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Proposal for a hierarchical, multidimensional, and multivariate approach to investigate cognitive aging

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ABSTRACT

Cognitive aging is highly complex. We applied a data-driven statistical method to investigate aging from a hierarchical, multidimensional, and multivariate approach. Orthogonal partial least squares to latent structures and hierarchical models were applied for the first time in a study of cognitive aging. The association between age and a total of 316 demographic, clinical, cognitive, and neuroimaging measures was simultaneously analyzed in 460 cognitively normal individuals (35–85 years). Age showed a strong association with brain structure, especially with cortical thickness in frontal and parietal association regions. Age also showed a fairly strong association with cognition. Although a strong association of age with executive functions and processing speed was captured as expected, the association of age with visual memory was stronger. Clinical measures were less strongly associated with age. Hierarchical and correlation analyses further showed these associations in a neuroimaging-cognitive-clinical order of importance. We conclude that orthogonal partial least square and hierarchical models are a promising approach to better understand the complexity in cognitive aging.

1. Introduction

Cognitive aging has been extensively investigated. Previous studies have consistently identified processing speed and executive functions as the most vulnerable functions to aging (Keys and White, 2000; Salthouse, 1996a; Tisserand and Jolles, 2003). Findings on episodic memory and language vary and depend on the component investigated. For example, studies often report an age-related decline in delayed free recall and word retrieval but not in the consolidation of previously learned information, semantic memory, or vocabulary (Barresi et al., 2000; Craik and Salthouse, 2008; Nilsson, 2003). Some abilities such as visuoperceptive, visuospatial, and visuoconstructive functions seem to have a later onset of decline (Hildebrandt et al., 2010). However, contrary results also exist (de Bruin et al., 2016; Ferreira et al., 2015; Verhaeghen and De Meersman, 1998).

This cognitive decline is primarily explained by age-related changes in brain integrity (Reuter-Lorenz and Cooke, 2016). Neuroimaging studies have reported a linear decline in total gray matter volume (Abe et al., 2008; Salat et al., 2004). Because volume is a combination of cortical thickness and area, studies investigating these 2 markers have provided relevant information. Cortical thickness is more sensitive to aging and neurodegenerative disorders such as Alzheimer's disease (Dickerson et al., 2009), whereas cortical area is more sensitive to disorders such as the Williams syndrome (Meda et al., 2012). Opposite to linear decline in total gray matter volume, deterioration in white matter microstructure and ventricular enlargement is nonlinear and accelerates after the age of 60 (Abe et al., 2008; Grieve et al., 2005). These associations between age, brain, and cognition are modest during middle age, without strong clinical implications (Ferreira et al., 2015), but may trigger different biological changes or chronic diseases leading to cognitive decline later in old age (Debette et al., 2011).

Importantly, age-related changes in cognition and brain integrity may be caused by multiple factors that are associated to each other

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(Blokh and Stambler, 2014). Furthermore, risk and protective factors are also present, modulating the association between brain changes, cognition, and clinical status. Univariate statistical methods do not take this complexity into account and may lead to opposite results, for instance, as it happens with episodic memory. Some studies refer a greater aging effect on verbal memory than on visual memory (Fastenau et al., 1996), but contrary results have also been reported (Jenkins et al., 2000). Furthermore, some studies have described a greater aging effect on free recall than on cued recall/recognition tasks (Nilsson, 2003; Zacks et al., 2000). Contrarily, other studies have demonstrated that age exerts comparable effects on all these memory components (Salthouse, 1995). Importantly, these memory components are highly interrelated to each other and with other cognitive functions such as executive functions and processing speed (Fastenau et al., 1996; Hultsch et al., 1990; Salthouse, 1996b). Therefore, cognitive measures should not be treated separately but in interrelation with other cognitive measures (Brickman et al., 2007; Habeck et al., 2015; Salthouse, 2009; Salthouse et al., 2015). The same applies to neuroimaging measures.

Because of this, numerous previous studies have investigated cognitive aging using different multivariate statistical methods (Habeck et al., 2015; Hildebrandt et al., 2010; Lövdén et al., 2010, 2013; Nyberg et al., 2012; Salthouse et al., 2015). Projection-based techniques such as principal components analysis and partial least squares (PLS) have recently received great attention (Raffard et al., 2016; Salami et al., 2012). An interesting approach is the orthogonal PLS (OPLS) to latent structures. OPLS is an extension of PLS that combines features from principal components analysis and multiple linear regression. However, although in multiple linear regression predictors are modeled independently and compete with each other to explain partial effects, in OPLS predictors are combined together forming a predictive component that explains the outcome variable. OPLS shares common advantages with other multivariate methods, for instance, reducing complexity and dimensionality in the data, making it possible to observe inherent patterns in the data, and avoiding issues related to multiple testing and multicollinearity (Abdi, 2010; Falahati et al., 2016). Similar to other multivariate approaches, OPLS separates the variation of the data into systematic and residual (i.e., noise). However, the addition of a rotation solution gives OPLS the advantage to maximize the variation in the data related to the variable of interest (criterion variable Y), by separating systematic variation into predictive and orthogonal (Eriksson et al., 2013). In part due to this, OPLS significantly facilitates results interpretation, and it has shown to be slightly superior to other multivariate methods (Aguilar et al., 2013). Thanks to this ability, OPLS has significantly contributed to our understanding of complex biological processes such as Alzheimer's disease (Falahati et al., 2014). OPLS has extensively been used on neuroimaging data (Aguilar et al., 2014; Westman et al., 2010, 2011), but to our knowledge, it has been used on cognitive data only in 1 previous study (Sparding et al., 2015). In that study, Sparding et al. applied OPLS on 47 cognitive measures and achieved good discrimination between bipolar patients and healthy controls, with patients showing worse cognitive performance.

