early cognitive decline in the prodromal stage of AD in DS.

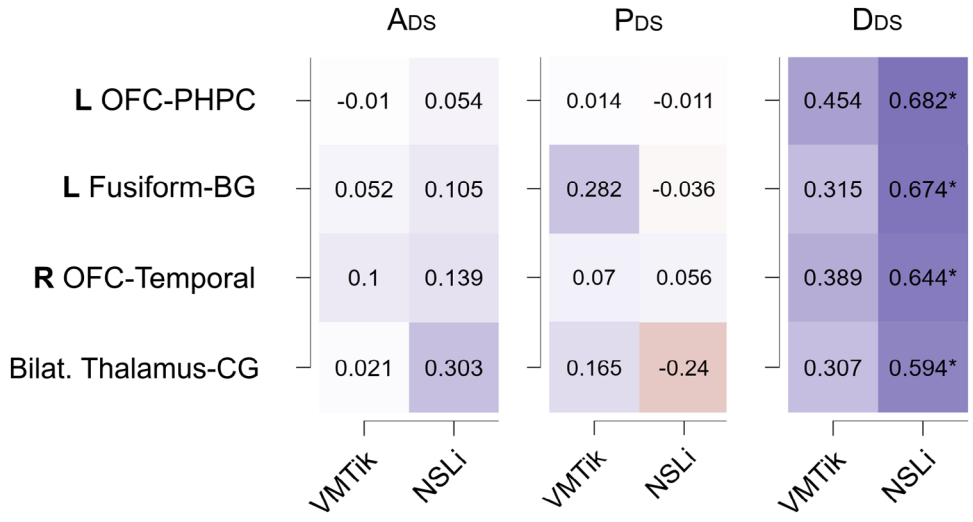

FIGURE 3 Heatmap with Spearman rank correlation coefficient ρ between volumes in the clusters identified in the VBM analysis and the two best predictive neuropsychological variables. The color of each cell indicates the strength and direction of the correlation between the corresponding row and column variables. Darker (lighter) colors indicate stronger (weaker) correlations. Blue (red) color shades indicate positive (negative) correlations. Statistical significance: * $P < .05$. A_{DS}, asymptomatic group; BG, basal ganglia; Bilat, bilateral; CG, cingulate gyrus; D_{DS}, dementia group; L, left; NSL_I, new serial learning (immediate); OFC, orbitofrontal gyrus; P_{DS}, prodromal group; PHPC, parahippocampal gyrus; R, right; VBM, voxel-based morphometry; VMT_{IK}, verbal memory texts (immediate key).

In addition, our results showed evidence of significant atrophy in the D_{DS} group in brain areas highly related to these neuropsychological deficits. Previous studies on brain anatomic changes showed a variety of findings.[28,37] Some studies[38,39] demonstrated a posterior cortical atrophy affecting temporo-parieto-occipital regions in amyloid-positive[38] and symptomatic[39] DS patients. When deep brain structures were analyzed, thalamus, hippocampus, and caudate/putamen volumes were significantly different between amyloid-positive and amyloid-negative DS cases.[38] Here, we failed to replicate the significant differences in parieto-occipital cortices observed in the above-mentioned studies, probably due to differences in sample characteristics and size (such as a more advanced age in our asymptomatic cases). Notwithstanding, our results mirrored previous literature consistently reporting medial-temporal atrophy, combined with prefrontal, basal ganglia, and thalamic volume reductions characterizing this group.[28,37–40] Interestingly, memory deficits correlated with atrophy patterns not only in medial-temporal structures and other memory-related substrates, but also in orbitofrontal and thalamic regions,[28,40] resembling atrophy patterns observed in non-DS AD.[19] Our results also paralleled Benejam et al.'s[39] findings, who reported a correlation between episodic memory measures and medial-temporal atrophy restricted to DS patients with AD. The authors attributed this result to a reduced dynamic range of the memory scores and a milder atrophy in asymptomatic cases. Our sample exhibits similar characteristics in this regard, making these results justifiable in a similar way.

