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Understanding brain resilience in superagers: a systematic review

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Abstract

Purpose Superagers are older adults presenting excellent memory performance that may reflect resilience to the conventional pathways of aging. Our contribution aims to shape the evidence body of the known distinctive biomarkers of superagers and their connections with the Brain and Cognitive Reserve and Brain Maintenance concepts.

Methods We performed a systematic literature search in PubMed and ScienceDirect with no limit on publication date for studies that evaluated potential biomarkers in superagers classified by validated neuropsychological tests. Methodological quality was assessed using the QUADAS-2 tool.

Results Twenty-one studies were included, the majority in neuroimaging, followed by histological, genetic, cognition, and a single one on blood plasma analysis. Superagers exhibited specific regions of cortical preservation, rather than global cortical maintenance, standing out the anterior cingulate and hippocampus regions. Both superagers and controls showed similar levels of amyloid deposition. Moreover, the functional oscillation patterns in superagers resembled those described in young adults. Most of the quality assessment for the included studies showed medium risks of bias.

Conclusion This systematic review supports selective cortical preservation in superagers, comprehending regions of the default mode, and salience networks, overlapped by stronger functional connectivity. In this context, the anterior cingulate cortex is highlighted as an imaging and histologic signature of these subjects. Besides, the biomarkers included pointed out that the Brain and Cognitive Reserve and Brain Maintenance concepts are independent and complementary in the superagers' setting.

Keywords Superagers · Biomarkers · Memory · Cognition · Neuroimaging

Key Points

- Superagers showed selective cortical preservation in some DMN and SN regions, overlapped by stronger functional connectivity akin to young adults (Cognitive Reserve and Brain Maintenance).
- The anterior cingulate cortex is a key structure of superagers in different biomarkers' sources (structural and functional MRI and histological studies).
- Levels of amyloid deposition were not related to the superager subjects, pointing out that brain resilience may be partially independent of neurodegeneration (Brain and Cognitive Reserve).
- Brain and Cognitive Reserve and Brain Maintenance concepts tend to exert independent and complementary roles in the setting of superagers.

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Abbreviations

ACC	Anterior cingulate cortex
AMC	Age-matched controls
DMN	Default mode network
MAC	Middle-age controls
PiB	Pittsburgh Compound B
SA	Superagers
SN	Salience network
y	Years old
YC	young controls

Introduction

Superagers are broadly defined as individuals over 80 years old with episodic memory performance similar or superior to middle-aged subjects (50–65 years old) [1]. To date, the literature has characterized this population using different terms, with superagers as the most common. Other less common terms include successful agers, highly performing older adults, and supernormals. Currently, the global increase in life expectancy has driven efforts to improve the functional capacity and, thus, quality of life for senior individuals, which has made understanding superagers of significant interest. To offer more comprehensive knowledge about the superagers phenotype, several biomarkers, including neuropsychological tests, neuroimaging, genetic, histopathological, and biochemical profiles, have been sought over the last decade.

Differences among individuals regarding cognitive and memory performance rely on two major concepts: (1) Reserve [2], and (2) Brain Maintenance [3]. (1) Reserve works as a mediator between pathology and clinical outcome. It can be conveniently divided into Brain Reserve, the passive model, and Cognitive Reserve, the active model. Brain Reserve refers to quantitative differences in the brain itself, such as larger brains and a greater number of neurons, which allow some individuals to tolerate better brain pathology (i.e., amyloid plaques and tau). Thus, a large brain might be able to endure the pathological effects before a critical threshold of the brain reserve is achieved, and memory impairment emerges. Conversely, Cognitive Reserve represents a form of dynamic and qualitative reserve based on the experience and environmental exposure developed throughout life [4, 5]. This concept relies mainly on the brain networks' cognitive processes and their proper functioning to cope with brain pathology, instead of the simple amount of neurons and synapses in a given region of the brain. Among the indirect markers of the Cognitive Reserve, we can mention the intelligence quotient, education, professional history, and the level of involvement in leisure and cultural activities [6]. Thereby, individuals with the same Brain Reserve, for instance, measured by the total volume of the brain, may have different degrees of Cognitive Reserve [7].

The (2) Brain Maintenance concept implies structural, functional, and neurochemical resistance changes over the years. In other words, rather than explaining why some individuals have preserved memory in the presence of brain pathology as the Reserve concept, Brain Maintenance focuses on the minimization of senescent brain changes as the most reliable predictor of superior memory performance in senior adults [3]. The superagers have emerged as a valuable population because they can act as a model to elucidate brain mechanisms underlying cognition, which may explain the theories of Reserve and Brain Maintenance.

Neuroimaging [structural and functional magnetic resonance imaging (MRI) and PET], histological (amyloid and tau), cognition (episodic memory and cognitive function), genetic (APOE ε4 allele and MAP2K3 gene), and plasma metabolite studies have been carried out in an attempt to establish a superager profile. We sought to systematically review the current information on different neurobiological markers associated with superagers and their relationships with the Reserve and Brain Maintenance concepts.

Methods

Study design

A systematic search of the literature considering studies in English and no limit on publication date was made following the 2010 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations. Included studies evaluated neuropsychological function, neuroimaging, histological, biochemical, and genetic outcomes as potential biomarkers in individuals who were 60 years old and older. To be classified as a superager, participants were required to perform validated neuropsychological tests that evaluated episodic memory function and other cognitive domains, which were subsequently compared with the scores of normative samples, including age-matched controls, middle-age controls, and young controls (Table 1). Only studies evaluating original data were included. Systematic reviews, meta-analyses, case reports, and other types of reviews were excluded from the systematic review eligible papers but were used for discussion if found pertinent. As anticipated, studies included in the qualitative synthesis showed extensive heterogeneity of the covered biomarkers, and consequently, a meta-analysis was not conducted. The protocol for this review was registered in PROSPERO (CRD42019140300), an international prospective register of systematic reviews, prior to initiating a literature search. Only published data were used. Neither ethical approval nor consent for participation or publication was required.

Table 1 Summary of findings for the studies included in the systematic review

Authors, publication year	Study type	Study design	Demographics (measurement unit is year)	Definition of superagers	Reference standard	Index test	Main outcomes	Analysis methods
Harrison et al. 2012 [8]	Neuroimaging—structural MRI	Cross-sectional, with control groups	SA $n = 12$; Age (SD): 83.5 (3); Education (SD): 14.8 (2.4). AMC $n = 10$. Age (SD): 83.1 (3.4); Education (SD): 17.5 (2.2). MAC $n = 14$; Age (SD): 57.9 (4.3); Education (SD): 16.1 (2.9)	Perform at or above average normative values for MAC in memory measures and within 1 SD for AMC in non-memory measures. Age ≥ 80 years	Episodic memory: RAVLT. Cognitive function in nonmemory domains: BNT; TMT-B; CFT	Whole-brain cortical thickness	SA showed thicker cerebral cortex than AMC ($p < 0.001$) and displayed no atrophy compared with MAC ($p = 0.08$). A region of left anterior cingulate cortex was thicker in SA than in both groups ($p < 0.05$)	ANOVA used for cortical volume comparison. Pearson correlations used to examine the relationship between cortical morphometry and memory performance
Pudas et al. 2013 [9]	Neuroimaging—task fMRI	Longitudinal prospective (20 years), with control groups	SA $n = 51$; Age (SD): 68.8 (7.1); Sex (M:F): 13:18; Education (SD): 14.4 (4.4). AMC $n = 51$; Age (SD): 68.8 (6.9); Sex (M:F): 28:23; Education (SD): 12.1 (4.7). YC $n = 45$; Age (SD): 35.3 (7.1); Sex (M:F): 23:22; Education (SD): 15.3 (2.6)	Have final scores greater than 1 SD from the estimated average score in each respective age cohort. Age 60–80 years	Composite of five episodic memory scores: (1) Immediate free recall of 16 imperative verb–noun sentences that were enacted by the participant; (2) Delayed cued recall of nouns from the previously enacted sentences; (3) Immediate free recall of 16 verbally and visually presented verb–noun sentences; (4) Delayed cued recall of nouns from the previously presented sentences; (5) Immediate free recall of 12 verbally presented nouns	BOLD sign while performing an episodic memory face–name paired associates task	Maintenance of high episodic memory performance across 15–20 years was correlated to higher BOLD signal and resembled the brain activation pattern of young adults, notably in the bilateral PFC ($F(1.94) = 11.32$, $p < 0.001$) and the left hippocampus ($F(1.94) = 8.08$, $p < 0.005$)	Two-sample t tests used to test group differences in the encoding-baseline and retrieval-baseline contrasts. Bonferroni-corrected statistical threshold for the ROI analyses, which was based on the number of clusters
Gefen et al. 2015 [10]	Neuroimaging—structural MRI	Cross-sectional, with control groups	SA $n = 31$; Age (SD): 82.52 (2.93); Sex (M:F): 10:21; Education (SD): 15.52 (2.51). AMC $n = 21$; Age (SD): 83.76 (4.0); Sex (M:F): 13:8; Education (SD):	Perform at or above average normative values for MAC in memory measures and within 1 SD for AMC in non-memory measures. Age ≥ 80 years	Episodic memory: RAVLT. Cognitive function in nonmemory domains: BNT; TMT-B; CFT	Cingulate cortical thickness	Right rostral anterior cingulate cortex displayed greater thickness in SA compared with AMC and with MAC (t [67] 3.24, $p = 0.002$)	A mixed-model ANOVA with Bonferroni-corrected pairwise comparisons used to compare cortical thickness