The aim of the present study was to investigate the association between age and brain structure, cognitive performance, and clinical status by using a multivariate data-driven method (OPLS) on data from a large cohort of cognitively normal individuals. A broad age span was covered from 35 to 85 years, and comprehensive clinical, cognitive, and neuroimaging data were used. We also aimed to analyze the hierarchical association between age and brain structure, cognition, and clinical status. Based on the previous literature, we hypothesized that OPLS would capture a strong association of age with structural magnetic resonance imaging (MRI) measures, mostly cortical and white matter regions of the frontal lobe (Fjell et al., 2009, 2014; Goodro et al., 2012; Kennedy and Raz, 2009; Walhovd et al., 2011); followed by a strong association with cognition, mostly executive functions and processing speed (Keys and White, 2000; Salthouse, 1996a; Tisserand and Jolles, 2003); and, finally, there would be a weak association with clinical variables because the present study includes cognitively healthy individuals and only subclinical variation was expected (Ferreira et al., 2017). Thus, we anticipated a hierarchy reflecting the temporal sequence seen both in normal aging and neurodegenerative disorders such as Alzheimer's disease, with changes in biological markers (e.g., MRI) coming first, followed by cognitive decline, and finally, changes in the clinical status (Iturria-Medina et al., 2016; Jack et al., 2013).

2. Materials and methods

2.1. Participants

A total of 528 participants between 35 and 85 years from the GENIC-database (Ferreira et al., 2015) were initially enrolled. Participants' recruitment was carried out through primary care health centers, advertisements in local schools, and relatives and acquaintances of the research staff. The aim was to cover a representative sample regarding age, sex, and education. The following selection criteria

Table 1
Demographic and clinical characteristics

	Whole sample			Subsample with MRI data			Subsample without MRI data			Subsamples comparison	
	N	M (SD)/count	Range/%	n	M (SD)/count	Range/%	n	M (SD)/count	Range/%	*p*-values ANOVA/U-Mann-Whitney	*p*-values ANCOVA/Ordinal Regression
Age, y	460	58.4 (11.4)	35–84	294	54.6 (10.6)	35–79	166	65.2 (10.9)	40–84	<0.001	-
Sex, female	460	251	54.6%	294	158	53.7%	166	93	56%	0.637	-
WAIS-III information	452	15.2 (6.2)	5–27	294	16.4 (5.9)	5–27	166	13.0 (6.1)	5–25	<0.001	<0.001[b]
MMSE	459	28.5 (1.5)	24–30	294	28.8 (1.3)	24–30	165	27.9 (1.6)	24–30	<0.001	0.021[c]
BDRS	456	0.9 (1.4)	0–7[a]	290	0.8 (1.3)	0–7	166	1.1 (1.4)	0–7[a]	<0.001	0.274[c]
FAQ	459	0.4 (0.8)	0–5	294	0.4 (0.8)	0–5	165	0.4 (0.9)	0–4	0.986	-

When 2 or more screening tests (MMSE. BDRS and/or FAQ) were not available, participants were excluded from this study.
Key: BDRS, blessed dementia rating scale; FAQ, functional activity questionnaire; M, mean; MMSE, mini–mental state examination; MRI, magnetic resonance imaging; SD, standard deviation; WAIS-III, wechsler adult intelligent scale–third edition.

[a] Although the BDRS scale cutoff for abnormality is frequently established at ≥4 points (Blessed et al., 1968; Erkinjuntti et al., 1988), the BDRS total score may be influenced by scores in the "BDRS-changes in personality, interests, and drive subscale" and do not necessarily reflect functional impairment. Therefore, individuals with total BDRS scores ≥4 were included in the study if: (a) 70% or higher percentage of the BDRS total score resulted from the "BDRS-changes in personality, interests, and drive subscale"; and (b) if a score ≤1.5 was obtained in the other 2 subscales ("BDRS-changes in performance of everyday activities" and "BDRS-changes in habits"). The purpose of this was excluding only individuals with functional impairment (further supported by normal scores in FAQ and MMSE). Fifteen participants were included according to this criterion.

[b] Age as covariate.

[c] Age and WAIS-III Information as covariates for MMSE, and age, WAIS-III Information, and MMSE as covariates for BDRS.

were followed for the present study: (1) age equal or over 35 years; (2) preserved global cognition and functional status operationalized as a mini–mental state examination (MMSE) score ≥24, a Blessed Dementia Rating Scale (BDRS) score <4 (or adjustment as explained in the caption of Table 1), and a Functional Activities Questionnaire (FAQ) score <6; (3) normal cognitive performance in comprehensive neuropsychological assessment using pertinent clinical normative data (i.e., individuals did not fulfill cognitive criteria for mild cognitive impairment nor dementia); (4) no abnormal findings such as stroke, tumors, hippocampal sclerosis, and so forth, in MRI according to an experienced neuroradiologist (L.D-F.); and (5) no psychiatric or neurologic disorders, systemic diseases with neuropsychological consequences, or history of substance abuse. Sixty-eight participants were excluded from the original GENIC-database according to these criteria. The final sample consisted of 460 participants. All participants gave written informed consent under the Declaration of Helsinki. The protocol was approved by the local ethics committee of the University of La Laguna (Spain).

