Brain structure and phenotypic profile of superagers compared with age-matched older adults: a longitudinal analysis from the Vallecas Project

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Summary

Background Cognitive abilities, particularly memory, normally decline with age. However, some individuals, often designated as superagers, can reach late life with the memory function of individuals 30 years younger. We aimed to characterise the brain structure of superagers and identify demographic, lifestyle, and clinical factors associated with this phenotype.

Methods We selected cognitively healthy participants from the Vallecas Project longitudinal cohort recruited between Oct 10, 2011, and Jan 14, 2014, aged 79·5 years or older, on the basis of their delayed verbal episodic memory score. Participants were assessed with the Free and Cued Selective Reminding Test and with three non-memory tests (the 15-item version of the Boston Naming Test, the Digit Symbol Substitution Test, and the Animal Fluency Test). Participants were classified as superagers if they scored at or above the mean values for a 50–56-year-old in the Free and Cued Selective Reminding Test and within one standard deviation of the mean or above for their age and education level in the three non-memory tests, or as typical older adults if they scored within one standard deviation of the mean for their age and education level in the Free and Cued Selective Reminding Test. Data acquired as per protocol from up to six yearly follow-ups were used for longitudinal analyses.

Findings We included 64 superagers (mean age 81·9 years; 38 [59%] women and 26 [41%] men) and 55 typical older adults (82·4 years; 35 [64%] women and 20 [36%] men). The median number of follow-up visits was 5·0 (IQR 5·0–6·0) for superagers and 5·0 (4·5–6·0) for typical older adults. Superagers exhibited higher grey matter volume cross-sectionally in the medial temporal lobe, cholinergic forebrain, and motor thalamus. Longitudinally, superagers also showed slower total grey matter atrophy, particularly within the medial temporal lobe, than did typical older adults. A machine learning classification including 89 demographic, lifestyle, and clinical predictors showed that faster movement speed (despite no group differences in exercise frequency) and better mental health were the most differentiating factors for superagers. Similar concentrations of dementia blood biomarkers in superager and typical older adult groups suggest that group differences reflect inherent superager resistance to typical age-related memory loss.

Interpretation Factors associated with dementia prevention are also relevant for resistance to age-related memory decline and brain atrophy, and the association between superageing and movement speed could provide potential novel insights into how to preserve memory function into the ninth decade.

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Introduction

Episodic memory, the memory of personal life experiences, is one of the cognitive domains that is most vulnerable to age-related deterioration.[1] Whereas neurodegenerative diseases such as Alzheimer's disease are often accompanied by a severe decline in episodic memory, some reduction in episodic memory performance is also expected as a part of normal ageing. However, some older adults—often termed superagers—appear to resist this age-associated decline, and instead show an episodic memory that is at least as good as that of healthy adults 20–30 years younger.[2–8]

A comprehensive characterisation of the mechanisms underlying the preservation of episodic memory function in superagers does not currently exist. One central question is whether superageing reflects a resistance or resilience to dementia or age-related processes. In the typical context of dementia,[9] the term resistance refers to the avoidance of disease, whereas resilience is understood as successfully coping with disease. However, if both superager and control groups are free of neurodegenerative biomarkers, the same framework can be used to describe ageing processes in the absence of neuropathology. Thus, in a healthy ageing context, and

Research in context

Evidence before this study

We searched PubMed on Jan 17, 2022, using the terms "superager" or "supernormal" or "superior memory" in English. Many studies have assessed successful ageing of episodic memory with slightly different criteria, but we focused predominantly on those using the superager criteria in populations older than 80 years with available brain neuroimaging data. The brain signature of superagers has been explored cross-sectionally and longitudinally in small samples, showing evidence for a slower total grey matter volume atrophy in superagers.

Added value of this study

To our knowledge, this is one of the largest superager longitudinal cohorts aged 80 years or older. This study contributes to the field with a detailed characterisation of longitudinal brain changes and the demographic, lifestyle, and clinical factors associated with superageing.

Implications of all the available evidence

The brain structural signature and clinical and lifestyle factors associated with the superageing phenotype probably reflect a resistance to age-related memory decline, and these factors overlap with those associated with dementia prevention. Additionally, the connection between preserved memory performance and motor function in people older than 80 provides novel insights into how to promote resistance to age-related memory loss. Taken together, the identified factors associated with superageing can inform the design of intervention trials to promote healthy ageing of episodic memory.

throughout this Article, resistance refers to an avoidance of typical age-related memory decline and translates, in terms of brain structure, to the preservation of memory-related areas in superagers. By contrast, resilience refers to successfully coping with ageing effects, and implies a brain structure that is similar between superagers and normally ageing peers.

Previous neuroimaging studies have shown that superagers have larger hippocampal volumes,[4,6] thicker anterior cingulate cortices,[2,3,10] and slower cortical atrophy[7] than do typical older adults. Previous studies also explored the association between superager status and some lifestyle factors, such as satisfaction with social relationships.[11] However, most studies had small sample sizes and were cross-sectional in nature, hindering distinction between long-standing structural differences and differential atrophy rates in superageing brains compared with normal ageing brains. One approach to obtaining larger samples of deeply phenotyped (a cohort of participants with a rich set of different variables, including data for clinical history, lifestyle, neuroimaging data, etc) superagers with longitudinal data is to investigate large longitudinal ageing cohorts. We applied this approach to the Vallecas Project longitudinal study aiming, first, to characterise superagers' cerebral grey matter volume, cross-sectionally and longitudinally, relative to that of age-matched typical older adults; and second, to apply machine learning to identify which demographic, lifestyle, and clinical variables are the greatest differentiating factors between superagers and typical older adults. We hypothesised, first, that the superager phenotype is part of the normal ageing spectrum, and that the amounts of Alzheimer's disease and neurodegeneration blood biomarkers in this group would be similar to that of typical older adults, with both groups showing resistance to Alzheimer's disease and neurodegeneration; second, that the superager phenotype would be associated with grey matter preservation in memory-related areas of the medial temporal lobe and adjacent limbic structures, as well as cholinergic nuclei, showing a mechanism of resistance to normal memory decline; and third, that the superager phenotype would be associated with lifestyle factors that promote better cognitive performance in ageing (eg, physical activity, educational attainment, and socioeconomic status).[12–15]