Table 1 (continued)

Authors, publication year	Study type	Study design	Demographics (measurement unit is year)	Definition of superagers	Reference standard	Index test	Main outcomes	Analysis methods
			16.19 (3.44). MAC $n = 18$; Age (SD) 58.39 (3.70); Sex (M:F): 6:12; Education (SD): 15.67 (2.25)					
Yang et al. 2016 [11]	Neuroimaging -Structural MRI	Cross-sectional, with control groups	TOTAL SAMPLE (70–89 y) $n = 207$; Age (SD): 78.7 (4.4); Sex (M:F): 99:108; Education (SD): 12.2 (3.5). TOTAL SAMPLE (90+ y) $n = 70$. Age (SD): 95.4 (3.5); Sex (M:F): 36:34; Education (SD): 11.3 (3.8). SA (70–89 y) $n = 117$; Age (SD) 78.6 (4.3); Sex (M:F): 52:65; Education (SD): 12.4 (3.8). SA (90+ y) $n = 43$; Age (SD): 96.6 (3.1); Sex (M:F): 23:20; Education (SD): 11.5 (3.6)	Intact neuropsychological performance across all tested cognitive domains (i.e., within 1.5 SD of normative values) and a preserved level of functioning on Bayer activities of daily living scale. Age ≥ 70 years	(1) Detailed written comments from trained research psychologist in relation to participants' performance; (2) The individual's test scores of the neuropsychological battery; (3) Quantitative informant questionnaires including the Short IQ CODE and the Bayer activities of daily living scale. Normative data from the 90+ y study: BNT; letter fluency and animal fluency; MMSE	Global and subcortical brain volumetrics	Mild preservation of the prefrontal and insular areas in SA. Age had a stronger negative relationship with hippocampal volume than with total gray matter (B's = − 8.96% versus − 5.30%, $F = 24.10$, $p < 0.05$)	Vertex-based general linear models used for cross-sectional estimates of the age effects across cortical mantle. To test equality of the regression coefficients of age in the linear model, the interaction between the age and selected ROIs were examined using repeated measures ANCOVA
Sun at al. 2016 [12]	Neuroimaging—structural and rs-fMRI	Cross-sectional, with control groups	SA $n = 17$; Age (SD): 67.8 (6.0); Sex (M:F): 5:12; Education (SD): 17.2 (2.2). AMC $n = 23$; Age (SD): 66.2 (5.1); Sex (M:F): 15:8; Education (SD): 16.2 (2.0). YC $n = 41$; Age (SD) 24.5 (3.6); Sex (M:F): 20:21; Education (SD): 16.0 (2.2)	Perform at or above the mean gender-adjusted value for young adults (age range, 18–32) on the CVLT-LD and perform no lower than 1 SD below the mean for their age group on TMT-B. Age 60–80 years	Episodic memory: CVLT. Cognitive function in nonmemory domains: TMT-B; Flanker and the Continuous Performance Task, 1- and 2-back	Structural integrity of the DMN and the SN	SA showed much less atrophy in key nodes of the DMN and SN ($p < 0.05$). SA exhibited full preservation of cortical thickness in several of these regions compared with YC	General linear model analysis in FreeSurfer, comparing cortical thickness between groups for each vertex of the cortical surface within the network-of-interest masks. Tukey post hoc tests
Cook et al. 2017 [13]	Neuroimaging—structural MRI	Longitudinal retrospective (18 months),	SA $n = 24$; Age (SD): 83.3 (3.5); Sex (M:F): 6:18;	Perform at or above average normative values for MAC in	Episodic memory: RAVLT. Cognitive function in	Annual percent change in whole-brain	SA showed a significant lower annual percent change of	Whole-brain cortical volume was compared between

Table 1 (continued)

Authors, publication year	Study type	Study design	Demographics (measurement unit is year)	Definition of superagers	Reference standard	Index test	Main outcomes	Analysis methods
		with control group	Education (SD) = 15 (2.4). AMC $n = 12$; Age (SD) = 83.4 (3.8); Sex (M:F): 7:5; Education (SD) = 15.6 (4.1)	memory measures and within 1 SD for AMC in non-memory measures. Age ≥ 80 years	nonmemory domains: BNT; TMT-B; CFT	cortical volume in 18-month follow-up	whole-brain cortical volume loss compared with AMC (difference, 1.18% [95% CI, 0.08%–2.28%]; unadjusted $p = 0.04$; adjusted $p = 0.02$)	groups unadjusted and adjusted for sex, handedness, and education using 2-tailed single- or two-samples tests at a p value < 0.05
Lin et al. 2017 [14]	Neuroimaging—rs-fMRI and amyloid PET	Cross-sectional, with control groups	SA $n = 9$; Age (SD): 73.53 (6.38); Sex (M:F): 1:8; Education (SD): 17.11 (2.42). AMC $n = 9$; Age (SD): 72.31 (5.57); Sex (M:F): 1:8; Education (SD): 16.89 (2.03). MCI $n = 9$. Age (SD) 72.92 (6.91); Sex (M:F): 1:8; Education (SD): 14.78 (2.49)	To be cognitively normal and have standardized episodic memory composite scores > 1.5 SD across all of the available clinical assessment visits with at least one follow-up assessment. Age 60–-80 years	Episodic memory: MMSE; ADAS-cog; RAVLT; Logical Memory test. Executive function: Wechsler Memory Scale-Revised Digit SpanTest; Digit Span Backwards; CFT; TMT-A; TMT-B; Clock Drawing	Relationships between Aß deposition and FC within the cingulate cortex (CC) and between CC and other regions involved in memory maintenance	SA had stronger FC between anterior CC and right hippocampus, middle CC and left superior temporal gyrus, and posterior CC and right precuneus (mean difference: 0.21–0.31, all $p < 0.001$). FC did not differ based on SUVR± (all FDR-corrected $p > 0.05$); however, SUVR+ subjects had significantly lower levels of memory ($t = 2.32$, $p = 0.044$) and MOCA ($t = 3.64$, $p = 0.006$) than SUVR− subjects	Independent t test used for group comparison in FC and cognitive function by SUVR ± levels
Dekhtyar et al. 2017 [15]	Neuroimaging—Structural MRI and amyloid PET	Longitudinal prospective (3 years), with control group	SA $n = 25$; Age (SD): 77.5 (6.7); Sex (M:F): 9:16; Education (SD): 16 (6). AMC $n = 100$; Age (SD): 78.89 (5.5); Sex (M:F): 47:53; Education (SD) = 16 (5)	Score in the top 20% (memory composite ≥ 0.5 SD). SA maintainers: 3-year follow-up with memory composite ≥ 0.5 SD. Age ≥ 75 years	Memory composite: delayed scores of the MCT; FNAME. executive functioning: letter fluency (F-A-S); letter-number of the WMS-III; DSB; flanker; TMT-B minus A. Processing speed: TMT-A; digit symbol of the WAIS-R	Hippocampal volume and Aß burden at baseline and 3-year follow-up	SA had larger hippocampal volumes at baseline compared with AMC ($p = 0.027$) but no differences in Aß burden ($p = 0.442$). Longitudinally, there was no hippocampal volume loss difference between SA and AMC ($U = 516$, $z = -0.99$,	Mann-Whitney U tests used to determine whether there were significant differences between groups

Table 1 (continued)