It is also important to point out that the mnesic decline is difficult to detect in people with DS due to their baseline cognitive profile, characterized by a low performance in verbal short-term memory compared to other cognitive domains,[41] and the IDD inherent to this population. In particular, although the percentage of correctly classified P_{DS} cases was high (75%), this sample was more difficult to classify compared to A_{DS} and D_{DS} cases. Typically, the detection of prodromal AD or MCI has always been a harder task than the detection of dementia cases.[42] Prodromal cases tend to exhibit "intermediate" scores in most of the measured variables and lay in the midst of an existent overlap between diagnostic groups. This problem may be even more accentuated within the DS population, as AD-related deterioration coexists with a premorbid IDD that increases the potential overlap by augmenting the variability of the cognitive scores.[26] Therefore, it is essential to use tests that have been adapted and validated for this population.

For example, our findings showed an impairment in prospective memory within the P_{DS} and D_{DS} groups compared to the A_{DS} group. Prospective memory, defined as the capability to remember and execute an intention in the future without having a permanent reminder, is a domain seldomly assessed.[43] Interestingly, recent studies in the general population have shown that a decline in prospective memory may be a good predictor of future cognitive impairment and incident dementia.[44] Although prospective memory has not been extensively studied as a cognitive marker of dementia in DS, our results suggest that it could certainly be an important cognitive function that could be included in the neuropsychological assessments for the diagnosis of AD in DS. The abstract thinking variable (CAMCOG-DS), a measure of executive function, also showed underperformance in the P_{DS} and D_{DS} groups (especially the latter). Abstraction was assessed through similarity interpretation, measuring the ability to think abstractly to find similarities between given words.[45] Recent reports found low scores in this cognitive domain within people with DS in the prodromal stage,[25,26,29] which suggests importance for this domain in the diagnostic characterization of this population.