Methods

Data source

All individuals included in this analysis were selected from the single-centre, community-based Vallecas Project established in Madrid, Spain—an ongoing longitudinal study cohort of White, community-dwelling individuals aged 70–85 years, independent in activities of daily living, with a survival expectancy of at least 4 years, and without any neurological or psychiatric disorders.[16] The Vallecas Project study was originally designed for one baseline visit and four annual follow-up visits to investigate risk factors leading to cognitive impairment, but was subsequently extended by an additional 4 years for a total of eight annual follow-up visits, with the extension approved in March, 2016. At each yearly visit, demographic and lifestyle data were collected, neuropsychological and clinical assessment and multisequence MRI scanning were performed, and blood samples were collected for measurement of blood dementia biomarkers and genetic analysis. All participants provided written informed consent, and the project was approved by the Ethics Committee of the Instituto de Salud Carlos III, Madrid, Spain.

Participant selection

We based our definition of superagers on the Northwestern criteria described by Harrison and colleagues,[2] defining a superager as a person aged 80 years or older with the episodic memory of a healthy

person 20–30 years younger; no definition of superager was specified in the original study protocol. Of note, the Northwestern criteria uses reference values for adults aged 50–65 years, whereas we used reference values for adults aged 50–56 years. Furthermore, we used the Free and Cued Selective Reminding Test[17] (instead of the Rey Auditory Verbal Learning Test used in the Northwestern criteria) to assess episodic memory, and the Digit Symbol Substitution Test (instead of the Trail Making Test Part B used in the Northwestern criteria) in non-memory assessments.

Participant selection criteria for this analysis were grouped into five categories, all of which must be met: age; episodic memory function; cognitive performance in non-memory domains; MRI data availability; and stability of episodic memory. Participants in the Vallecas Project aged 79·5 years old or older were screened by free delayed recall performance on the verbal memory Free and Cued Selective Reminding Test. Participants performing at or above the mean of the score of adults aged 50–56 years with the same educational attainment met the requirement for superagers, and those performing within a normal range (within 1 SD from the mean of normative values from the Spanish NEURONORMA project[18]) for their age and educational attainment met the requirement for typical older adults.

Cognitive performance in non-memory domains was assessed with the Spanish-language version of three different tests: the 15-item version of the Boston Naming Test,[19] the Digit Symbol Substitution Test,[20] and the Animal Fluency Test (also known as Animal Naming Test).[21] Participants' performances were compared with normative values for their age and education group, and those scoring within or above 1 SD from the mean of their age in the three tasks fulfilled the criteria of superager. To be classified as superagers, participants had to fulfil the performance criteria above for both episodic memory and non-memory assessments.

Although the original Northwestern criteria[2,3] required typical older adults' performance to be within 1 SD from the mean of their age group in all three non-memory tasks, when this criterion was applied to our sample, the resulting control group was too small and thus unbalanced with the superager group. We therefore relaxed the criteria for control performance and created a larger control group without applying non-memory criteria. All analyses were done comparing the superagers with the larger control group of typical older adults, and then repeated using the smaller control group of typical older adults meeting Northwestern criteria (appendix 2 pp 9–10).

All participants underwent a structural MRI at the visit in which they fulfilled the previous criteria to be classified either as superagers or typical older adults. Finally, given the longitudinal nature of the study, stability of episodic memory performance was also included as a selection criterion. Participants from either group with changes in their memory classification (superager or typical older adult) over the course of the study were excluded to avoid the inclusion of participants whose memory performance improved as a result of practice, thus preventing participants that met the typical older adult criteria at early visits from meeting the superager criteria at subsequent follow-ups. We elected not to exclude participants who showed signs of mild cognitive impairment or dementia later in the study. Selection criteria were only applied from the second to sixth visits because the 15-item version of Boston Naming Test was not administered at baseline. The visit used for the cross-sectional analyses was adjusted to match in age the group of superagers and the group of typical older adults.

Additional investigations of neuropsychological variables, *APOE* genotyping, blood biomarkers, and MRI acquisition are shown in appendix 2 (p 2).

Analysis of grey matter volume

Grey matter volume analysis was done using the CAT12.7 toolbox[22] implemented in SPM12. Using a standard pipeline, T1-weighted images were bias-field corrected, then segmented[23] and spatially normalised using the DARTEL algorithm.[24] Grey matter volumes were generated after modulation of segmented normalised grey matter images. A longitudinal pipeline to estimate ageing effects in CAT12 that additionally considers deformations between timepoints was used, allowing the estimation and detection of the larger changes that usually occur during ageing. CAT12 provides a retrospective quality control framework for the empirical quantification of key image parameters, such as noise (ie, due to head motion), intensity inhomogeneities, and resolution, and combines these values into an overall image quality parameter. We only included data with an overall image quality of grade 3 or higher, as recommended by the CAT12 manual. Image outliers were identified by calculating a Spearman's rank correlation coefficient, which depends on the quality of the image processing and anatomic characteristics of each brain, ensuring that the segmentation is of sufficient quality and that the included data are homogeneous (ie, without outliers). Finally, the segmentations were smoothed with a Gaussian kernel of 6 mm (full width at half maximum). To guarantee that we only examined grey matter regions, we applied an absolute grey matter threshold of 0·1. For the cross-sectional analysis, total intracranial volume was introduced as a covariate. Self-reported sex was considered as a covariate but excluded from the final analysis because it did not change the model output. For the longitudinal analysis (scans from visit one to visit six were used), follow-up loss was handled by the general linear model used. Age at each visit was included in the model and no covariate was used. The corrected statistical threshold was set to $p<0·05$ and the threshold free cluster enhancement approach was implemented with default