2.2. Clinical and neuropsychological assessment

Cognition was assessed using a comprehensive neuropsychological assessment covering processing speed, attention, executive functions, premotor functions, verbal and visual episodic memory, visuoperceptive, visuoconstructive and visuospatial functions, and language (please see the Supplementary Table S1 for a complete list of the tests). In addition, global cognition was assessed with the MMSE. Functional status was assessed with the BDRS and the FAQ. Depressive symptomatology was assessed with the Beck Depression Inventory (BDI) when individuals were younger than 63 years and the Geriatric Depression Scale (GDS) when 63 years or older. BDI and GDS scores were transformed into z scores and combined into 1 single variable to study depressive symptomatology (BDI-GDS composite). The Wechsler Adult Intelligence Scale (WAIS-III) Information subtest was scored and used as an indicator of crystallized intelligence and/or education. Previous studies from this cohort have shown that the WAIS-III information subtest better represents achievements and usage of educative opportunities in comparison with educational attainment or years of education (Correia et al., 2015; Ferreira et al., 2014, 2015). The reason for this is the existence of heterogeneous formal education across the age span in the study population.

2.3. MRI acquisition and data processing

Participants were scanned using a 3.0 T General Electric imaging system (General Electric, Milwaukee, WI, USA) located at the *Hospital Universitario de Canarias*, Tenerife (Spain). A 3-dimensional T1-weighted Fast Spoiled Gradient Echo sequence was acquired in sagittal plane with the following parameters: repetition time/echo time/inversion time = 8.73/1.74/650 ms, field of view = 250 × 250 mm, matrix 250 × 250 mm, flip angle 12°, slice thickness = 1 mm. Full brain and skull coverage was required for all MRI data sets, and detailed quality control was carried out according to previously published criteria (Simmons et al., 2009).

Cortical reconstruction and volumetric segmentation were performed using FreeSurfer 5.1.0 (http://surfer.nmr.mgh.harvard.edu/) through our database system (Muehlboeck et al., 2014) as detailed elsewhere (Ferreira et al., 2014). Visual quality control was performed on all output data. This consisted of a thorough inspection of the cortical reconstruction and subcortical segmentation (i.e., appropriate Talairach registration, appropriate segmentation constrained to intensity boundaries, proper delineation of pial and white surfaces, and proper segmentation of the T1-weigthed white matter hypointensities [WMH]). Manual edition was performed on the output that did not meet the quality control criteria. The data were processed until satisfactory output was obtained or, otherwise, discarded for this study. Measures from the cortical reconstruction pipeline include regional cortical thickness, cortical surface area, and cortical volume (Desikan et al., 2006; Fischl et al., 2004b). Measures from the volumetric segmentation pipeline include regional white matter volume (including WMH), various subcortical gray matter structures, and the ventricles (Fischl et al., 2002, 2004a) (all these MRI regions are displayed in Supplementary Fig. S1 in Appendix A—Supplementary Tables and Figures). An estimation of the total intracranial volume (ICV) was also calculated with FreeSurfer 5.1.0 and included in the models to correct for between-individual differences in brain size (Voevodskaya et al., 2014). The ICV correction was performed on volume and area measures only since cortical thickness does not need to be corrected for ICV (Schwarz et al., 2016).

2.4. Statistical analysis

Multivariate data analysis was conducted using OPLS (Trygg and Wold, 2002) with the SIMCA software (Sartorius Stedim Biotech). Preprocessing was performed using mean-centering and unit variance scaling to transform the data into a suitable form for analysis (Eriksson et al., 2013). The data were inspected for distributional properties and detection of outliers previous to the extraction of the models. Missing data were imputed by the nonlinear iterative PLS algorithm present in OPLS (Eriksson et al., 2013; Nelson et al., 1996). Once the components were extracted, all the models were inspected for optimal dimensionality (please see the Appendix B—Supplementary Methods—"model diagnostics" section for further information).

Briefly, OPLS maximizes the covariance between the dependent and the independent variables (Eriksson et al., 2013). To quantify the performance of the OPLS models, 2 parameters are used: goodness of fit (R^2) and goodness of prediction (Q^2). R^2 is the fraction of the total variation of the data that can be explained by the components of the model. R^2 thus shows how well the model fits the data. Q^2 is the fraction of variation of the data that can be predicted by the model. Q^2 shows how reliable the model predicts new data (Falahati et al., 2016). The significance of a model is based on the Q^2 parameter and is reported as acceptable ($Q^2 > 0.1$), good ($Q^2 > 0.5$), and optimal ($Q^2 > 0.9$) (Eriksson et al., 2013). Model results can be visualized in loading plots where the direction (positive or negative) and the distance (load) between the predictive variables and criterion variable are shown. Confidence intervals or Jack-knifes represented in the loading plots are used to estimate the bias and standard error of each predictive variable. If confidence intervals contain the zero value, the variable has low reliability in the model (Wiklund et al., 2008). All OPLS models were validated using 7-fold cross-validation and permutations plots (Eriksson et al., 2013), as further explained in Appendix B (Supplementary Methods).

In all the OPLS models, age was the criterion variable (Y). A total of 316 predictive variables (X) were analyzed. In particular, the demographic-clinical measures (n = 6), cognitive measures (n = 73), and MRI measures (n = 237) were grouped into 3 different "dimensions" according to our hypothesis: a hierarchy reflecting a strong association of age with MRI measures, followed by cognition and, finally, by clinical measures. These 3 dimensions were initially modeled in separated base OPLS models, and then a hierarchical model was performed. In this data-driven hierarchical OPLS model, the scores of the 3 base dimensional models were treated as predictors for the new OPLS top level model (further detail is provided in Appendix B—Supplementary Methods).

