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Brain morphology, cognition, and β-amyloid in older adults with superior memory performance

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ABSTRACT

The mechanisms underlying superior cognitive performance in some older adults are poorly understood. We used a multimodal approach to characterize imaging and cognitive features of 26 successful agers (SA; defined by superior episodic memory ability) and 103 typical older adults. Cortical thickness was greater in multiple regions in SA including right anterior cingulate and prefrontal cortex and was related to baseline memory performance. Similarly, hippocampal volume was greater in SA and associated with baseline memory. SA also had lower white matter hypointensity volumes and faster processing speed. While PiB burden did not differ, there was a significant group interaction in the relationship between age and PiB such that older SA individuals were less likely to have high brain β-amyloid. Over time, memory performance in typical older adults declined more rapidly than in SA, although there was limited evidence for different rates of brain atrophy. These findings indicate that superior memory in aging is related to greater cortical and white matter integrity as well as slower decline in memory performance.

1. Introduction

Cognitive decline is a common feature of normal aging (Hedden and Gabrieli, 2004). Aging trajectories, however, are inconsistent across individuals, and variance of cognitive performance on neuropsychological tests is positively correlated with advancing age. Older adults who avoid cognitive decline and perform similarly to much younger people contribute to this age-related variance. There is great interest in these individuals and the underlying factors that mediate their unusually successful aging.

By definition, successful agers (SA) have not only avoided normal age-related cognitive decline but also clinical expression of Alzheimer's disease (AD) including both mild cognitive impairment and dementia. AD, however, also has a prolonged asymptomatic prodrome that can be characterized by biomarkers of pathology. Thus, a crucial and tractable question is whether preserved cognition in successful aging reflects avoidance of AD-related pathology. There is evidence to suggest that SA defined by preserved episodic memory performance avoid age-related cortical thinning and have cortical morphology that more closely resembles middle-aged adults than their age-matched peers (Harrison et al., 2012). This could reflect greater brain reserve (e.g., larger cortex thinning at the same rate) or slower progression of age-related atrophy. In this regard, a recent study of "SuperAgers" showed that this unique group had a lower rate of whole cortex thinning over 18 months compared to a typical control group (Cook et al., 2017). SA have also been shown to have greater hippocampal volume than their peers (Sun et al., 2016). These findings suggest a unique successful aging trajectory in which individuals resist changes in brain morphometry.

Two important pathological processes that are related to the development of cognitive decline and dementia in aging are β-amyloid (Aβ) deposition and cerebrovascular disease. Aβ can be quantified with positron emission tomography (PET) tracers, and a widely reported measure of cerebrovascular disease is reflected in changes in white matter, often detected in hypointensities on T1 images. In contrast to differences in cortical thickness or hippocampal volume, Aβ accumulation and white matter signal abnormalities cannot be explained by higher lifetime brain reserve or slower age-related structural brain changes. Individuals with superior memory performance in the presence of age-related brain pathology such as Aβ accumulation and white matter disease would be resilient to the effects of the pathology rather than resistant to the pathology itself (Latimer et al., 2017). It remains unclear whether SA also avoid Aβ accumulation and white matter disease, or if they are resilient to these pathologies. The factors underlying resistance to pathology (e.g., the avoidance of pathology itself) and resilience to pathology (e.g., the avoidance of typical cognitive

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consequences of pathology or coping with pathology) in cognitively superior older adults are underexplored.

In the present study, we aimed to first replicate previous findings with cross-sectional structural magnetic resonance imaging (sMRI) and second to expand the literature with investigations of Aβ burden, white matter hypointensities, longitudinal changes in cortical thickness, as well as longitudinal cognition in unusually SA. We were further interested in how Aβ is related to age in superior memory performers and whether Aβ is predictive of cognitive changes. We examined cognitive trajectories in our cohort of SA using longitudinal cognitive follow-up data (mean total follow-up time = 5.2 [2.5] years) to determine whether superior memory performance in older adults is predictive of future cognitive changes. Finally, we examined basic medical data and self-report questionnaires to search for factors underlying our successful aging cohort's superior memory performance.