Authors, publication year	Study type	Study design	Demographics (measurement unit is year)	Definition of superagers	Reference standard	Index test	Main outcomes	Analysis methods
							$p = 0.319$). SA nonmaintainers exhibited higher Aß burden at baseline in contrast with maintainers ($p = 0.008$)	
Wang et al. 2017 [16]	Neuroimaging-rs-fMRI	Longitudinal prospective (1 year), with control groups	SA $n = 13$; Age (SD): 76.46 (7.52); Sex (M:F): 5:8; Education (SD): 16.23 (2.24). AMC $n = 16$; Age (SD): 75.19 (6.62); Sex (M:F): 8:8. Education (SD): 16.13 (2.5). MCI $n = 57$; Age (SD) 71.95 (7.89); Sex (M:F): 31:26; Education (SD): 16.18 (2.63). AD $n = 26$; Age (SD): 73.75 (7.35); Sex (M:F): 13:13; Education (SD): 15.38 (2.67)	SA exhibited high and stable episodic memory and executive function longitudinally (5 years) relative to AMC. Age 60–-80 years	Episodic memory: RAVLT; Logical Memory test. Executive function: Clock Draw Test; CFT; TMT-A, TMT-B. MCI and AD: Wechsler memory scale-revised; MMSE; Clinical dementia rating global score; NINCDS-ADRDA criteria for probable AD	Resting-state brain regional low-frequency oscillations	A "Supernormal map" was identified predicting 1-year change in global cognition (measured using MOCA, adjusted R2 ranged 0.62–0.68).	Statistical significance was calculated using permutation tests. As a comparison, the study used ALFF features from the "map at baseline," "map at follow-up," and "discrepancy map," respectively, and repeated the regression using the 2 types of analytical strategies. Same sets of covariates were applied
Harrison et al. 2018 [17]	Neuroimaging—structural MRI and amyloid PET	Longitudinal prospective (5 years), with control groups	SA $n = 26$; Age (SD): 74.9 (4.6); Sex (M:F): 3: 23; Education (SD): 17.5 (1.9). AMC: $n = 103$; Age (SD): 75.9 (4.5); Sex (M:F): 48:55; Education (SD): 16.5 (2.0). YC $n = 64$; Age (SD): 24.1 (0.29); Sex (M:F): 30:34; Education (SD): 16.21 (1.8)	Score of 14 or above (max score = 16) on the CVLT, LDFR and normal-for-age performance on Trails B; the CVLT threshold of 14 reflects average performance for an individual aged 18–-32 years. Age ≥ 70 years	Episodic memory: CVLT LDFR; VR immediate recall total; VR recognition; Logical Memory story A plus B1; Visual Paired Associates Total Score. Working memory: Digit Span total score; Listening Span total recall. Processing speed:TMB minus A; Stroop number	Longitudinal changes in cortical thickness and Aß burden in the baseline. Evaluate if Aß is predictive of cognitive changes in 5-year follow--up.	SA showed a thicker cerebral cortex in multiple regions than AMC ($p < 0.05$ vertex-wise, uncorrected). SA displayed greater hippocampal volume than AMC ($p < 0.001$). Aß burden did not differ between SA and AMC ($p = 0.512$), however more Aß was associated with faster memory	Multiple linear regression models used to examine the relationships between cognition, structural MRI measures, and PiB DVR at baseline. LME model to investigate how cognition and imaging biomarkers at baseline affect longitudinal cognition

Table 1 (continued)

Authors, publication year	Study type	Study design	Demographics (measurement unit is year)	Definition of superagers	Reference standard	Index test	Main outcomes	Analysis methods
					correct in 1 min; Digit Symbol total		decline in AMC but not SA ($p = 0.01$) in 5-year follow-up. Longitudinally, there was no hippocampal volume loss difference between SA and AMC ($p = 0.715$)	
Baran, Lin, and Alzheimer's Disease Neuroimaging Initiative 2018 [18]	Neuroimaging—FDG PET and amyloid PET	Cross-sectional, with control groups	SA $n = 122$; Age (SD): 73.88 (6.64); Sex (M:F): 50:72; Education (SD): 16.88 (2.40). AMC $n = 172$; Age (SD): 74.56 (6.17); Sex (M:F): 102:70; Education (SD): 16.48 (2.69). MCI $n = 69$; Age (SD) 71.27 (7.84); Sex (M:F): 35:34; Education (SD): 16.23 (2.68). AD $n = 27$; Age (SD): 73.18 (7.34); Sex (M:F): 13:13; Education (SD): 15.15 (2.51).	Perform episodic memory greater than 1.5 SD above the AMC norms with longitudinal stability, while other cognitive domains (e.g., executive function) should be similar to or better than population norms with longitudinal stability. Age 60–80 years	Episodic memory: RAVLT; ADAS-cog; MMSE; Logical Memory test. Executive function: WAIS-R Digit Symbol Substitution; Digit Span Backwards; TMT-A; TMT-B; CFT; Clock Drawing	Cortical Aß deposition and glucose metabolism	SA showed lower Aß uptake only in the right isthmus cingulate than AMC ($MD = -0.05$, $SE = 0.02$, $t = 2.34$, $df = 295$, $p = 0.020$). Whole cortex FDG-PET significantly distinguished SA from AMC and MCI	ANOVA, chi-square test, or ANCOVA used to examine group differences in demographic characteristics, PET values, cortical thicknesses, and cognitive scores, with post hoc testing performed comparing SA with other groups
Dang et al. 2019 [19]	Neuroimaging—amyloid PET	Longitudinal prospective (8 years), with control groups	SA Aß - $n = 102$; Age (IQR): 70.57 (9); Sex (M:F): 43:59; Education >12 years %: 64.70. SA Aß + $n = 70$; Age (IQR): 72.26 (7); Sex (M:F): 33:37; Education > 12 years %: 65.70. AMC Aß - $n = 103$; Age (IQR): 71.30 (7); Sex (M:F): 40:63; Education > 12 years %: 62.10. AMC Aß + $n = 69$; Age	Perform above the normative average for adults aged 30–44 years on the CVLT-LD (≥ 13 for women, ≥ 12 for men), and perform above 1 SD for their age on all nonmemory tests. Age 60–80 years	Episodic memory: CVLT LDFR. Cognitive function in nonmemory domains: Digit Symbol Substitution Test; Victoria Stroop Test (words trial); Digit Span; Letter Fluency (FAS); Category Fluency	Rates of cortical atrophy over 8 years by SA classification and Aß status	SA and AMC showed similar baseline levels of Aß + ($p < 0.001$). SA and AMC displayed similar rates of cognitive and morphological variation controlled both by age and Aß over the follow up	Separate linear mixed models used for assessment of Aß status and SA classification on longitudinal neuroimaging measures. For each comparison, the magnitude of effect was expressed using Cohen's d

Table 1 (continued)

Authors, publication year	Study type	Study design	Demographics (measurement unit is year)	Definition of superagers	Reference standard	Index test	Main outcomes	Analysis methods
			(IQR): 73.67 (12); Sex (M:F): 36:33; Education > 12 years %: 69.60					
Zhang et al. 2020 [20]	Neuroimaging—structural and rs-fMRI	Cross-sectional, with control groups	SA $n = 17$; Age (SD): 67.8 (6.0); Sex (M:F): 5: 12; Education (SD): 17.2 (2.2). AMC $n = 23$; Age (SD): 66.2 (5.1); Sex (M:F): 15:8; Education (SD): 16.2 (2.0). YC $n = 41$; Age (SD) 24.5 (3.6); Sex (M:F): 20:21; Education (SD): 16.0 (2.2)	Perform at or above the mean gender-adjusted value for young adults (age range, 18–32) on the CVLT-LD and perform no lower than 1 SD below the mean for their age group on TMT-B. Age 60–80 years	Episodic memory: CVLT. Cognitive function in nonmemory domains: TMT-B; Flanker and the Continuous Performance Task, 1- and 2-back	FC of the DMN and the SN	SA showed stronger FC within DMN and SN than AMC ($p < 0.05$) and similar connectivity than young adults ($p > 0.05$)	For each network 2-sample t test between SA and AMC was conducted
Gefen et al. 2015 [10]	Histological	Cross-sectional, with control groups	SA $n = 5$; Age (SD): 88.6 (5.1); Sex (M:F): 0: 5; Education (SD) = 17.2 (1.7). AMC $n = 5$; Age (SD): 86.6 (8.6); Sex (M/F): 1:4; Education (SD) = 13.8 (2). MCI $n = 5$; Age (SD): 92.4 (3.91); Sex (M:F): 2:3; Education (SD) = 14.6 (2.41).	Perform at or above average normative values for MAC in memory measures and within 1 SD for AMC in non-memory measures. Age ≥ 80 years	Episodic memory: RAVLT. Cognitive function in nonmemory domains: BNT; TMT-B; CFT. Careful chart review if neuro-psychological data not available	Alzheimer-type neurofibrillary tangles and neuronal size or count in the cingulate cortex	SA showed a lower frequency of Alzheimer-type neurofibrillary tangles in comparison with other groups ($p < 0.05$)	Wilcoxon rank-sum tests and a mixed-model repeated measures ANOVA with Bonferroni-corrected pairwise comparisons for tangles, plaques, neuronal counts, and neuronal size
Janeczek et al. 2018 [21]	Histological	Cross-sectional, with control groups	SA $n = 5$; Age (SD): 90.2 (2.9); Sex (M:F): 0:5. AMC $n = 15$; Age (SD): 83.3 (8); Sex (M:F) 9: 6. MAC $n = 3$; Age (SD): 53 (3.61); Sex (M:F): 1:2. YC $n = 5$; Age (SD): 34.2 (10.13); Sex (M: F): 2:3. Adolescent $n = 2$; Age (SD): 16	Perform at or above average normative values for MAC in memory measures and within 1 SD for AMC in non-memory measures. Age ≥ 80 years	Episodic memory: RAVLT. Cognitive function in nonmemory domains: BNT; TMT-B; CFT. Careful chart review if neuro-psychological data not available	Density and staining intensity of neuronal AChE levels using histochemical procedures	SA showed lower staining intensity and density of AChE-positive cortical pyramidal neurons compared with AMC, notably in the supplementary motor cortex and inferior parietal lobe (57% and 71% decrease, $p < 0.03$ and	Two-way, non-repeated measures ANOVAs used to compare measures between cortical areas and across groups for numerical density and optical density of cortical AChE-positive pyramidal neurons. Bonferroni post hoc