The OPLS models were repeated including sex and WAIS-III Information subtest as additional predictive variables (X), given the well-known effect of these 2 measures on cognition (Proust-Lima

et al., 2008). Furthermore, both sex and the WAIS-III information subtest have shown an association with cognition in previous studies performed in subsamples of the current cohort (Correia et al., 2015; Ferreira et al., 2015). Differences between the goodness of fit (R^2) and prediction (Q^2) estimations of these models were checked; and statistical differences were tested through paired *t* test of the predicted Y variables, to determine the possible contribution of sex and WAIS-III Information subtest in the different OPLS models.

Chi-square was used for dichotomous variables and ANOVA/ANCOVA for continuous variables after Box-Cox transformations when needed (Osborne, 2010). When Box-Cox transformations were not possible, U-Mann Whitney and Ordinal Regression were performed. Simple and partial Pearson correlations were used to investigate the association between continuous variables. Furthermore, multiple linear regression and random forest analyses were applied for comparison with the OPLS results (please see the Appendix C-Supplementary Results). A *p*-value of <0.05 (2-tailed) was deemed significant.

3. Results

The main demographic and clinical characteristics of the study sample (N = 460) are presented in Table 1. MRI data were available for 294 participants. The MRI subsample was younger and had higher scores on MMSE and the WAIS-III Information subtest (Table 1). This finding is due to lack of MRI data in the first wave of the study where mostly participants of 65 years or older were assessed.

3.1. Association of age with demographic-clinical, cognitive, and MRI measures

The OPLS model based on demographic-clinical measures resulted in $Q^2 = 0.112$ and $R^2 = 0.125$. MMSE, WAIS-III information subtest, BDI-GDS composite, and BDRS were the variables contributing the most to the model (Fig. 1A). Older age was associated with lower scores in MMSE and the WAIS-III