2. Methods

2.1. Participants

The present study included 150 participants enrolled in the Berkeley Aging Cohort Study (BACS), an ongoing longitudinal study of normal cognitive aging, who were aged 70 years or older, and had MRI and PiB-PET data quantifying Aβ in the brain. Additional eligibility requirements included no imaging contraindications; baseline Mini–Mental State Examination score ≥25; no neurological, psychiatric, or major medical illness; no medications affecting cognition; and that all participants were community dwelling. Of the 150 participants, 26 met criteria for superior memory performance and were called SA. Criteria for SA included a score of 14 or above (max score = 16) on the California Verbal Learning Test (CVLT) long delay free recall (LDFR) and normal-for-age performance on Trails B; the CVLT threshold of 14 reflects average performance for an individual aged 18–32 years (Sun et al., 2016). Of the remaining participants, 103 met criteria for typical older adults (TOA). TOA were required to score at or above 1 standard deviation below normal for age on the CVLT LDFR, making a score of 7 the inclusive cutoff. Thus, TOA scored in the range of 7–13 on the CVLT LDFR. A total of 21 participants scored too low on the CLVT LDFR to be included in either experimental group. These criteria are based on previous studies and were designed to maximize interpretability in the context of the "SuperAging" literature and to allow for replication efforts within the present study (Gefen et al., 2015; Harrison et al., 2012; Sun et al., 2016). Baseline cognition was defined as the neuropsychological testing visit that was closest in time to each participant's PiB-PET scan. Twenty-five of 26 SA and 90 of 103 TOA had follow-up neuropsychological testing visits (Table 1). All older adult participants reported basic medical history including present or past history of hypertension, hypocholesterolemia, arthritis, macular degeneration, and diabetes. An unweighted linear comorbidity index score was created based on these 5 age-related medical conditions to examine whether medical comorbidity influences SA. Height and weight were measured for body mass index (BMI) calculation, and BMI differences between groups were also measured.

Sixty-four participants aged 20–30 years were also recruited using the same criteria (except age) to serve as a young control group. The young adults (YA) participated in neuropsychological testing and baseline structural MRI studies but did not undergo PiB-PET or longitudinal MRI scanning.

The institutional review board at Lawrence Berkeley National Laboratory (LBNL) and the University of California Berkeley approved the present study, and written, informed consent was obtained from all participants.

2.2. Cognitive assessment

All participants in the BACS, including YA, undergo neuropsychological testing to measure performance on specific cognitive tasks including those related to verbal and visual memory, working memory, processing speed, executive function, language, and attention. Participants also complete questionnaires designed to assess lifetime cognitive activities, symptoms of depression, and sleep quality. In the present study, composite scores were calculated to measure 3 cognitive domains: episodic memory (omitting all CVLT scores), working memory, and processing speed. Episodic memory tests were Visual Reproduction (VR) immediate recall

Table 1
Cohort characteristics

	SA	TOA	SA vs. TOA; *p*-value	YA
n	26	103	—	64
Age (y)	74.9 ± 4.6	75.9 ± 4.5	0.321	24.1 ± 0.29
Sex (M/F)	3/23	48/55	**0.001**	30/34
Education (y)	17.5 ± 1.9	16.5 ± 2.0	**0.031**	16.21 ± 1.8
APOE (% of ε4 carriers)	30	27 (3 N/A)	0.810	—
Family history of dementia (Y/N)	12/13 (1 N/A)	21/80 (2 N/A)	**0.010**	—
BMI	28.2 ± 6 (2 N/A)	26.7 ± 4.4 (2 N/A)	0.265	—
History of hypertension (Y/N)	8/18	37/66	0.818	—
Comorbidity Index Score	1.54 ± 1.2	1.45 ± 0.99	0.716	—
Hippocampal volume[a] (cm^3)	2.4 ± 0.3	2.2 ± 0.3	**<0.001**	2.71 ± 0.2
WM hypointensities[a] (cm^3)	1.5 ± 1.0	2.1 ± 1.8	**0.029**	0.61 ± 0.3
Whole cortex thickness (mm)	2.3 ± 0.2	2.3 ± 0.1	0.432	2.51 ± 0.1
sMRI follow-up (y)	4.5 ± 2.7	3.5 ± 1.9	0.145	—
PiB DVR	1.13 ± 0.20	1.10 ± 0.17	0.512	—
CVLT LDFR	14.8 ± 0.8	10.2 ± 1.9	—	13.21 ± 2.4[b]
Cognition follow-up (y)	5.5 ± 2.5	5.1 ± 2.6	0.535	—
LEQ	123.6 ± 18.5 (6 N/A)	117.1 ± 19.8 (42 N/A)	0.187	—
Wilson cognition: present	4.06 ± 0.45 (1 N/A)	3.84 ± 0.56 (7 N/A)	**0.042**	—

SA and TOA were compared using Welch's *t*-tests for continuous variables and Fisher's exact test for sex, *APOE* status, family history of AD, and history of hypertension (significant differences at $p < 0.05$ are bolded).

Key: AD, Alzheimer's disease; *APOE*, apolipoprotein E; BMI, body mass index; CVLT LDFR, California Verbal Learning Test long delay free recall (16 words); LEQ, Lifetime Experiences Questionnaire; PiB DVR, Pittsburgh Compound-B distribution volume ratio; SA, successful agers; TOA, typical older adults; WM, white matter; YA, young adults.

[a] Denotes volumes that have been adjusted by intracranial volume (ICV).

[b] In raw CVLT LDFR score, SA performed better than YA while TOA performed worse than YA (both $p < 0.0001$).