For the **CAT12.7 toolbox** please see https://neuro-jena.github.io/cat

For the **SPM12 toolbox** please see https://www.fil.ion.ucl.ac.uk/spm

See **Online** for appendix 2

For the **TFCE toolbox** please see https://www.neuro.uni-jena.de/tfce

parameters (5000 permutations) using the threshold free cluster enhancement toolbox version r186 for SPM12. The Automated Anatomical Labelling Atlas 3,[25] was used to map thalamic nuclei. Cortical and subcortical volume measurements were derived from FreeSurfer and CAT12 for replication purposes (appendix 2 pp 2–3).

Random forest analysis

Participants were classified into superagers and typical older adults by random forest analysis,[26] a supervised learning method for classification, computed with a total of 89 predictors regarding demographics, lifestyle, and clinical variables (appendix 2 pp 2–3). Neuropsychological and brain imaging comparisons between superagers and typical older adults (as well as the subgroup of Northwestern-criteria typical older adults) were done, but the random forest model could not be estimated for the Northwestern-criteria typical older adults group due to the small sample size.

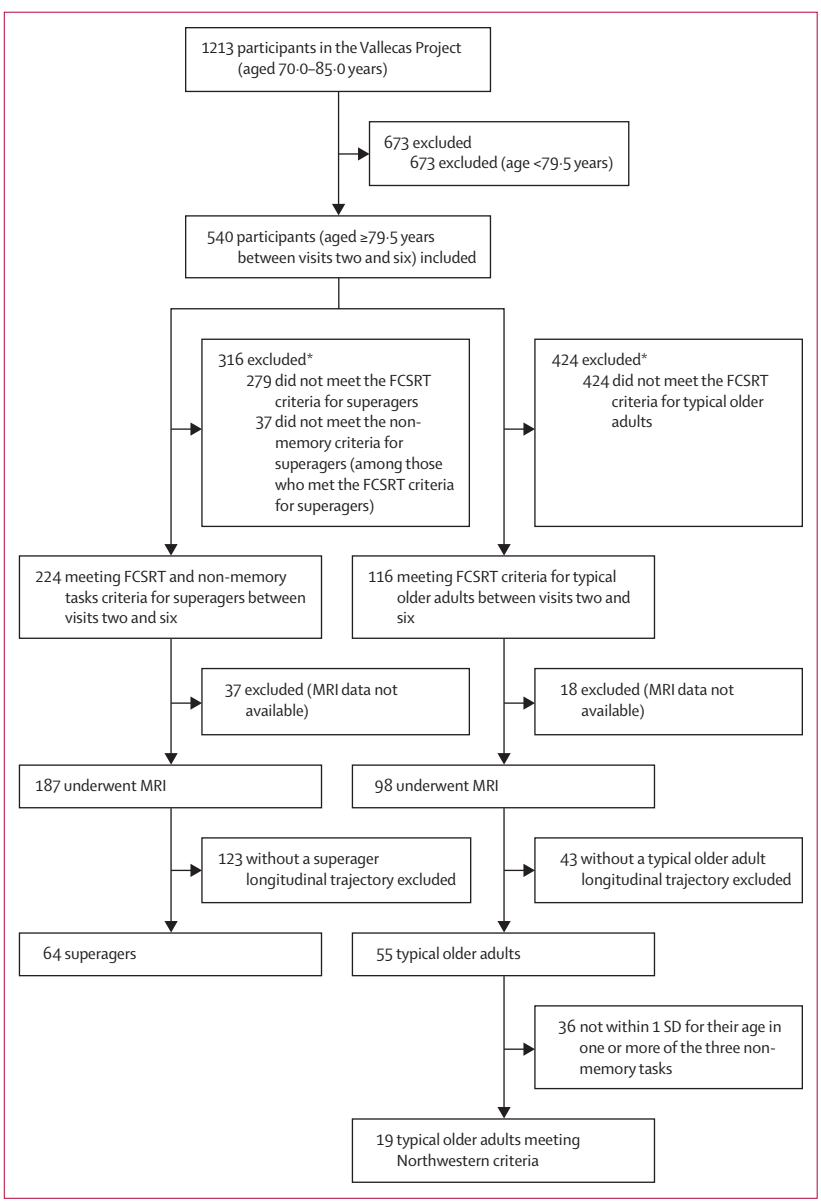

Figure 1: **Flow diagram of selection criteria**
FCSRT=Free and Cued Selective Reminding Test. *Both groups were examined using different and mutually exclusive reference values for the neuropsychological tests. Among the participants excluded from the superagers candidates, typical older adult candidates were found, and vice versa. Thus, the totals for exclusion do not equal 200.

Statistical analysis

All statistical tests not described above were performed in R software, version 3.5.1. χ^2 tests and Fisher's exact tests were used for comparisons of categorical data, and two-sample *t* tests and two-tailed Mann-Whitney *U* tests were used for continuous variables, with the significance level set at p=0·05. Log transformation was performed on blood biomarker variables to fit a normal distribution. To examine cross-sectional, between-group differences in total grey matter volume, an analysis of covariance model was done using total intracranial volume as a covariate. The false discovery rate method was used to correct for multiple comparisons.