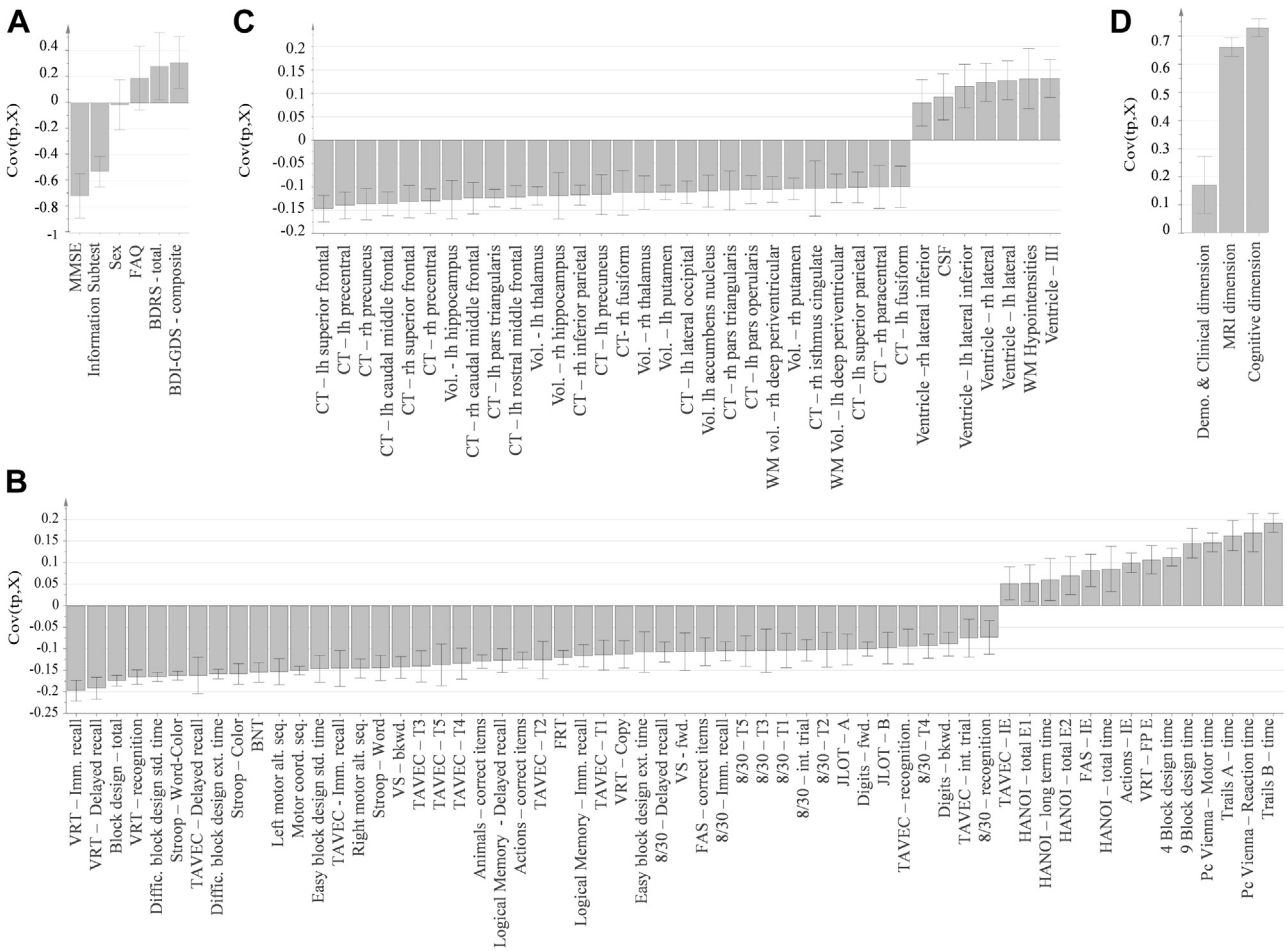

Fig. 1. The association of age with demographic-clinical, cognitive, and MRI measures (loading plots from the OPLS models). (A) The association of age (Y-variable) with demographic-clinical measures (X-variables). (B) The association of age (Y-variable) with 60 cognitive measures (X-variables). The variable "Trails-A" refers to the combination of the Trail Making Test part A and the Color Trail Test part 1, whereas the "Trails-B" represents the Color Trail Test–part 2. Please see the loading plot including all the 73 cognitive variables in Supplementary Fig. S2. (C) The association of age (Y-variable) with MRI-model 7 (X-variables: only the first 35 significant variables in the model are displayed. Please see the loading plot including the first 70 significant variables in the model displayed in Supplementary Fig. S3). (D) Hierarchical association of age (Y-variable) with the demographic-clinical, cognitive, and MRI (model 7) dimensions (X-variables). The plot shows the loadings and their corresponding jack-knifed confidence intervals. Measures with confidence intervals that include zero have low reliability in the model. A measure with high covariance is more likely to have a greater contribution to the prediction of age (Y-variable), when analyzed simultaneously with the rest of the variables in the model. Measures above the zero axis indicate a positive association with age, whereas variables below the zero axis indicate a negative association with age. The vertical axis indicates how X variables covariate in the predictive component of the model (Cov [tp,X]). Abbreviations: alt, alternate; bkwd, backwards; BNT, boston naming test; CSF, cerebrospinal fluid; CT, cortical thickness; Diffic, difficult, designs of higher difficulty; E, error; ext., extended; FRT, facial recognition test; fwd, forward; FP, false positive; IE, intrusion error; imm, immediate; int, interference; JLOT, judge line orientation test; lh, left hemisphere; MRI, magnetic resonance imaging; OPLS, orthogonal partial least square; PE, perseveration error; rh, right hemisphere; std, standard; seq, sequence; T, trial; VRT, visual reproduction test; TAVEC, spanish version of CVLT (Californian verbal learning test); VS, visuospatial span; vol, volume; WM, white matter; III, third ventricle.

Table 2
The association of age with MRI measures (OPLS models)

Brain compartment	Model	Marker	Number of measures	N	Q^2	R^2
Gray matter	1	Cortical thickness	68	294	0.388	0.545
	2	Cortical area (+ICV)	68	294	0.156	0.314
	3	Cortical volume (+ICV)	69	294	0.282	0.489
	4	Subcortical structures volume (+ICV)	17	294	0.334	0.372
White matter	5	Volume (+ICV)	77	294	0.384	0.537
Ventricular system	6	Volume (+ICV)	8	294	0.383	0.415
Combined model	7	Cortical thickness (68) + white-matter volume (76) + ventricular system volume (7) + subcortical gray matter structures volume (16) (+ICV)	168	294	0.741	0.561

Key: ICV, intracranial volume; MRI, magnetic resonance imaging; N, sample size; OPLS, orthogonal partial least squares; Q^2, goodness of prediction; R^2, goodness of fit.

information subtest, and higher scores in the BDI-GDS composite and BDRS.

The cognitive OPLS model resulted in $Q^2 = 0.564$ and $R^2 = 0.620$. As expected, age showed a strong association with executive functions and processing speed. For example, the Trails-B was a measure with high contribution in the model. However, most importantly, our results showed a stronger association of age with delayed recall of visual memory (Visual Retention Test), with this measure achieving the highest contribution in the model (Fig. 1B). In all cognitive measures, older age was associated with worse cognitive performance. The correlation of all cognitive variables with age, sex, and the WAIS-III Information subtest can be observed in Supplementary Fig. S4.

Concerning MRI measures, analyses were carried out in 2 steps. In the first step, several individual OPLS models were conducted for gray matter (model 1 = cortical volume, model 2 = cortical thickness, model 3 = cortical area, model 4 = subcortical gray matter structures), regional white matter volumes (model 5), and ventricular volumes (model 6) (Table 2). Cortical thickness, regional white matter volumes, and ventricular volumes were the models achieving highest predictive performance ($Q^2 > 0.380$), and the cortical area was the model achieving the lowest predictive performance ($Q^2 = 0.155$). In the second step, several combinations of these individual MRI models were tested in separate hierarchical OPLS models to investigate which combination of MRI models showed the highest predictive performance. The highest Q^2 value resulted from the combination of the following 4 individual MRI models (in order of load contribution): cortical thickness (model 1), regional white matter volumes (model 5), ventricular volumes (model 6), and subcortical gray matter structures (model 4) ($Q^2 = 0.680$; $R^2 = 0.691$). The MRI measures included in these 4 individual MRI models were combined in a single model (model 7 in Table 2) to create the "MRI dimension" for the subsequent hierarchical model of demographic-clinical, cognitive, and MRI dimensions. Frontal and parietal cortical thickness measures, the third and lateral ventricles, WMH, and hippocampal volume were the variables with higher contribution in this model (model 7 in Table 2 and Fig. 1C). Older age was associated with thinner cortex, smaller hippocampus, larger ventricles, and a higher burden of WMH.

The cognitive and MRI models reported above were repeated including sex and the WAIS-III Information subtest as additional predictive variables. Differences in Q^2 and R^2 parameters were minimal and non-significant (Table 3). These results indicate a minimal contribution of sex and the WAIS-III Information subtest to the prediction of age in the cognitive and MRI OPLS models.