Table 1 (continued)

Authors, publication year	Study type	Study design	Demographics (measurement unit is year)	Definition of superagers	Reference standard	Index test	Main outcomes	Analysis methods
			(4.24); Sex (M:F): 2:0. Child $n = 2$; Age (SD): 6.25 (5.3); Sex (M:F): 1:1				$P < 0.003$, respectively)	tests used for pairwise comparisons
Gefen et al. 2018 [22]	Histological	Cross-sectional, with control groups	SA $n = 5$; Age (SD): 88.6 (5.1); Sex (M:F): 0:5. AMC $n = 5$; Age (SD): 86.6 (8.6); Sex (M:F): 1:4. YC $n = 5$; Age (SD): 47.8 (13.7); Sex (M:F): 2:3. MCI $n = 5$; Age (SD): 92.4 (3.9); Sex (M: F): 2:3. AD $n = 5$; Age (SD): 80.4 (5.5); Sex (M:F): 3:2	Perform at or above average normative values for MAC in memory measures and within 1 SD for AMC in non-memory measures. Age ≥ 80 years	Episodic memory: RAVLT. Cognitive function in nonmemory domains: BNT; TMT-B; CFT. Careful chart review if neuro-psychological data not available	VEN and total neuronal densities in the anterior cingulate cortex. The influence of age and the severity of AD on VEN density	SA showed highest mean VEN density, even when compared with YC ($p < 0.05$). A significant negative correlation was found between VEN density and Braak staging ($r = 0.603$, $p < 0.001$)	Three separate one-way, ANOVAs with post hoc Bonferonni corrections for multiple comparisons conducted for anterior cingulate VEN density, total neuronal density, and ratio of VEN/total neuronal density. Spearman correlation was conducted between VEN density, neuronal density, ratio of VEN/total neuronal density, and Braak staging in all subject groups combined
Rogalski et al. 2019 [23]	Histological	Cross-sectional, without control group	SA n = 10; Age (SD): 91.2 (3.94); Sex (M:F): 0:10. Education (SD): 15.5 (2.64)	Perform at or above average normative values for MAC in memory measures and within 1 SD for AMC in non-memory measures. Age ≥ 80 years	Episodic memory: RAVLT. Cognitive function in nonmemory domains: BNT; TMT-B; CFT	Alzheimer and no-Alzheimer neuropathology	The hippocampus and entorhinal cortex contained neurofibrillary degeneration mostly in the Braak II-III stages. The neocortex was generally free of neurofibrillary degeneration	Frequencies (descriptive statistics)
Gefen et al. 2014 [24]	Cognitive	Longitudinal prospective (18 months), without control group	SA $n = 18$; Age (SD) = 82.2 (2.4)	Perform at or above average normative values for MAC in memory measures and within 1 SD for AMC in non-memory measures. Age ≥ 80 years	Episodic memory: RAVLT. Cognitive function in nonmemory domains: BNT; TMT-B; CFT	Change in episodic memory and cognitive function throughout 18 months	SA did not show decline on memory, attention, language or executive function after 18-month follow-up ($p > 0.05$)	Paired t tests used to determine stability of longitudinal cognitive performance

Table 1 (continued)

Authors, publication year	Study type	Study design	Demographics (measurement unit is year)	Definition of superagers	Reference standard	Index test	Main outcomes	Analysis methods
Cook Maher et al. 2017 [25]	Cognitive	Cross-sectional, with control group	SA $n = 31$; Age: 83.4 (81.7–85.4); Sex (M:F) 17:23; Education: 16 (14–18). AMC = 19; Age: 84.4 (81.7–86.3); Sex (M:F) 7:12; Education: 18 (16–18)	Perform at or above average normative values for MAC in memory measures and within 1 SD for AMC in non-memory measures. Age ≥ 80 years	Episodic memory: RAVLT. Cognitive function in nonmemory domains: BNT; TMT-B; CFT	Psychological Well-Being	SA and AMC showed similarly high levels of psychological well-being across multiple dimensions, however, SA endorsed greater levels of positive social relationships ($p = 0.005$)	Spearman correlations were used to examine the association between episodic memory performance and psychological well-being. All tests were two-tailed
Rogalski et al. 2013 [26]	Genetic	Cross-sectional, with control group	SA n = 12; Age (SD) = 83.5 (3); Education (SD) = 14.8 (2.4). Elderly controls $n = 330$: Age: 70	Perform at or above average normative values for MAC in memory measures and within 1 SD for AMC in non-memory measures. Age ≥ 80 years	Episodic memory: RAVLT. Cognitive function in nonmemory domains: BNT; TMT-B; CFT	Apo E ε4 allele	SA had a lower frequency of at least one ε4 allele compared with elderly controls (8% vs. 26%)	Frequencies (descriptive statistics)
Huentelman et al. 2018 [27]	Genetic	Cross-sectional, with control group	SA $n = 56$; Age (SD): 83.0 (3.3); Sex (M:F) 17: 39; Education (SD): 15.8 (2.3). AMC $n = 22$; Age (SD): 82.8 (2.6); Sex (M:F): 19:3; Education (SD): 17.7 (1.8)	Perform at or above average normative values for MAC in memory measures and within 1 SD for AMC in non-memory measures. Age ≥ 80 years	Episodic memory: RAVLT. Cognitive function in nonmemory domains: BNT; TMT-B; CFT	Associations between genetic variations and the SA phenotype using Whole Exome Sequencing	The SA phenotype was associated with variants in the MAP2K3 gene (Q = 37, padj = 0.018; Q = 73.4, padj = 0.0011, respectively).	Association analysis was performed at the gene-level using the Sequence Kernel Association Combined test. Significant signals were further checked by visual inspection of BAM file reads. p values were Bonferroni corrected
Mapstone et al. 2017 [28]	Plasma metabolites	Cross-sectional, with control groups	SA $n = 41$; Age (SD) 83.2 (3.3); Sex (M:F): 20: 21; Education (SD): 16.4 (2.6). AMC n = 41; Age (SD) = 83.2 (3.8); Sex (M:F): 20:21; Education (SD): 16.2 (2.4). MCI/AD $n = 74$; Age (SD): 81.94 (4.37); Sex (M:F): 20:54;	Performed a composite memory Z-score >1.35 SD. Other cognitive functions were required to be > − 1.35 SD. Age ≥ 70 years	Episodic memory: RAVLT. Cognitive function in nonmemory domains: FDS (of the WMS-III); TMT-A; TMTB; BNT; CFT; HVOT	Metabolomic analyses in blood samples	SA demonstrated higher levels of 12 plasma metabolites relative to controls (ROC AUC = 0.89).	Logistic regression was used to create a classifier model and the classification performance of the model was assessed using area under the ROC curve (AUC)

Table 1 (continued)

Authors, publication year	Study type	Study design	Demographics (measurement unit is year)	Definition of superagers	Reference standard	Index test	Main outcomes	Analysis methods
			Education (SD): 15.36 (2.45)					

Abbreviations for Table 1

M:F male:female; *y* year-old; *MRI* magnetic resonance imaging; *ApoE ε4* apolipoprotein E epsilon 4 allele; *Aβ* - amyloid ß negative; Aß + amyloid ß positive; *fMRI* functional magnetic resonance imaging; *rs-fMRI* resting-state functional magnetic resonance imaging; *FDG* fluorodeoxyglucose; *PET* positron emission tomography; *PiB* Pittsburgh Compound B; *DVR* distribution volume ratio; *MAP2K3* mitogen-activated protein kinase kinase 3; *SA* superager; *MAC* middle-age control (50–65 years old); *AMC* age-matched control; *MCI* mild cognitive impairment; *AD* Alzheimer's disease; *YC* young control; *SD* standard deviation; *RAVLT* Rey Auditory-Verbal Learning Test; *TMT* trail making test; *CFT* category fluency test; *FDS* forward digit span; *WMS-III* Wechsler Memory Scale—3rd edition; *BNT* Boston Naming Test; *HVOT* Hooper Visual Organization test; *MCT* Memory Capacity Test; *FNAME* Face Name Associative Memory Exam; *DSB* Digit Span Backwards; *WAIS-R* Wechsler Adult Intelligence Scale—Revised; *CVLT* California Verbal Learning Test; *LDFR* Long Delay Free Recall; *VR* Visual Reproduction; *MMSE*: Mini-Mental State Examination; *NINCDS-ADRDA* National Institute of Neurological Disorders and Stroke—Alzheimer's Disease and Related Disorders Association; *Short IQ CODE* Short form of the Informant Questionnaire on Cognitive Decline in the Elderly; *AChE* acetylcholinesterase; *VEN* Von Economo neurons; *DMN* default mode network; *SN* salience network; *ROC* receiver operating characteristic curve; *AUC* area under curve; *MOCA* Montreal Cognitive Assessment; *CC* cingulate cortex; *SUVR* standardized uptake value ratio; *FC* functional connectivity; *PFC* prefrontal cortex; *ANOVA* analysis of variance; *Post hoc*: (Latin, meaning "after this"); *LME* linear mixed-effects; *ROI* regions of interest; *ANCOVA* analysis of covariance; *ADAS-cog* Alzheimer's Disease Assessment Scale-Cognition subscale; *IQR* interquartile range