Between-group longitudinal differences in grey matter volume were tested with a linear mixed model using R's lme4 package, a model that can handle missing data once participants are lost. Grey matter volume was adjusted by total intracranial volume and both measurements were extracted from the CAT12 pipeline. Group, scaled age, and the interaction between the two were introduced in the model as fixed effects. Participant intercept and scaled age slope were included as random effects.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Participants for the Vallecas Project study were recruited between Oct 10, 2011, and Jan 14, 2014, and we identified participants of interest between June 4, 2018, and Nov 4, 2019. We identified 64 superagers and 55 age-matched typical older adults (of which 19 [35%] meet Northwestern criteria) from the total 1213 participants in the Vallecas Project.[16] All superagers and typical older adults were 79·5 years or older when meeting the selection criteria (figure 1, table 1).

No significant differences in age or sex were noted between groups, but superagers had a significantly higher number of years of education than did typical older adults (table 1). None of the 119 participants had a diagnosis of mild cognitive impairment or dementia at the reference visit for cross-sectional analyses; however, six (11%) typical older adults developed mild cognitive impairment within 1 year of meeting inclusion criteria. Removing these participants from grey matter volume analyses did not change the group comparison results.

Although the *APOE* ε4 allele increases the risk of non-familial Alzheimer's disease (compared with the ε3 allele),[27] the ε2 allele is believed to be protective against Alzheimer's pathology.[28] Despite a previous suggestion that the ε4 allele is underexpressed in a cohort of 12 superagers,[10] we did not find a between-group difference in *APOE* gene allelic composition (table 2; appendix 2 p 11).

Concentrations of five blood biomarkers for neurodegeneration were assessed by single-molecule array, with no significant differences noted (table 2; appendix 2 p 11), no significant association between amyloid-β42 to amyloid-β40 ratio and phosphorylated tau and grey matter volume in the whole cohort, and no interaction between blood biomarker concentrations and group (data not shown).

Grey matter volume was analysed cross-sectionally and longitudinally over 5 years with yearly follow-up scans, which also included scans in some superagers and typical older adults before their 80th birthday (MRI scans conducted before the visit used for cross-sectional analyses are available as the selection criteria were applied from visits 2 to 6). The median number of follow-up visits was 5·0 (IQR 5·0–6·0) for superagers and 5·0 (4·5–6·0) for typical older adults. At cross-sectional analysis, superagers had a larger total grey matter volume than did typical older adults (table 1; appendix 2 pp 9–10, 12). Longitudinal analysis, using the linear mixed model, of total grey matter volume showed a significant effect of group (coefficient b –11·9 [SE 4·9]; p=0·015) and age (–7·5 [SE 1·1]; p<0·0001), as well as a group-by-age interaction (–4·1 [SE 1·7]; p=0·015). Typical older adults showed a faster decline in grey matter volume across time (–11·6 cm³ per standard deviation of scaled age [SE 1·1]) than did superagers (–7·5 cm³ per standard deviation of scaled age [1·1]; figure 2A; appendix 2 pp 4–5, 14–20) indicating a slower rate of total grey matter atrophy in superagers than in typical older adults. Inspection of linear fit of the atrophy rate of each group showed similar total grey matter volumes at the age of 75 years for both superagers and typical older adults, with the differences becoming more evident with advancing age (figure 2A).

We next explored whether the differences in total grey matter volume were localised to specific brain areas by

	Superagers (n=64)	Typical older adults (n=55)	Mean difference (95% CI)	Group comparison test statistic	p value for the mean or distribution difference	False discovery rate p value
Age, years	81·6 (80·4–83·1)	82·1 (81·3–83·0)	–0·5 (–1·2 to 0·2)	–1·5*	0·13*	0·16
Sex						
Women	38 (59%)	35 (64%)	..	–0·1†	0·77†	0·83
Men	26 (41%)	20 (36%)	..	–0·1†	0·77†	0·83
Education, years	16·0 (10·0–19·0)	10·0 (6·0–17·5)	2·9 (0·5 to 5·4)	2·4*	0·019*	0·026
Neuropsychological selection criteria variables						
Free and Cued Selective Reminding Test free delayed recall score	13·0 (12·0–14·25)	7·0 (5·0–8·0)	6·9 (6·3 to 7·4)	25·5*	<0·0001*	<0·0001
Animal Fluency Test total score	21·2 (4·8)	15·9 (4·1)	5·3 (3·7 to 6·9)	6·5*	<0·0001*	<0·0001
Digit Symbol Substitution Test total score	21·2 (6·1)	15·3 (5·8)	5·9 (3·8 to 8·1)	5·4*	<0·0001*	<0·0001
15-item Boston Naming Test total score	14·0 (13·0–15·0)	12·0 (9·0–13·5)	2·3 (1·6 to 3·1)	6·1*	<0·0001*	<0·0001
Other neuropsychological variables (not used for selection)						
Mini Mental State Examination total score	29·0 (28·8–30·0)	28·0 (27·0–29·0)	1·3 (0·7 to 1·8)	4·7*	<0·0001*	<0·0001
Functional Activities Questionnaire total score	0·0 (0·0–0·0)	0·0 (0·0–1·0)	–0·4 (–0·7 to –0·1)	3·0*	0·0033*	0·0050
Rey-Osterreith Complex Figure delayed recall score	15·5 (4·3)	10·4 (5·2)	5·1 (2·2 to 7·9)	3·6*	<0·0001*	<0·0001
Lexical Fluency with the letter P total score	17·1 (4·4)	12·8 (4·3)	4·3 (2·7 to 5·9)	5·3*	<0·0001*	<0·0001
National Adult Reading Test (Spanish) total score	56·0 (48·0–58·3)	50·0 (40·0–56·0)	6·5 (2·4 to 10·5)	3·2*	0·0023*	0·0038
Brain volumetry						
Total intracranial volume, cm³	1400·06 (156·42)	1404·99 (155·51)	–4·1 (–61·1 to 52·9)	–0·1*	0·89*	0·89
Grey matter volume, cm³	523·09 (42·05)	511·64 (43·35)	11·5 ($6·03 \times 10^{-3}$ to 1·0)	6·3‡	0·013‡	0·020

Data are median (IQR), n (%), or mean (SD). *Comparisons done with *t* test (numerical data). †Comparisons done with a χ^2 test (categorical data). ‡Comparisons done with ANOVA *F*-test.