3.2. *Hierarchical association of age with demographic-clinical, cognitive, and MRI dimensions*

The hierarchical OPLS model based on the previous 3 "dimensional" models (demographic-clinical, cognitive, and MRI [model 7] dimensions), resulted in $Q^2 = 0.776$ and $R^2 = 0.771$ (Fig. 1D). This hierarchical OPLS model showed that the MRI dimension had a major contribution to the model, followed by the cognitive dimension and, finally, the demographic-clinical dimension. The age-predicted values (cross-validated) of each dimensional model were calculated, and pair correlations were tested. Results confirmed this hierarchy with a strong correlation between the MRI dimension and the cognitive dimension ($r = 0.589$; $p < 0.001$); a moderate correlation between the cognitive dimension and the demographic-clinical dimension ($r = 0.359$; $p < 0.001$); and a weak correlation between the MRI dimension and the demographic-clinical dimension ($r = 0.163$; $p = 0.005$) (Fig. 2).

4. Discussion

Numerous previous studies have applied different multivariate statistical methods to better understand the complexity within

Table 3
Potential effect of sex and the WAIS-III Information subtest on the cognitive and MRI OPLS models

Variables of interest	Extraneous variables	N	Q^2	R^2	Pair	t	*p*
73 cognitive measures	-	460	0.564	0.620			
73 cognitive measures	Sex	460	0.562	0.618	1	0.296	0.767
73 cognitive measures	WAIS-III Information	460	0.590	0.640	2	0.215	0.830
73 cognitive measures	Sex and WAIS-III Information	460	0.586	0.635	3	0.276	0.783
168 MRI measures	-	294	0.561	0.741			
168 MRI measures	Sex	294	0.565	0.743	4	0.142	0.887
168 MRI measures	WAIS-III Information	294	0.565	0.743	5	0.414	0.679
168 MRI measures	Sex and WAIS-III Information	294	0.568	0.745	6	0.393	0.695

Comparison pair 1 (Cognitive vs. Cognitive and sex), pair 2 (Cognitive vs. Cognitive and WAIS-III Information), pair 3 (Cognitive vs. Cognitive, sex, and WAIS-III Information), pair 4 (MRI vs. MRI and sex), pair 5 (MRI vs. MRI and WAIS-III Information), pair 6 (MRI vs. MRI, sex, and WAIS-III Information).
Key: MRI, magnetic resonance imaging; N, sample size; OPLS, orthogonal partial least squares; Q^2, goodness of prediction; R^2, goodness of fit; WAIS-III Information subtest, wechsler adult intelligent scale—third edition.

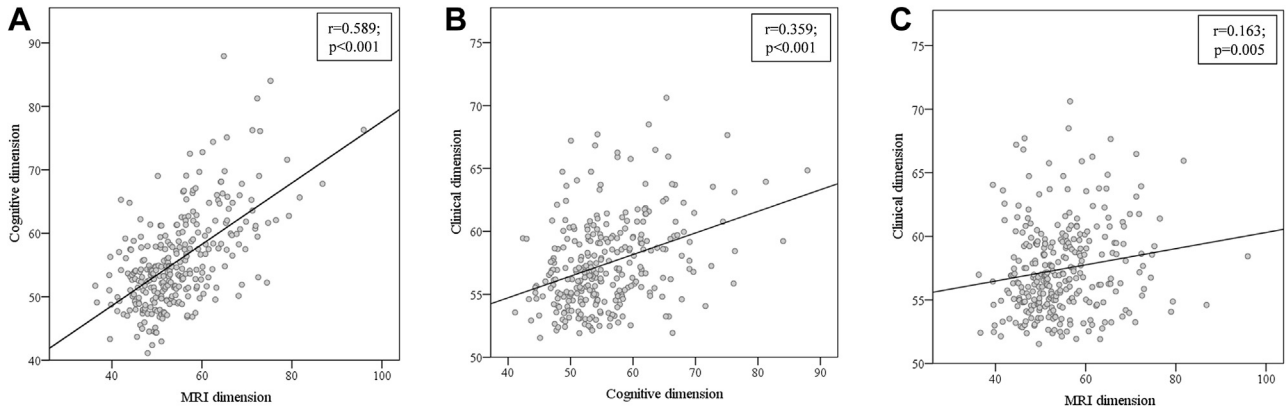

Fig. 2. Scatter plots of the correlations between the MRI, cognitive, and clinical OPLS dimensions. From left to right, (A) the association between MRI and cognitive dimension showed a higher correlation (r = 0.589) than (B) the correlation between the cognitive and clinical dimension (r = 0.359) and, (C) between the MRI and clinical dimension (r = 0.163). Abbreviations: MRI, magnetic resonance imaging; OPLS, orthogonal partial least square.

cognitive aging (Habeck et al., 2015; Lövdén et al., 2013; Nielsen and Wilms, 2015; Park et al., 2002; Proust-Lima et al., 2016; Ritchie et al., 2016; Salthouse, 2009; Salthouse et al., 2015). This is necessary because univariate statistical methods could lead to overestimated and inaccurate conclusions because almost no cognitive or neuroimaging variable exists in isolation (Salthouse, 2009; Salthouse et al., 2015). In the present study, we investigated the multivariate and hierarchical association of age with brain structure, cognition, and clinical status by using OPLS in a data-driven fashion.

Regarding demographic-clinical measures, older age was associated with lower performance in MMSE and WAIS-III Information subtest, and higher scores in BDRS and depressive symptomatology. Age-related decline in MMSE is a common finding (Bravo and Hébert, 1997; Tombaugh and McIntyre, 1992). Contrary to our results, no age-related differences have been found in WAIS-III Information performance in previous cross-sectional studies (Ryan et al., 2000). Our result could thus be related to a cohort effect derived from our recruitment procedure. Although we aimed to recruit a homogeneous sample in terms of education across age, older individuals have lower education in the study source population. Since the level of education attained and WAIS-III Information are strongly correlated, recruiting a sample with slightly lower education the older the age led to lower WAIS-III Information scores in older individuals.

