

# Youthful Memory Capacity in Old Brains: Anatomic and Genetic Clues from the Northwestern SuperAging Project

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## Abstract

■ The Northwestern University SuperAging Project recruits community dwellers over the age of 80 who have unusually high performance on tests of episodic memory. In a previous report, a small cohort of SuperAgers was found to have higher cortical thickness on structural MRI than a group of age-matched but cognitively average peers. SuperAgers also displayed a patch of ACC where cortical thickness was higher than in 50- to 60-year-old younger cognitively healthy adults. In additional analyses, some SuperAgers had unusually low densi-

ties of age-related Alzheimer pathology and unusually high numbers of von Economo neurons in the anterior cingulate gyrus. SuperAgers were also found to have a lower frequency of the  $\epsilon 4$  allele of apolipoprotein E than the general population. These preliminary results show that above-average memory capacity can be encountered in advanced age. They also offer clues to potential biological factors that may promote resistance to age-related involuntional changes in the structure and function of the brain. ■

## INTRODUCTION

A principal function of the human brain is to accumulate knowledge over time so that the individual can benefit from experience. This process unfolds within two inter-related anatomical substrates. First, genetically programmed species-specific axonal connections determine which sets of neurons will be responsive to which types of information. Second, modifications in the synaptic strengths of these connections establish a record of personal experience and enable the gradual accumulation of a knowledge base that is unique for each individual. These acquired patterns are not encoded at the level of the genome and cannot be transmitted through mitosis, which may be why the brain is a largely post-mitotic organ (Mesulam, 2000). As an inevitable outcome of this arrangement, each neuron in the brain becomes exposed to the cumulative effect of biological wear-and-tear throughout the life span.

The elderly frequently complain of declining cognitive skills, especially in the area of episodic memory. Such complaints are so widespread that they have led to the belief that a gradual loss of intellectual ability is part of “normal” aging. It turns out that this disarmingly simple assumption is extremely difficult to substantiate or refute. Aging and time overlap only in the simplest of systems. In the process of radioactive decay, for example, the aging

of a nucleotide, defined as the loss of its radioactivity, is entirely dependent on the passage of time. In more complex systems, such as the brain, however, aging depends on an interaction among three major variables: time, the constitutional or genetic background of the vehicle within which time flows, and the cumulative impact of stochastic encounters with diverse events such as stress, hypertension, oxidation, head trauma, exposure to xenobiotics, and so on (Mesulam, 2000).

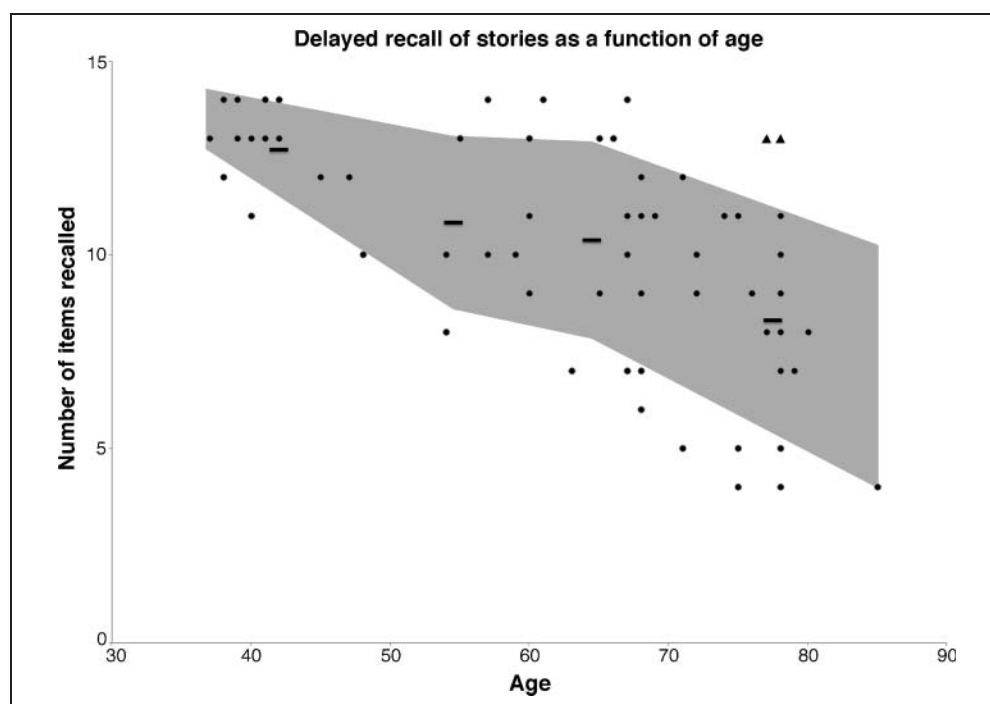
Much of the existing literature on aging overlooks these complex relationships and assumes that lower memory scores or synaptic densities in groups of older individuals reflect changes that are intrinsic to aging, that is to say, caused by the passage of time. However, such changes could also reflect the impact of particularly common (i.e., endemic) but theoretically preventable events. Aging may not cause these events but may increase the probability of encountering them. Differentiating the inevitable consequences of time from the cumulative but preventable impact of stochastic phenomena embedded within time is one of the most important goals of current aging research (Mesulam, 2000).