Table 1: **Demographic, neuropsychological, and brain volume differences between superagers and typical older adults**

	Superagers (n=64)	Typical older adults (n=55)	Mean difference (95% CI)	Group comparison test statistic	p value for the mean or distribution difference	False discovery rate p value
***APOE* alleles**						
ε2, ε3	7 (11%)	10 (18%)	..	..	0·47*	0·86
ε3, ε3	47 (73%)	37 (67%)	..	..	0·47*	0·86
ε3, ε4	10 (16%)	7 (13%)	..	..	0·47*	0·86
ε4, ε4	0	1 (2%)	..	..	0·47*	0·86
Blood biomarkers of neurodegeneration						
Amyloid-β42 to amyloid-β40 ratio, pg/mL	–2·74 (0·26)	–2·79 (0·24)	0·05 (–0·04 to 0·14)	–1·09†	0·28†	0·86
Total tau, pg/mL	0·91 (0·41)	0·91 (0·24)	0·00 (–0·12 to 0·12)	–0·04†	0·97†	0·97
Phosphorylated tau 181, pg/mL	1·41 (0·96–1·93)	1·37 (0·95–2·06)	..	–0·21‡	0·84‡	0·97
Phosphorylated tau 181 to amyloid-β42 ratio	0·12 (0·08–0·18)	0·12 (0·09–0·20)	..	–0·75‡	0·45‡	0·86
Glial fibrillary acidic protein, pg/mL	5·08 (0·64)	5·16 (0·69)	–0·08 (–0·33 to 0·16)	–0·69†	0·49†	0·86
Neurofilament light polypeptide, pg/mL	2·78 (0·49)	2·74 (0·69)	0·03 (–0·25 to 0·19)	0·31†	0·76†	0·97

Data are n (%), mean (SD), or median (IQR). Amyloid-β42, amyloid-β40, total tau, and tau phosphorylated at threonine 181 were measured in plasma. Glial fibrillary acidic protein and neurofilament light polypeptide were measured in serum. *Fisher's test. †t test (for biomarkers that followed a normal distribution after log-transformation). ‡Mann-Whitney *U* test (for biomarkers that did not followed a normal distribution after log-transformation, original values and not log-tranformed were used in the test).

***Table 2:* *APOE* genotype and neurodegenerative blood biomarkers in superagers and typical older adults.**

doing a cross-sectional MRI analysis of grey matter volume with a whole-brain approach. Superagers had greater grey matter volume than did typical older adults in the bilateral thalamus, basal forebrain, angular gyrus, and regions within the medial temporal lobe, including bilateral effects on grey matter volume in the hippocampus, amygdala, entorhinal cortex, parahippocampal gyrus, and fusiform gyrus (family-wise error-corrected p<0·05; figure 2B; appendix 2 pp 4–5, 14–20). Grey matter volume differences were observed in multiple nuclei within the thalamus (figure 2B), but notably not the anterior nucleus, which is the thalamic nucleus most implicated in memory function.[29,30] Instead, grey matter volume differences were greatest in the ventral lateral nucleus, a major component of the motor thalamus,[31] as well as in the lateral dorsal nucleus, part of the limbic thalamus.[32] Given the difference in years of education between superagers and typical older adults, we repeated the model adjusting for years of education, with no difference in the results (data not shown). Cortical thickness findings consistent with previous literature were found (appendix 2 p 7).

The slower superager atrophy in total cortical volume prompted us to examine region-specific longitudinal changes in grey matter volume over the 5 year follow-up period. Brain loci showing slower grey matter volume loss over time in superagers than in typical older adults included the bilateral hippocampus, entorhinal cortex, parahippocampal gyrus, left amygdala, bilateral basal forebrain, caudate nucleus, anterior insula, and right posterior cingulate cortex (family-wise error-corrected p<0·05; figure 2C; appendix 2 pp 4–5, 14–20). This between-group difference in atrophy rate is illustrated by plotting volume trajectories from left hippocampus and right parahippocampal gyrus (figure 2C; appendix 2 pp 4–5). For this measure, superagers and typical older adults have a visibly similar status around the age of 75 years (figure 2D); however, memory superiority in superagers is evident before structural brain differences (appendix 2 p 8). Consistent neuroimaging findings were found comparing superagers with Northwestern-criteria typical older adults (appendix 2 pp 4–5, 9–11).

A random forest machine learning approach was used to identify the demographic, lifestyle, and clinical variables that best distinguished superagers from typical older adults. With 89 variables, the model reached a discrimination accuracy of 66·4% (68·8% sensitivity and 63·6% specificity). Each variable's importance for classification as a superager and associated p value is shown in figure 3 (appendix 2 pp 21–22).