The association between older age and increased depressive symptomatology has previously been reported (Fiske et al., 2003). To note, individuals with clinical depression and/or taking antidepressants were excluded from our study. Thus, this finding refers to depressive symptomatology within the normal range. The association between older age and higher scores in BDRS could be connected to increased depressive symptomatology, rather than functional difficulties. We observed that higher scores in BDRS were mainly explained by the "BDRS-changes in personality, interests, and drive" subscale, rather than the "BDRS-changes in performance of everyday activities" or "BDRS-changes in habits" subscales. The facts that FAQ showed no association with age, and that BDRS and depressive symptomatology were highly correlated with each other (data not shown), support this explanation. BDRS has also been shown to capture passive behavior as a result of decreased activity in normal aging (Hope, 1994).

The association between age and cognition was investigated in this study by analyzing a total of 73 cognitive measures covering a broad range of cognitive functions and multiple components within those functions. Of note, all these cognitive measures were analyzed simultaneously with OPLS, taking into account complex associations between them. Our findings demonstrated the strong association of age with memory, executive functions, processing speed, and visuoconstructive functions.

Executive functions and processing speed are commonly referred as the most vulnerable functions to aging (Keys and White, 2000; Tisserand and Jolles, 2003), and OPLS was able to capture that effect.

The association of age with memory is traditionally regarded as less strong than the association of age with executive functions and processing speed. Furthermore, it has been suggested that the association of age with memory could be influenced by the association of age with executive functions and processing speed (Fastenau et al., 1996). However, some studies have shown a significant residual association of age with memory after statistical control of processing speed and other relevant covariates (Salthouse, 1996a,b). Other studies have reported a less prominent residual association of age with memory (Hultsch et al., 1990) or, indeed, no residual association (Fastenau et al., 1996). To investigate whether the strong association of age with memory in this study was a result of using OPLS, we applied other 2 common multivariate methods (i.e., random forest and multiple linear regression), as well as univariate methods in a simplified set of variables (data shown in Appendix C—Supplementary Results). Both multiple regression and random forest showed that the strong association of age with visual memory remained after including sex, WAIS-III information, processing speed, and executive functions in the models. The same finding has been obtained in similar studies (Fastenau et al., 1996; Hultsch et al., 1990; Salthouse, 1996b). Thus, the statistical method does not seem to completely account for this finding. Another explanation could be related to the test used to measure visual memory in our study. Many of the previous studies have used the Benton Visual Retention Test (Benton, 1954), or similar, which represents immediate recall and has a strong visuoperceptive component. In contrast, the memory component reflected in our OPLS model, that is, delayed recall, is known to have a stronger association with age than immediate recall (Davis et al., 2003). On top of this, age has shown a stronger association with visual memory when compared to verbal memory (Haaland et al., 2003). Therefore, the fact that most of the previous studies have focused on verbal memory, and those that investigate visual memory have preferentially focused on immediate recall, could explain why our finding is less common in the literature. We cannot exclude that our finding may also be related to our cohort, and replication in other independent cohorts is important. Given that previous literature has put less attention to delayed recall of visual memory, our study suggests that this component is important and should be taken into account in future aging studies.

Finally, visuoconstructive functions were also among the measures showing a strong association with age, which has been shown in a previous study from our group conducted in a younger subsample (Ferreira et al., 2014). Age-related decline of visuoconstructive functions is well documented (Kaufman and Lichtenberger, 2006), even when the influence of processing speed or education is accounted for (Bugg et al., 2006; Ryan et al., 2000).

Concerning the MRI measures, age showed a strong association with (ordered by importance) thickness in association regions of the frontal and parietal cortex; volume of white-matter tissue adjacent to these frontal and parietal cortical regions; volume of white-matter tissue in deep and periventricular regions, as well as adjacent to the hippocampus; volume of the lateral and third ventricles; and volume of subcortical structures such as hippocampus and thalamus. In addition, older age was also strongly associated with a higher burden of WMH. These results are consistent with previous studies showing that frontal regions are more vulnerable to aging (Fjell et al., 2009, 2014; Kennedy and Raz, 2009). Some studies have also reported an age effect on posterior brain regions (Salat et al., 2004; Ziegler et al., 2010). Our findings are also consistent with studies indicating age effects in several subcortical structures, mainly the hippocampus and thalamus (Fjell et al., 2009; Raz et al., 2004; Walhovd et al., 2011). A higher burden of WMH and decrease of white-matter volume in frontal and temporal regions, as well as in deep and periventricular white matter have also been consistently associated with age in previous studies (Kennedy and Raz, 2009; Raz et al., 2005). Finally, previous studies have also shown increased lateral and third ventricles with aging (Goodro et al., 2012; Walhovd et al., 2011). Thus, our MRI findings perfectly align with the previous literature. The main contribution and novelty of the present study is the investigation of all these different measures in a combined hierarchical model, thus exploring the multivariate association between cortex, subcortical structures, white matter regions, WMH, and the ventricles. In summary, age showed a strong association with cortical thickness, followed by regional white matter volumes, the ventricular system, and certain subcortical gray matter structures. Cortical volume and surface area were the MRI measures less strongly associated with age, as in a previous study (Lemaitre et al., 2012).