Search strategy

A search was conducted in PubMed and ScienceDirect by two independent authors, *LLG* and *CAA* (Supplementary file 1). Superagers, elders with high cognition and memory performance, is a recent and non-conventional term; therefore, a mix of non-Mesh terms and Mesh terms was used. Non-Mesh terms included *Superagers*; *Supernormals*; *Superior Memory*; and *Superior Cognition*. Mesh terms included *Magnetic Resonance Imaging*; *Positron Emission Tomography*; *Neuropsychological Tests*; *Pathology*, *surgical*; *Biomarkers*; and *Gene.* Terms were combined using "OR" and "AND" functions in each search engine as follows: "*Superagers" OR "Supernormals" OR* "*Superior Memory*" *OR* "*Superior Cognition*" *AND* "*Magnetic Resonance Imaging*" *OR* "*Positron Emission Tomography*" *OR* "*Neuropsychological Tests*" *OR* "*Pathology*, *surgical*" *OR* "*Biomarkers*" *OR* "*Gene*." When available, the search engine's filters were used to show only original research articles. Additionally, authors searched for additional references among their personal files, and references of included articles were also screened to identify additional papers.

Study selection and quality assessment

Screening of abstracts or titles was performed independently by *LLG* and *CAA*. Results from the search were imported to Mendeley (online), and duplicates were removed. Abstracts were pre-selected for full-text review according to the inclusion criteria. The risk of bias was evaluated using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) [29]. QUADAS-2 evaluated the quality of primary diagnostic accuracy studies. It used four key domains comprising (1) patient selection (method for patient selection and those who were included), (2) index test (test that was studied and how it was conducted and interpreted), (3) reference standard (reference standard test used and how it was conducted and interpreted), and (4) flow and timing (flow of patients through the study and timing of the index tests and reference standard). Each one was evaluated in terms of risk of bias, and the first three domains considered the interests regarding applicability. Signaling questions were also included to help with the judgment of the risk of bias, which could be classified as high, low, or unclear. All disagreements were solved by a third reviewer (*SB*) and final consensus.

Data collection

Data were extracted from the included papers by each reviewer independently. Discrepancies were solved by consensus or by a third reviewer (*SB*). Title, year, journal, country, and type of study (e.g., randomized clinical trial and cohort study) were recorded for every study. We also recorded the type of biomarker (radiological, histological, genetic, molecular, or other), memory performance, other cognitive assessment tools, number of included subjects, quantitative results, and the main conclusion from each study.

Data analysis

Only a qualitative summary of the results was performed. We grouped studies according to the type of biomarker evaluated and compared results among them. No study was excluded based on quality evaluation, but quality results from QUADAS-2 were considered at the moment of comparing results.

Results

General characteristics and quality assessment

A total of 25 full texts were assessed; four were excluded, and a final sample of 21 papers was included (see the flowchart in Fig. 1). A total of 682 superagers, mean age of 76.5 years old (y), were evaluated within the included articles, and the sample size of superagers ranged from 5 to 172 subjects. Ten of the 21 studies were conducted by researchers from Northwestern University [8, 10, 13, 21–27], and three papers employed superager subjects from the ADNIGO/ADNI2 databases [14, 16, 18]. The actual total sample size of superagers was calculated retrospectively, taking into account the largest cohort of each database, 56 superagers from the Northwestern University SuperAging Study [27], and 122 superagers from ADNIGO and ADNI2 datasets [18], avoiding any participants' overlap. The remaining superagers subjects are part of diverse and independent databases. Gefen et al. [10] used morphometric and histological biomarkers to evaluate older adults with different samples of superagers and controls; thus, this paper appears both in the neuroimaging and histological subsections of the Results part.

High-performing older adults were described with different terms, namely "superagers" [8, 10, 12, 13, 19–27], "supernormals" [14, 16, 18, 28], "optimal performers" [15], "successful agers" [9, 17], and "cognitively high-functioning elders" [11]. Lin et al. [14] and Baran et al. [18] chose the "supernormal" term because older adults with high memory performance were compared with age-matched peers, whereas the "superagers" term would be more appropriate if compared with younger adults. However, this definition was not constant across all remaining papers. We decided to use the term "superagers" because it has been the most common terminology employed in the literature.

All included studies required a formal assessment of cognitive function using validated tests to evaluate episodic memory performance and other cognitive domains. The protocols had some differences (Table 1). Ten studies compared the

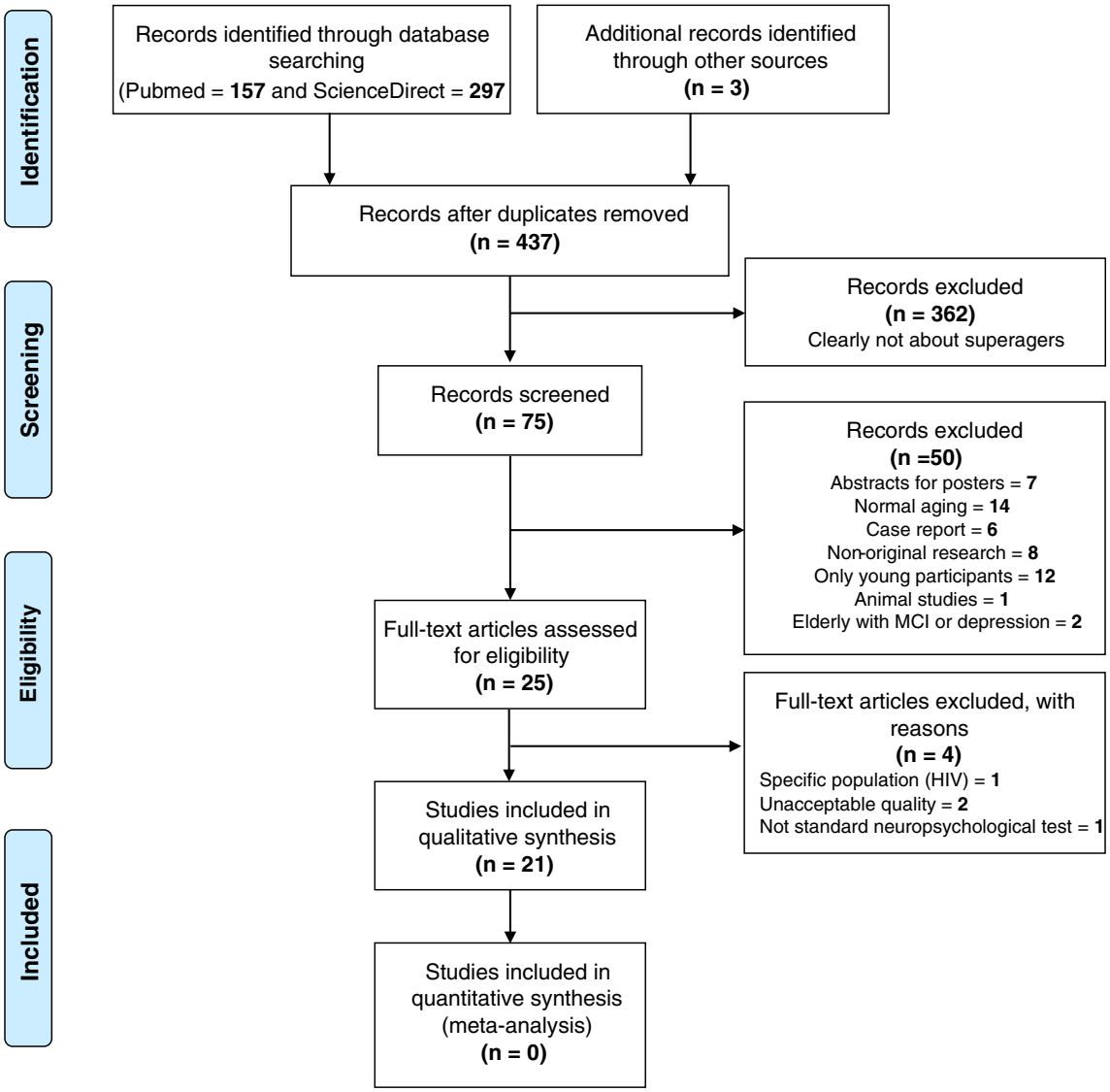

Fig. 1 PRISMA 2009 flow diagram

scores of superagers with middle-aged controls (50–65 years old) for episodic memory performance and with age-matched controls for other cognitive domains [8, 10, 13, 21–27]. Seven articles compared the scores only with age-matched controls [9, 11, 14–16, 18, 28], and four studies compared the results for episodic memory performance with young adults, and with age-matched controls for other cognitive domains [12, 17, 19, 20].