Superagers' superior performance in the timed up-and-go test and the finger tapping test with the dominant hand suggest that, in addition to exceptional memory, superagers have better mobility, agility, and balance than do typical older adults (appendix 2 pp 23–45). This association between episodic memory and better mobility is supported by the significant correlation between Free and Cued Selective Reminding Test free delayed recall score and timed up-and-go test (r –0·39; p<0·0001; table 1). Despite these differences in motor function, we found no significant differences in the self-reported exercise frequency between groups (appendix 2 pp 23–45). Superagers also had better self-reported mental health and lower scores in the State-Trait Anxiety Inventory and in the Geriatric Depression Scale than did typical older adults (appendix 2 pp 23–45). On the depression scale, both superagers (mean 1·13 [SD 2·06]) and typical older adults (2·72 [3·06]) had average scores of 5 or less out of a possible score of 15, a frequently used low cutoff point for diagnosing depression.[33,34] Superagers complained

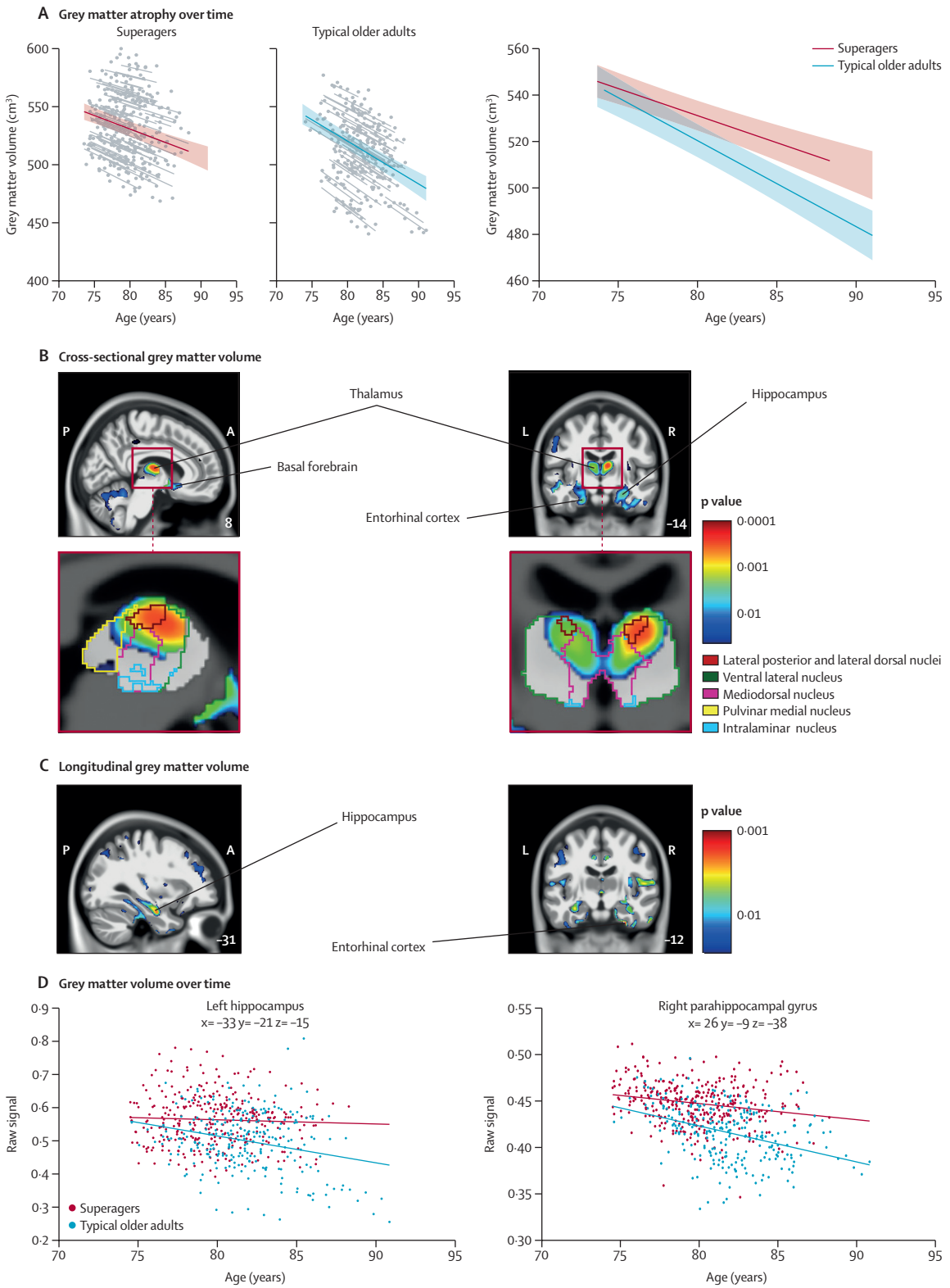

Figure 2: **Neuroanatomical differences between superagers (n=64) and age-matched typical older adults (n=55)**

Grey matter atrophy rates, individual trajectories and means (left) and means only (right). Shaded areas depict 95% confidence intervals. (A) Colourmaps of cross-sectional differences in grey matter volume. Figure insets show the thalamic nuclei where grey matter volume is greater in superagers than in typical older adults. Anatomical demarcations from the Automated Anatomical Labelling Atlas 3; family-wise error-corrected p<0·05; p values overlaid on sagittal and coronal sections. (B) Colourmaps of longitudinal differences in grey matter volume, showing slower grey matter volume loss in superagers than in typical older adults over time. Significant group by time interaction; family-wise error-corrected p<0·05; p values overlaid on sagittal and coronal sections. (C) Grey matter volume over time in two representative voxels (left hippocampus and right parahippocampal gyrus) showing the group mean and individual observations. (D) Section coordinates refer to standard MNI space and are given in mm. A=anterior. L=left. P=posterior. R=right. MNI=Montreal Neurological Institute.