The hierarchical model including the demographic-clinical, cognitive, and MRI dimensions is, to our knowledge, the first of this kind in a study of cognitive aging. The advantage of this analysis is the study of complex associations between these dimensions in a simultaneous and integrated manner. Our finding indicates that the strongest association of age occurs with MRI measures, followed by cognitive measures and, finally, the clinical measures. These dimensions are indeed correlated with each other, showing a strong association between MRI measures and cognition, a moderate association between cognition and clinical measures, and a weak association between MRI measures and clinical measures. This hierarchy and these correlations likely reflect the primary age effect on the neural substrate that leads to the age-related decline in cognition (Reuter-Lorenz and Cooke, 2016). Indeed, in a previous study using a small subsample, we demonstrated that the association between age and cognition is mediated by age-related differences in gray matter (Ferreira et al., 2014). To note, protective and compensatory processes are still capable of maintaining cognitive performance within the normal range during this stage (Arenaza-Urquijo et al., 2015), despite age-related changes in the neural substrate. We previously demonstrated also in this cohort that higher reserve buffers the effect of cortical thinning on cognition (Ferreira et al., 2016). Thus, the association of age and clinical measures of functional impairment (i.e., activities of daily living) is subtle in this cohort. This is reflected in our hierarchical model and subsequent correlation analyses with the demographic-clinical dimension showing the weakest association with age. This weak association of age with clinical measures was anticipated given that only cognitively healthy individuals were included in the present study. This temporal succession of events where the effect of age on brain integrity has an impact on cognition and this eventually affects clinical status is amplified and evident in neurodegenerative disorders such as Alzheimer's disease (Jack et al., 2013), in contrast to healthy aging (Walhovd et al., 2014).

Sex and crystallized intelligence are widely considered as extraneous variables when investigating the effect of age on cognitive performance and brain structure (Proust-Lima et al., 2008). We performed several analyses to explore the possible contribution of sex and the WAIS-III Information subtest (as an indicator of crystallized intelligence) in the cognitive and MRI OPLS models. None of the results discussed above changed after accounting for these variables, further supporting the use of advanced multivariate approaches such as OPLS in studies of this kind. However, univariate analyses are more vulnerable to the effect of these extraneous variables as often shown in previous studies where statistical control of sex and education/crystallized intelligence changed the results (Ganguli et al., 1991) (please also see the Appendix C—Supplementary results).

This study has several strengths. The sample includes a large group of healthy individuals with a comprehensive variety of demographic, clinical, cognitive, and MRI data. Furthermore, aging is studied and conceptualized from a dimensional and lifespan perspective (Walhovd et al., 2014). Different relevant dimensions were investigated in this cohort spanning individuals from 35 to 85 years of age. Finally, since very few, if any, variables exist in isolation (Salthouse, 2009), the multivariate technique implemented in the present study may be an optimized statistical approach in cognitive aging to investigate associations between different cognitive functions, compensatory processes, and extraneous variables. OPLS seems a suitable data-driven method to generate new hypotheses and theories to be tested in future research.

Some limitations should also be considered. OPLS is a linear method, but some of the variables investigated in this study may have a nonlinear association with age. To investigate how OPLS handles nonlinear associations, we also conducted OPLS models with the squared age as the criterion variable. Comparable results were obtained (age: $Q^2 = 0.564$, $R^2 = 0.620$; age^2: $Q^2 = 0.573$, $R^2 = 0.631$; paired t-test, $t_{(459)} = 1.093$, $p = 0.275$). Additional analyses investigating whether the linear or quadratic relation of age with cognitive variables would modify the model goodness of fit showed that OPLS was capable to handle nonlinear associations (data not shown). Other groups have reached similar conclusions (Fonville et al., 2011). Another limitation is that our analyses are based on cross-sectional data. Our hierarchical and correlation findings fit well in the temporal ordering of events previously described in both normal and pathological aging (Iturria-Medina et al., 2016; Jack et al., 2013; Walhovd et al., 2014). Within this context, our findings could be interpreted as a primary age effect on brain integrity, that has an impact on cognition, and this eventually affects clinical status. However, longitudinal analyses are warranted to substantiate our current findings. In addition, cross-sectional designs might be susceptible to cohort effects related to generational influences. Since cohort effects are mainly related to differences in social and environmental influences, previous studies have tried to account for them by including key variables such as sex and crystallized intelligence as covariates to remove the influence of these factors. Our findings showed that sex and crystallized intelligence had minimal contribution to the tested models. However, cohort effects that are less closely related to sex and crystallized intelligence and are confounded with age might have remained in our models because OPLS extracts the variance of the predictive variables

toward the age variable. This would be the situation for any other statistical method unless cohort effects can entirely be operationalized with proxies that are subsequently included in the models. Finally, we studied brain structural MRI measures, but investigating MRI connectivity measures such as diffusion tensor imaging and resting state in functional MRI are warranted in future studies.

5. Conclusion

The use of multivariate methods (i.e., OPLS) and hierarchical analyses revealed a strong association of age with the brain structure, followed by a fairly strong association with cognitive performance, and a very modest association with the clinical status of healthy individuals from 35 to 85 years of age. A novel finding is the strong association of age with visual memory. This finding accompanied the strong association of age with executive functions and processing speed, which has frequently been reported in previous aging studies. Our results also help to further clarify previous contradictory results concerning episodic memory. If these findings are replicated in other independent cohorts, this methodology could help to refine and update the understanding of cognitive aging, in which cognitive functions are interrelated with each other and are modulated by risk and protective factors. Thus, future studies are warranted to further explore the use of OPLS as an optimal method to better understand and disentangle complexity in cognitive aging. Such knowledge will not be trivial, and we anticipate it will be relevant for the early diagnosis, prognosis, and prevention of pathological aging, especially relevant when new disease-modifying treatments are available.

Disclosure statement

All the authors declared no conflict of interest relevant to the current study.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.neurobiolaging.2018.07.017.

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