All studies reported clinical, neurological, and/or psychiatric screening criteria to confirm the health status of their study sample. The studies were adjusted by age, sex, and education, except for Harrison et al. [8] and Gefen at al. [24], which did not mention the gender of the included individuals. Histological biomarkers were analyzed only in highly performing females, while the control group included both genders. Several studies (19/21; 90%) used control groups for the index text comparisons (Table 1).

Overall, superagers and age-matched controls did not differ in years of education [8, 10–16, 18–22, 25–28]. Nevertheless, there was a significant main effect of education level when comparing the superagers with mild cognitive impairment and Alzheimer's disease groups, from which superagers were more highly educated [14, 16, 18, 28]. Cook Maher et al. [25] is the only study that has investigated psychological well-being (PWB-42 scores) as a possible outcome to differentiate superagers from normative older adults. The authors highlighted in superagers a significantly increased level of positive relations with others, defined by truthfulness and satisfaction; however, superagers and age-matched controls did not differ on other PWB-42 subscales (autonomy, environmental mastery, personal growth, purpose in life, and self-acceptance).

There is no consensus on how to define the age cut-off for superagers in the literature. Within the 21 papers added, seven

included superagers with ages over 60 years [9, 12, 14, 16, 18–20], two included superager over 70 years [11, 17], one paper included superagers over 75 years [15], and 11 papers included superagers over 80 years [8, 10, 13, 21–28]. Yang et al. [11] shared the subjects that were included in two different samples ranging between 70 and 89 years old and over 90 years old.

The risk of bias was assessed through QUADAS-2 (Table 2; Fig. 2), according to the domains described in the Methods section. Of the 21 articles, 17 (17/21; 80%) were assessed as having an overall medium risk of bias [8–12, 15–23, 25–27], two (2/21; 9%) as having a low risk [13, 28], and two (2/21; 9%) as having a high risk [14, 24]. Eleven articles (11/21; 52%) had a small sample of superagers [8, 10, 12, 14, 16, 20–24, 26] and nine articles (9/21; 43%) assessed a medium-sized sample [9, 10, 13, 15, 17, 19, 25, 27, 28]. Fourteen papers (14/21; 67%) had a cross-sectional design [8, 10–12, 14, 18, 20–23, 25–28]. Only four (4/21; 19%) of the included articles [13, 21–23] had a clear description indicating that the index text (neuroimaging, histological, and others) was interpreted without knowledge of the reference standard (neuropsychological tests). Overall, the included studies showed low concern regarding applicability to the research question.

Cognitive findings in superagers

All studies have classified older adults according to their episodic memory performance. The Rey Auditory-Verbal Learning Test (RAVLT) was applied in 14 studies (14/21; 67%) [8, 10, 13, 14, 16, 18, 21–28], and the California Verbal Learning Test (CVLT) was implemented in 4 studies (4/21; 19%) [12, 17, 19, 20]. For the same purpose, Dekhtyar et al. [15] used a composite memory score that included the Memory Capacity Test and the Face Name Associative Memory Exam. Pudas et al. [9] used a composite of five

Table 2 Detailed quality assessment of included diagnostic accuracy studies

Study	Risk of bias				Applicability concerns			
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard	Risk of bias overview
Harrison et al. 2012 [8]	?	?	☺	?	☺	☺	☺	Medium
Pudas et al. 2013 [9]	?	?	☺	☺	☺	☺	☺	Medium
Gefen et al. 2015 [10]*	☺	?	☺	?	☺	☺	☺	Medium
Yang et al. 2016 [11]	☺	?	☺	?	☺	☺	☺	Medium
Sun et al. 2016 [12]	☹	?	☺	☺	☺	☺	☺	Medium
Cook et al. 2017 [13]	☺	☺	☺	?	☺	☺	☺	Low
Lin et al. 2017 [14]	☹	?	☺	?	☺	☺	☺	High
Dekhtyar et al. 2017 [15]	☺	?	?	?	☺	☺	☺	Medium
Wang et al. 2017 [16]	☹	?	☺	☺	☺	☺	☺	Medium
Harrison et al. 2018 [17]	?	?	☺	☺	☺	☺	☺	Medium
Baran, Lin et al. 2018 [18]	?	?	☺	?	☺	☺	☺	Medium
Dang et al. 2019 [19]	?	?	☺	☺	☺	☺	☺	Medium
Zhang et al. 2020 [20]	☹	?	☺	☺	☺	☺	☺	Medium
Gefen et al. 2015 [10]**	?	☺	?	?	☺	☺	☺	Medium
Janeczek et al. 2018 [21]	?	☺	?	?	☺	☺	☺	Medium
Gefen et al. 2018 [22]	?	☺	?	?	☺	☺	☺	Medium
Rogalski et al. 2019 [23]	?	?	☺	☺	☺	☺	☺	Medium
Gefen et al. 2014 [24]	?	?	☺	☹	☺	☺	☺	High
Cook Maher et al. 2017 [25]	☺	?	☺	?	☺	☺	☺	Medium
Rogalski et al. 2013 [26]	?	?	☺	?	☺	☺	☺	Medium
Huentelman et al. 2018 [27]	☺	?	☺	☹	☺	☺	☺	Medium
Mapstone et al. 2017 [28]	☺	?	☺	☺	☺	☺	☺	Low

*Neuroimaging study. **Histological study

Note: Most index texts received an unclear risk of bias because the respective studies are not clear if the index text had access to the reference standard tests

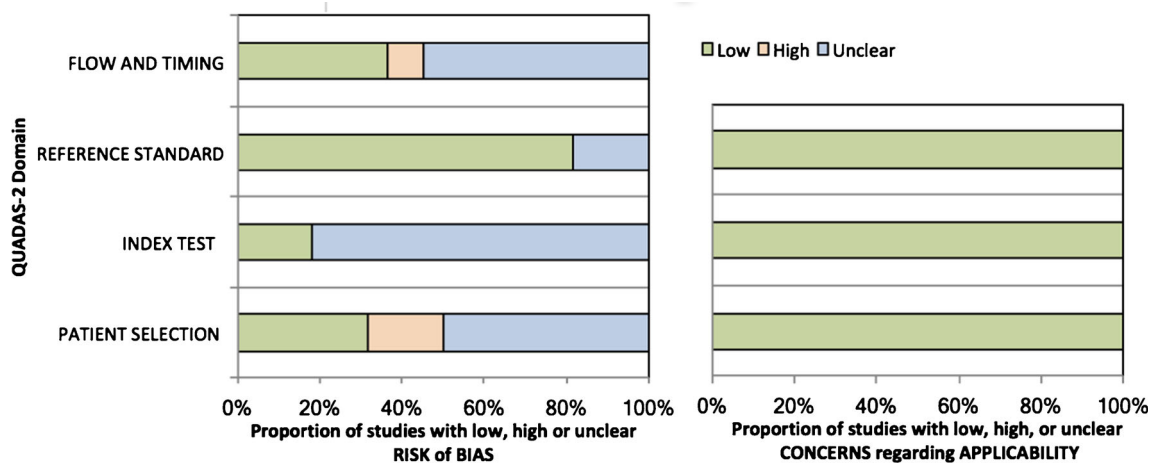

Fig. 2 Quality assessment of included diagnostic accuracy studies

episodic memory scores, and Yang et al. 2016 [11] used the individual's test scores of the neuropsychological battery. For the analysis of non-memory scores, Trail Making Test Part B, the 30-item Boston Naming Test, and the Category Fluency Test were the most frequently used methods to evaluate fluency, naming, and attention skills (Table 1).

Regarding studies that have used longitudinal neuropsychological evaluation, four (4/10; 33%) papers showed episodic memory decline in some superagers over time. A total of 30% (7/23) of superagers showed a decline after 3 years of follow-up [15]; 11.1% (3/27) of superagers showed decline after 18 months follow-up and were excluded from the study [13]; 30% (3/10) of superagers showed a decline after 4.9 years follow-up [23]. Last, Dang et al. [19] showed that superagers and age-matched controls displayed similar rates of cognitive change during 8 years of follow-up. On the other hand, Gefen et al. [24] and Harrison et al. [17] monitored the superagers over 18 months and 5 years, respectively, and did not observe memory decline.

Gefen et al. [24] is a clinical-focused study that has followed superagers to figure out memory decline; however, the absence of a control group and the short time of follow up put this paper in a high risk of bias. Thus, most of the studies with a low and medium risk of bias have shown at least part of superagers with memory decline throughout the time.

Neuroimaging findings in superagers

Thirteen studies (13/21; 62%. SA $n = 604$, mean age = 75.5 years; AMC $n = 759$, mean age 75.6 years) included in this review used neuroimaging sources. Subjects underwent amyloid PET in five of these studies (5/13; 38%. SA $n = 345$, mean age = 72.9 years; AMC $n = 547$, mean age = 75.7 years) and functional MRI (fMRI) in five studies (5/13; 38%. SA $n = 81$, mean age = 69.1 years; AMC $n = 90$, mean age = 69.2 years), being four in resting-state fMRI (rs-fMRI), and one in task-fMRI. Structural MRI was performed in all 13 studies (13/13; 100%) (Table 1).