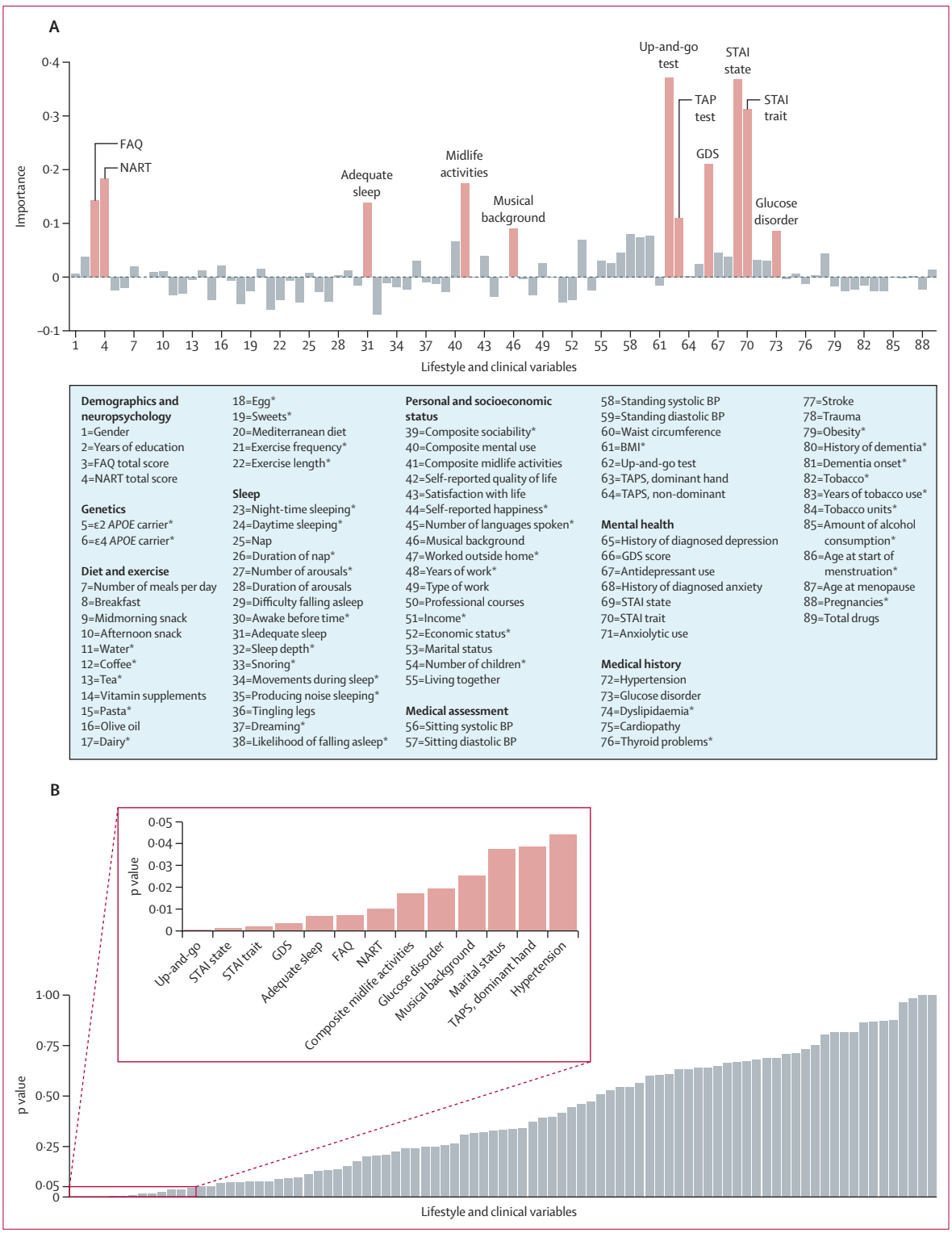

Figure 3: **Contributions of lifestyle and clinical variables to the classification of superagers**
Importance of the 89 variables included in the model. Variables with highest importance for superager classification are highlighted (red); negative importance values (marked with an asterisk) have no beneficial contribution to the superager classification of the predictive model. (A) Variables plotted by p value of importance. (B) Further details about all the variables included in this analysis are shown in appendix 2 (pp 21–45). BP=blood pressure. FAQ=Functional Activities Questionnaire. GDS=Geriatric Depression Score. NART=National Adult Reading Test (Spanish version). STAI=State-Trait Anxiety Inventory, where state reflects how an individual currently feels, and trait is how they generally feel. TAPS=finger tapping test.

less frequently about not getting enough sleep than did typical older adults, despite no differences in self-reported sleep duration (6·84 h [SD 1·29] for superagers, 6·64 h [1·30] for typical older adults; appendix 2 pp 23–45). Superagers were less likely to have a history of glucose disorders and hypertension, and were more likely to have a more active lifestyle during midlife and a higher musical background (either formal or not) than did typical older adults (appendix 2 pp 23–45). The proportion of separated or divorced individuals was higher in the superager group than in the typical older adults group (appendix 2 pp 23–45), regardless of gender. Superagers had higher independence in activities of daily living and a higher score in the National Adult Reading Test (appendix 2 pp 23–45).

Discussion

Our findings illustrate marked differences, both in brain structure and in multiple clinical and lifestyle features, between superagers and a healthy control group with normal memory function for its age range. The two groups show no differences in *APOE* ε4 frequency, the major genetic risk factor for non-familial Alzheimer's disease, nor in blood biomarkers of dementia,[35] which is consistent with previous studies reporting no difference in amyloid burden between superagers and typical older adults.[6,36,37] The observed between-group differences are therefore likely to reflect a superager resistance to age-related memory decline, rather than two groups at different points of a dementia-related process.