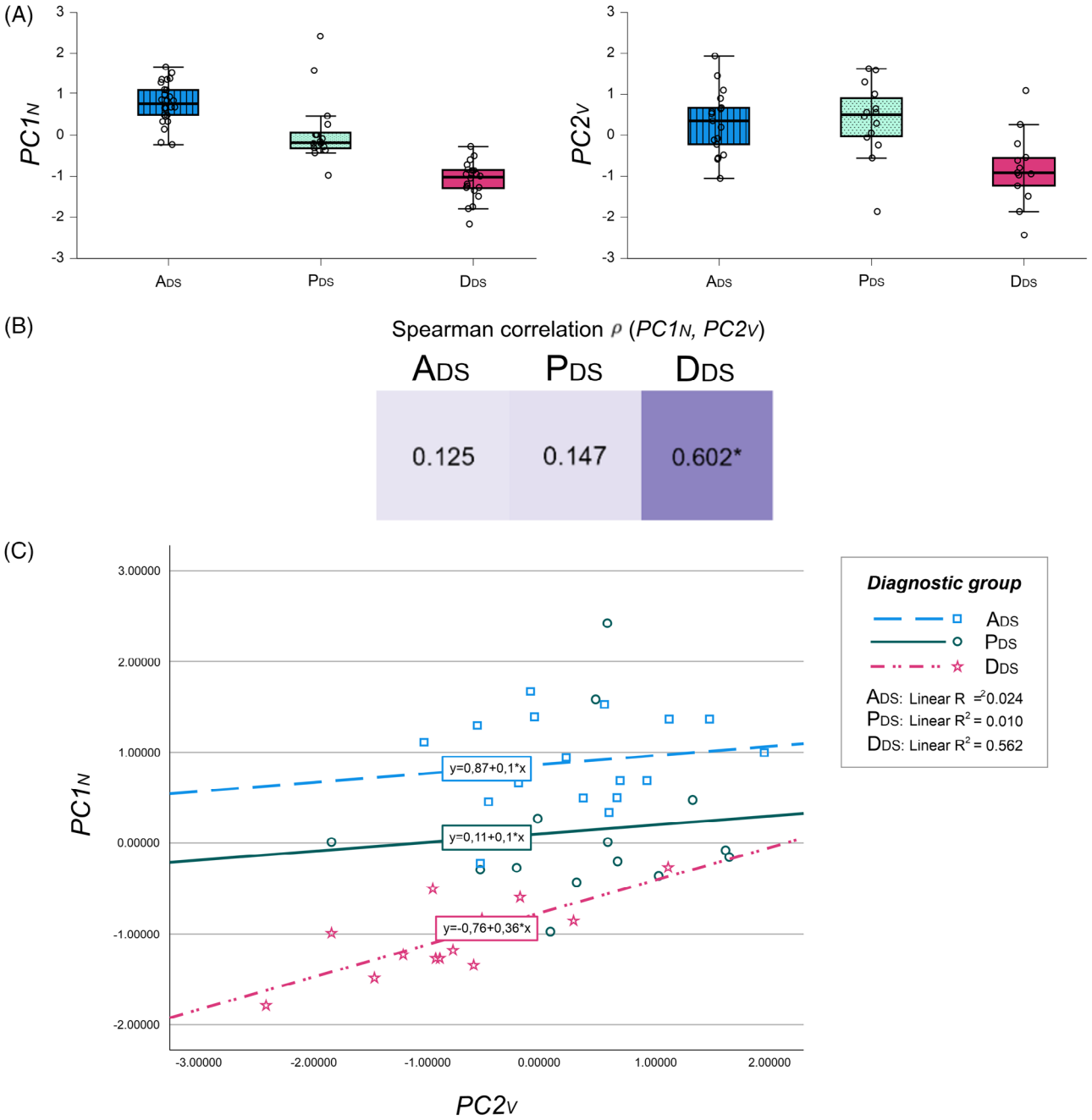

FIGURE 4 A, Boxplots of principal components $PC1_N$ and $PC2_V$ per diagnostic group. B, Heatmap with Spearman rank correlation coefficient ρ between $PC1_N$ and $PC2_V$ per diagnostic group. C, Regression line of $PC1_N$ on $PC2_V$ per diagnostic group. The regression coefficient in the D_{DS} group ($\beta = 0.36$, 95% confidence interval [0.15, 0.56]) indicates that an increase of 1 unit in $PC2_V$ corresponds, on average, to an increase of 0.36 units in $PC1_N$ (Student t test = 3.76, P value = 0.0032 < 0.05). A_{DS}, asymptomatic group; D_{DS}, dementia group; P_{DS}, prodromal group; $PC1_N$, principal component including verbal memory texts (immediate key) and new serial learning (immediate); $PC2_V$, principal component including the four volumetric clusters.

Our study has several limitations. In particular, the sample size was relatively small considering the type of data described here: cases with mild/moderate IDD were considered a single group. This, together with the lack of an a priori power analysis, might restrict the statistical inferences and the generalizability of the results. Sample size limitations will be palliated in future research via multi-center collaborations. It is also important to keep in mind that people with DS exhibit different levels of basal functioning depending on their degree of IDD. Consequently, cognitive changes due to AD-related decline are more complex to detect in people with moderate IDD. This fact was commented on by our investigation group in previous publications.[28]

Overall, our results allowed us to conclude that neuropsychological tests might be sufficient to diagnose a prodromal or dementia case in DS. As a general remark at this point in our longitudinal investigation,

a clear characterization of the most affected cognitive domains in prodromal AD via properly adapted and validated tests seems essential in this population. The cognitive domains and volumetric variables that demonstrate a better capability to distinguish between asymptomatic and prodromal AD in DS will be prioritized for further investigation. To conclude, more specific assessments and definition of diagnostic criteria in this field are needed and will lead to better diagnosis in clinical settings, potentially providing better tailored therapeutic strategies to overcome the deficits in this population.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest relevant to this manuscript. Author disclosures are available in the supporting information.

CONSENT STATEMENT

All subjects provided informed consent.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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