Cortical morphometry of the anterior cingulate cortex was reported as a potential biomarker in four studies [8, 10, 12, 17]. These studies showed a significantly thicker anterior cingulate cortex in superagers compared with that in age-matched controls [8, 10, 12, 17], some evaluated comparisons with middle-aged controls (MAC $n = 32$; mean age = 58.2 years) [8, 10], and one study showed full preservation compared with younger controls (YC $n = 41$, mean age = 24.5 years) [12]. The mean cortical thickness of the cingulate cortex had a positive correlation with baseline episodic memory performance [8, 10, 12, 17].

Six articles [11, 14, 16–19] did not report statistical differences between superagers and age-matched controls concerning the whole-brain cortical thickness (mean whole-brain cortical thickness was 2.29–2.34 mm vs 2.27–2.32 mm, respectively). Only Harrison et al. [8] demonstrated a higher whole-brain cortical volume in superagers compared with age-matched controls and a similar volume to middle-aged control subjects (superagers vs. middle-aged controls vs. age-matched controls was 288.05 mm^3 vs. 306.43 mm^3 vs. 244.13 mm^3, respectively).

Four studies [11, 12, 15, 17] showed larger hippocampal volumes at baseline in superagers compared with age-matched controls (the mean hippocampal volume was 2.4–7.29 cm^3 vs 2.2–6.88 cm^3, respectively), and thicker medial prefrontal cortex and insula in superagers than in age-matched controls [11, 12, 17]. Longitudinal studies did not demonstrate different rates of hippocampal atrophy progression between these groups at 3 years, 5 years, and 8 years under surveillance [15, 17, 19], respectively.

Amyloid PET imaging in four studies (4/5; 80%) [15, 17–19] revealed similar baseline levels of amyloid uptake between superagers and age-matched controls (median PiB distribution volume ratio – DVR – was 1.13–1.16 vs. 1.1–1.11, respectively) [15, 17]. Lin et al. [14] was only one of five studies that found statistically reduced levels of amyloid uptake in superagers compared with age-matched controls

(standardized uptake value ratio: 1.04 vs 1.16, respectively); however, due to the small sample size (nine superagers and nine controls), selection bias should be considered.

Dekhtyar et al. [15] classified all superagers whose memory scores did not decline within 3 years as "maintainers." This subgroup of superagers maintainers showed lower amyloid burdens at baseline compared with superager non-maintainers (median amyloid DVR was 1.11 vs. 1.43, respectively). Both subgroups had non-significantly different amyloid accumulation rates in the follow-up. Harrison et al. [17] showed that baseline global amyloid DVR was a good predictor for evaluating episodic memory performance decline in age-matched controls (p value = 0.01) but not in superagers (p value = 0.38). Moreover, superagers and age-matched controls displayed similar rates of morphological variation controlled by amyloid deposition over eight [19] and 5 years of follow-up [17].

Harrison et al. [17] showed a lower bilateral volume of white matter hypointensities (WMH) in T1-weighted MRI, indicative of small vessel disease, in superagers compared with age-matched controls (mean volume was 1.5 cm^3 vs. 2.1 cm^3, respectively, p value = 0.020). The article further described no association between the volume of WMH with baseline episodic memory, working memory, or processing speed. Two studies [11, 19] observed similar levels of WMH in the fluid attenuation inversion recovery (FLAIR) sequence between superagers and age-matched controls, and Dang et al. [19] also demonstrated the absence of a significant correlation between amyloid status and WMH.

Wang et al. [16], through a rs-fMRI study, yielded a "supernormal map," defined as a set of brain regions with longitudinal stability in their low-frequency oscillations at baseline and at the 1-year follow-up, representing regions resistant to the aging-associated neurodegenerative process. The regions include the right fusiform gyrus, right middle frontal gyrus, right anterior cingulate cortex (ACC), left middle temporal gyrus, left precentral gyrus, and left orbitofrontal cortex. The map strongly predicted the 1-year change in global cognition. Superagers showed more powerful functional connectivity between the ACC with the right hippocampus, middle CC (MCC) with the left superior temporal gyrus, and posterior CC with the right precuneus in the rs-fMRI study [14]. Superagers in some regions of the default mode network (DMN) (bilateral angular gyrus, bilateral prefrontal cortex, right ACC, left superior frontal cortex, right middle temporal gyrus, and right hippocampal formation) and in some regions of the salience network (SN) (bilateral MCC and right supramarginal gyrus) presented stronger FC compared with age-matched controls and similar connectivity compared with young adults (18–32 years old) [20]. All of these functional connectivity maps were significantly related to both recall and recognition memory [14, 20]. The maintenance of high episodic memory performance across 15–20 years was associated with higher fMRI BOLD signals, while performing an episodic memory face-name paired-associates task, in the bilateral prefrontal cortex and the left hippocampus, also resembling the brain activation pattern of young adults [9].

Summary:

The results of the neuroimaging section revealed that, although the included papers did not show a greater whole-brain cortical thickness in superagers, some particular regions, such as the anterior cingulate cortex and hippocampus, were larger in superagers than in controls. Overall, there were no differences in the baseline amyloid deposition between superagers and age-matched controls. Last, the functional connectivity of the brain networks involved in memory and other cognitive domains in superagers resembled the pattern of young individuals.

Histological findings in superagers

Four of 21 studies (4/21; 19%. SA = 12, mean age 90.2 years. AMC = 16, mean age 84.0 years) [10, 21–23] examined postmortem brains of superagers using the database linked to the Northwestern University SuperAging Study. Three of these studies (3/4; 75%) [10, 21, 22] used a cohort of superagers made up of only five female subjects. Superagers from the Northwestern University SuperAging Study [10, 21, 22] had a significantly lower frequency of neurofibrillary tangles and amyloid plaques than age-matched controls in the anterior cingulate cortex, but not in the posterior cingulate cortex. Overall, superagers had exhibited mixed Braak staging, ranging from 0 to III (reference 0–VI) [10, 21–23]. Tangles varied from scattered to clustered in the hippocampus and were absent in neocortical regions in nine (9/10; 90%) superagers [23].

There were no differences regarding the total neuronal size or count between superagers and age-matched controls. Superagers displayed the highest number and density of Von Economo Neurons (VENs) in the anterior cingulate compared with age-matched controls [10, 22] and compared with younger controls of 47.8 years average age [22]. It was also noted that there was a negative correlation between Braak staging of neurofibrillary tangles and VENs density (p value < 0.001) [22].

Superagers showed a consistent decrease in the density of acetylcholinesterase (AChE) activity in pyramidal neurons when compared with age-matched controls (30.6–69.2% decrease) [21], notably in the supplementary motor cortex and inferior parietal lobe (57% and 71% decrease, p value < 0.03 and p value < 0.003, respectively). In the age-matched controls and superager groups combined, there was no significant

correlation between the Braak stage and the numerical density or staining intensity of AChE in cortical pyramidal neurons in any of the regions examined [21].

Summary:

The results of the histological section revealed that the anterior cingulate cortex of superagers stood out compared with age-matched controls and younger controls due to its intrinsic neurochemical characteristics, including a lesser degree of amyloid plaques and neurofibrillary tangles (Alzheimer's disease biomarkers), and a higher concentration of VEN.

Genetic findings in superagers

Genotyping for APOE ε4 was described in ten articles (10/21; 48%. SA $n = 587$, mean age 77.3 years; AMC $n = 1056$, mean age 74,7 years). Nine of them used age-matched controls for comparison. Four of nine studies (44%) did not find statistically significant differences between superagers and age-matched controls regarding the ε4 allele [10, 11, 17, 28]. Even though Dang et al. [19] did not find significant differences between superagers and controls, when comparing the amyloid negative group (SURV < 1.4 at the most recent PET), a higher prevalence of APOE ε4 carriage was found in the amyloid positive group (SURV ≥ 1.4 at the most recent PET). Four of nine studies (44%) showed a lower frequency of at least one ε4 allele in superagers when compared with age-matched controls (mean of ε4 allele 8–30.8% vs. 26–37.5%, respectively) [15, 16, 18, 26]. In a cross-sectional study, Rogalski et al. [23] showed two (2/10; 20%) superagers carrying the ε4 allele. The *MAP2K3* gene was further investigated by Huentelman et al. [27]. This gene belongs to a signaling cascade correlated with beta-amyloid mediated apoptosis and has enhanced expression in microglia. The study pointed out that the superager phenotype was associated with variants in the *MAP2K3* gene, which has been shown to be associated with mild decreased *MAP2K3* activity since birth.

Summary:

The results of the genetic section revealed that, to date, there is no consensus in the APOE ε4 role for the definition of superagers. In addition, the variants in the *MAP2K3* appear to be associated with this selected population.