One possible explanation for preserved brain structure in the superager phenotype is that these individuals are born with larger brains, which results in an age-related atrophy that is less evident than that of typical older adults. However, superagers show a reduced rate of atrophy in the entire brain cortex and circumscribed memory-related areas, such as the anterior[38] hippocampus and the cholinergic basal forebrain. Reduced atrophy in the hippocampus and basal forebrain, taken together with previous reports of lower acetylcholinesterase activity in the cortical pyramidal neurons of superager brains assessed post-mortem,[39] could indicate an enhanced effect of acetylcholine on hippocampal and cortical neurons in superageing. Our finding of a slower rate of total grey matter atrophy in superagers than in age-matched typical older adults is also in accordance with previous observations.[7] However, our 5 years of longitudinal study show that the values for total grey matter volume and focal grey matter volume appear to be equivalent in both groups around the age of 75 years. Furthermore, memory performance is superior in superagers than in typical older adults before this age, suggesting a lag between declining cognitive abilities and visible atrophy, or that other factors beyond maintained brain structure, such as functional properties, underlie a superager memory phenotype before the age 75 years.[40]

The observation that grey matter volume in the motor thalamus (one of the thalamic groups that atrophies less in normal ageing) is preserved in superageing[41] has also been associated with faster episodic memory learning[42] and concurs with our classification analysis, that highlights the importance of finger tapping and timed up-and-go tests in identifying a superager status. Gait speed, balance, and finger tapping are slower in patients with mild cognitive impairment and Alzheimer's disease than in typical older adults.[43–45] We have shown that superagers are faster in both gait speed and finger tapping than a control group with similar concentrations of blood biomarkers for neurodegenerative disease, suggesting that movement speed is associated with better memory, even in the absence of an evident dementia process. Although superagers self-report exercise frequencies similar to that reported by typical older adults, their faster movement speed could reflect a greater engagement in non-exercise physical activity (eg, climbing stairs or gardening),[46] although further assessment of physical activity through an objective and measurable approach would be needed to increase the generalisability of the findings. The potential mechanisms through which physical exercise can improve cognition (or prevent dementia) include indirect effects on other modifiable risk factors (eg, cardiovascular fitness, obesity, insulin resistance, hypertension, dyslipidaemia) and direct effects on the brain, such as increased cerebral blood flow and expression of brain-derived neurotrophic factor.[47] However, the direction of the association could also possibly be in the opposite direction (ie, better brain health might be responsible for the faster speed of movement).

Of the four most important variables for classification of the superager phenotype, three were related to mental health: the two questionnaires for anxious state and anxious trait and the Geriatric Depression Scale—in all of which superagers show better mental health than do typical older adults. An episode of depression or anxiety can impair performance on a memory test in both younger (mean age 38·4 years [SD2·5])[48] and older adults (65–94 years, mean 73·6 [SD 6·0]).[49] In the long term, a history of depression and anxiety is not just a risk factor[50,51] but also a symptom[52] of dementia. Previous work on superageing has shown that superagers are more resilient than typical older adults to post-operative delirium,[53] a condition with multifactorial causes and that can be aggravated by existing depression.[54]

Our classification model highlights other variables that provide further insights into activities that could optimise memory function into the ninth decade. Superagers complain less frequently about not getting enough sleep, although self-reported sleep duration was not found to be important in our classification model. Self-reported sleep duration shows an inverted U-shaped association with global cognitive decline in ageing,[55] but the average sleep duration for both superagers and typical older adults is within the non-deleterious range. The classification model

highlighted musical background as a differentiating factor between groups, with superagers being more likely to have either a formal or amateur musical background than typical older adults. This finding is in keeping with reports that early-life to midlife formal musical training is associated with improved late-life episodic and semantic memory[56] and with larger grey matter volume.[57]

Previous research has found an association between satisfaction in social relationships and superageing,[58] with superagers reporting satisfying, high-quality relationships. Our classification model did not ascribe significant importance to a composite social variable that included frequency of interactions with family and friends, feelings of solitude, and leisure activities. We did, however, observe an effect of marital status without gender differences. Being married or cohabiting with a partner is typically associated with better cognitive health later in life,[13,59–61] but in our study cohort, superagers were more likely than typical older adults to be separated or divorced. These discrepancies between our results and previous literature could be explained by the different dependence of social relations in various cultures.[62]

Having more years of formal education is commonly associated with the construct of cognitive reserve, and consequently with a reduced risk of dementia.[13,63] Years of education did not, however, reach significant importance in classifying superagers. Although superagers had more years of education than individuals in the group of 55 typical older adults, comparing education attainment in superagers and in the 19 Northwestern-criteria typical older adults showed no significant difference (appendix 2 pp 9–10). The superager memory phenotype is therefore unlikely to be a product of more years of education, although this variable might influence performance on non-memory tasks.

As with any observational study, causality of the factors reported here and superageing cannot be inferred. The identification of a causal relationship would require intervention trials involving, for example, prescribed activities to promote movement speed, tight control over psychiatric symptoms, promoting awareness of the benefits of musical training, and activities that improve perceived sleep quality.[64] Any physical or psychiatric interventions might, however, have to be implemented in or before midlife. Aerobic exercise interventions in healthy older adults do not appear to yield cognitive benefit even when the intervention leads to improved cardiorespiratory fitness,[65] and psychiatric symptoms can accelerate ageing from early midlife.[66] We also acknowledge that, despite introducing 89 variables into our statistical model, the classification accuracy of 66·4% indicates that further variables, possibly including genetic factors,[14] are associated with the superageing phenotype. The hypothesis that a potential overlap exists between a genetic basis for superageing and muscle phenotypes for fast movements in older adults[67] could help to direct further research in the topic.

Contributors
MG-P, LZ, and BAS conceptualised the study. MG-P, CG, LZ, JT, and MM developed the methods. MG-P, CG, LZ, and JT did the investigation with supervision from CG, MM, and BAS. MG-P and BAS drafted the original manuscript. MG-P, CG, LZ, JT, MM, and BAS revised the manuscript. MM, BAS, LZ, and MGP have accessed and verified all the underlying data. All authors had access to all the included data. MM and BAS had final responsibility for the decision to submit to publication.

Declaration of interests
We declare no competing interests.

Data sharing
The Vallecas Project data collection is expected to be completed by the end of 2023. Anonymised data can be accessed upon request to direccioncientifica@fundacioncien.es.

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