Plasma metabolites in superagers

An analysis of the metabolites in superagers was described only in one article (SA $n = 41$, mean age 83.2 years; AMC $n = 41$; mean age 83.2 years) [28]. Mapstone et al. [28] found 12 metabolites that comprised critical metabolic pathways, such as oxidative stress, inflammation, and nitric oxide bioavailability, that were enriched in superagers compared with age-matched controls (ROC AUC = 0.89). The panel of 12 metabolites comprised aspartate, hydroxyhexadecadienylcarnitine, 3-hydroxypalmitoleylcarnitine, lysophosphatidylcholine, arginine, valerylcarnitine, lysophosphatidylcholine, asparagine, citrulline, nitrotyrosine, phosphatidylcholine, and histamine. This study also showed an inverse proportion of these plasma metabolites in mild cognitive impairment, Alzheimer's disease, and preclinical Alzheimer disease groups compared with controls.

Discussion

This systematic review of superagers underlying brain physiology showed distinct features in several biomarker groups whose synthesis expands the unique neurochemical, histological, and imaging profile of superagers. We sought to shed light on the inherent features of some individuals to avoid or postpone the deleterious process of aging, maintaining a neuropsychological performance level as well as a structural and functional appearance similar to younger subjects.

Based on our results, the two major concepts previously introduced in this manuscript, that is, (1) Reserve (Brain Reserve and Cognitive Reserve) and (2) Brain Maintenance, start to converge as independent and complementary processes that can explain uneventful cognitive aging [30]. The Reserve theory relies on the dissociation between the level of brain damage (i.e., amyloid plaques) and clinical manifestations. The Brain Reserve subtype is predetermined for a threshold related to greater brain volumes and more neurons and synapses [2]. The Cognitive Reserve subtype refers to differences in how individuals process tasks. Their brain functional component is the major source of memory performance instead of the brain size to cope with neuropathology. Nevertheless, the theory itself should not be entirely dissociated from the Brain Reserve, also showing physiologic or morphometric evidence in specific brain regions. In summary, Cognitive Reserve strengthens anatomic variability at the brain networks level, while Brain Reserve presumes differences in the amount of available neural substrates. However, these hallmarks alone do not give a whole explanation for superagers demonstrating brain and cognitive preservation throughout the lifespan [31]. At this point, the Brain Maintenance concept, which supports the minimization of pathological changes over time, can explain the similarity of the superagers' brains with young individuals in several perspectives [3].

A remarkable finding observed in structural MRI studies was the selective cortical preservation in some brain regions of superagers when compared with age-matched controls, even without differences in the analysis of the whole brain cortical thickness [11, 14, 16–19]. The most relevant areas were the ACC [8, 10, 12, 17], hippocampus [11, 12, 15, 17], medial prefrontal cortex [11, 12, 17], comprehending structures of the DMN (episodic memory function), and insula [11, 12, 17], part of the SN (attention and executive processes involved in

encoding and retrieval). Overlapping the superagers' structural integrity, some regions of the DMN and SN were also found to have stronger functional connectivity in superagers, resembling young adults (mean age 29.7 years old) [9, 20]. This statement is of paramount importance once the authors understand that those findings support the Cognitive Reserve, defined by the stronger functional component, and the Brain Maintenance, characterized by the youth pattern, as a concomitant, and possible explanations for the superior memory performance in superagers.

Beyond the structural integrity, the ACC in superagers demonstrated particular features in histopathologic analysis with a distinct topography of neuronal preservation represented by a lower frequency of Alzheimer-type neurofibrillary tangles and amyloid plaques, and relatively higher density of VEN compared with controls [10, 22]. rs-fMRI studies in the ACC showed higher intrinsic connectivity associated with better memory and global cognition [14, 20]. Hence, the ACC may represent a key region both in terms of imaging and histology for superior performance in older adults, by preventing aging-related degeneration, thus supporting the Brain Maintenance concept.

Analysis of the hippocampus volume has also been of interest in the field of memory, because of its greater susceptibility to the aging process than that of the total cortical volume [11, 32, 33]. Several studies [11, 12, 15, 17] revealed higher hippocampal volumes at baseline in superagers compared with age-matched controls, supporting the causal connection between hippocampal volumes and episodic memory performance. Notably, results from longitudinal studies [15, 17, 19] demonstrated no differential rate of hippocampal volume loss between these two groups. These single time-point and longitudinal studies support the Brain Reserve as the most acceptable theory to elaborate the superager phenomenon, in which subjects endowed with a larger hippocampus cope better than others with brain pathology.

With the exception of the Lin et al. study [14] that has a high risk of bias, the included studies showed a weak correlation between levels of amyloid deposition and cognition among superagers and age-matched controls in a cross-section analysis [15, 17–19] following previous works in unimpaired adults [34–36]. In addition, histological studies demonstrated abundant deposition of neurofibrillary tangles in the hippocampal-entorhinal complex [23] and in the posterior cingulate cortex of superagers [10, 21, 22]. However, the anterior cingulate cortex, as anticipated, had a preserved morphometry and metabolism associated with higher memory scores. The synthesis of these findings strengthened the hypothesis that variable regional disposition to Alzheimer's disease pathophysiology is decisive for maintaining cognitive performance [34].

Studies with a longitudinal design were able to correlate the amyloid burden with cognitive changes during follow-up in healthy non-superager individuals [37–39]. A plausible explanation for the absence of the amyloid burden and cognition correlation in the superagers group was proposed by Harrison et al. [17], which suggested that superagers may be resilient to the adverse neuropathology outcomes due to their higher brain volumes in critical structures until the threshold is reached, which is in line with the Brain Reserve concept.

Results from studies that applied rs-fMRI on cognitive normal older adults indicated an expected cognitive decline that depended on the contingency of function-specific memory networks [40–44], which showed a nonlinear course across the lifespan [45]. Superagers displayed oscillation patterns resembling those described in younger adults [9, 16, 20, 46], corroborating the Brain Maintenance concept. To understand this variation, longitudinal studies are necessary to rule out any age-related increases [47].

The study of genetic biomarkers linked to the aging process is a field currently involved in in-depth analysis; however, differences between superagers and age-matched controls are still being debated regarding the importance of the ε4 allele, and no conclusions have been obtained at this point. The low frequency of the ε4 allele may be the substrate that justifies the resistance of superagers to the deleterious process of aging [26]. The lack of statistical importance could be explained by the peak effect of the ε4 allele appearing to occur in subjects in their 60s evolving into mild cognitive impairment before the 75th year of life [48, 49]. Other genes associated with the superager phenotype and higher brain volumes are variants of the *MAP2K3* gene [27] and *KLOTHO* (KL) gene [50]. Identifying genetic influences that alter anatomic and functional features of the aging brain may yield preventative strategies for improving brain function in later life.

Limitations

This systematic review has some limitations. The main limitation is, until now, there has been no consensus among studies regarding the definition criteria for superagers. However, it is important to highlight that, even though the determination of superagers has some variability as a reference standard, all the studies included accessed their participants using validated neuropsychological tests regarding either episodic memory or other cognitive domains; further, scores were compared at least with age-matched controls. Thus, the methodology has reliability for an adequate superagers classification. In this systematic review, the minimum age of superagers was 60 years old, which is in contrast with the definition of E. J. Rogalski et al. [26], that considered a cut-off age of 80 years old. A younger cut-off age may introduce bias, as the age-related memory decline starts to manifest after the age of 60–65 years [9]. However, the rationale for this strategy relies on the fact that some recent and pertinent publications have established this earlier age cut off as an inclusion criterion, and at this point of life, several individuals start to experience

memory decline [3]. Another limitation is the small sample of superagers that were included in the design of the cross-sectional studies, hence partially limiting the generalization of the results. Future epidemiological studies are definitely needed to estimate the prevalence and demographic characteristics of the superagers. Since most of the papers did not clearly state whether the index text was evaluated without a priori knowledge of neuropsychological tests, observer bias cannot be ruled out. Finally, the inclusion of fundamentally different biomarkers to understand the superior memory performance in later-life precluded a meta-analysis.

Conclusion

This systematic review supports the presence of specific brain regions with cortical preservation in superagers. Some anatomical structures involved in the DMN and SN show unimpaired cortical thickness along with higher functional connectivity (Cognitive Reserve) akin to young adults (Brain Maintenance). The cumulative evidence for different biomarkers highlights the anterior cingulate cortex as the key structure for distinct cognitive performance in superagers. In addition, important markers of neuropathology, such as the levels of amyloid deposition, were not related to the superager phenotype, suggesting that brain resilience may be partially independent of neurodegeneration (Brain and Cognitive Reserve). In this way, this systematic review tended to adopt the notion of independent and complementary roles for Brain and Cognitive Reserve and Brain Maintenance concepts in the setting of superagers. To entirely understand the complex phenomenon of cognitive aging, future studies should consider longitudinal evaluation with multimodal imaging techniques and genetic targets.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent For this type of study informed consent is not required.

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