A very common misunderstanding in this field arises from the failure to distinguish “average” from “intact” performance. As Figure 1 shows, a memory score that would be considered average and, therefore, normal in an 80-year-old could be distinctly abnormal in 50- or 60-year-olds. Therefore, a performance deemed to be normal (or average) at the age of 80 does not mean that brain and

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**Figure 1.** Increase in the magnitude of interindividual variation in memory performance over the life span. Gray shading reflects  $\pm 1SD$  from the mean and demonstrates the widening of the standard deviation over the life span due to higher interindividual variation in aging. Triangles represent elite performers who may be immune to the common age related declines in episodic memory. Circles represent individual data. Lines represent averages for 35–49, 50–59, 60–69, and 70–85 from left to right, respectively. Reprinted (with modifications) from McDaniel, Einstein, and Jacoby (2008).



intellect have remained intact; it just means that the decline over time has remained within boundaries that are average for that population. Figure 1 also shows that variability of performance in a group increases with age, reinforcing the notion that age acts as a sink for the accumulation of diverse chance events and their interactions with individual genetic backgrounds.

Although Figure 1 is based on a cross-sectional study, its results can cautiously be extrapolated to conceptualize three longitudinal trajectories of aging. The trajectory identified as normal is associated with test scores that remain within the shaded zone in the figure, even though this performance may represent a decline from a higher former level. The second category includes performance levels that fall below the shaded zone, raising the specter of age-related pathological processes such as Alzheimer’s disease or its precursor stages. The third category, illustrated by the triangles at the top right of Figure 1 and the one that motivated the Northwestern SuperAging Project, contains individuals with performance levels that are distinctly above the normative range. The presence of such outliers raises questions of fundamental importance to the neurobiology of brain aging. Have these superior performers resisted age-related changes or have they simply started from a much higher baseline? Do they have identifiable peculiarities of genetic background? Is there something special about their brain structure or perhaps their resistance to age-related processes such as amyloid deposition and neurofibrillary degeneration? These are the questions that are being addressed in a cohort of individuals over the age of 80 who were selected on the basis of their scores on episodic memory

tests that were at least in the average range for much younger individuals in their 50s and 60s and who also performed at least in the average range for their age in other domains of cognition. This article summarizes initial structural neuroimaging, genetic, and pathologic results that emerged from an investigation of this cohort.

## METHODS AND RESULTS

### SuperAging Criteria

The delayed recall score of the Rey Auditory Verbal Learning Test (RAVLT) was used as a measure of episodic memory, and the 30-item Boston Naming Test (BNT; Kaplan, Goodglass, & Weintraub, 1983), Trail Making Test Part B (Randolph, 1998), and the Category Fluency Test (Morris et al., 1989) were used to measure cognitive function in nonmemory domains that are particularly vulnerable to age-related change and dementia (see Weintraub et al., 2009). To be designated a SuperAger, an individual was required to perform at or above average normative values for individuals in their 50s and 60s (midpoint age = 61; RAVLT delayed-recall raw score  $\geq 9$ ; Schmidt, 2004) and within one standard deviation of the average range for their age and education for the nonmemory measures according to published normative values based on age, gender, and race/ethnicity (Heaton, Miller, Taylor, & Grant, 2004; Saxton et al., 2000; Randolph, 1998). Recruitment occurred through Northwestern’s Alzheimer’s Disease Center (ADC) Clinical Core, community lectures, and word of mouth. Two other cognitively average participant groups, middle-aged controls and elderly controls, were identified

for the comparative cognitive and structural studies. Details regarding subject recruitment and inclusion criteria have been described (Harrison, Weintraub, Mesulam, & Rogalski, 2012). Briefly, the cognitively healthy middle-aged elderly controls were required to score within one standard deviation of the average range for their age and education according to published normative values on the same neuropsychological measures administered to the SuperAgers, which are described above. All participants were required to have preserved activities of daily living and lacked clinical or structural evidence of a history of or concurrent neurological or psychiatric disease.

### Structural Imaging Features of SuperAgers

An initial investigation of the biological features of cognitive SuperAging, originally published in by Harrison et al. (2012), quantified the integrity of the cerebral cortex using the computational toolkit FreeSurfer to estimate differences in cortical thickness on T1-weighted three-dimensional magnetization prepared rapid gradient echo (MPRAGE) sequences (repetition time = 2300 msec, echo time = 2.86 msec, flip angle = 9°, field of view = 256 mm) among 12 SuperAgers (average age = 83.5 ± 3.0 years), 10 cognitively average elderly individuals (average age = 83.1 ± 3.4 years), and 14 cognitively average middle-aged controls (average age = 57.9 ± 4.3 years; Harrison et al., 2012). Cortical thickness measurement by FreeSurfer provides a sensitive and well-validated method capable of detecting submillimeter cortical thickness differences between groups (Kuperberg et al., 2003; Fischl & Dale, 2000).

As specified by the inclusion criteria, episodic memory performance for the elderly and middle-aged controls was within one standard deviation of published normative values for their respective comparison groups (Schmidt, 2004), whereas SuperAgers performed at least as well as middle-aged controls ( $p = .09$ ) and significantly better than elderly controls ( $p < .001$ ; average RAVLT delayed recall score (of a possible 15): SuperAgers = 11.8 ± 1.2, middle-aged controls = 10.21 ± 2.6, elderly controls 5.1 ± 0.9). Cognitive performance in non memory domains was significantly different among the groups for Trails B ( $p = .027$ ) but not for Category Fluency or 30-item BNT (Trails B: average score SuperAgers = 96.2 ± 46.1, middle-aged controls = 61.8 ± 22.0, elderly controls = 128.5 ± 92.7; Category Fluency: average score SuperAgers = 22.4 ± 6.0, middle-aged controls = 23.7 ± 5.6, elderly controls = 18.4 ± 3.8; 30-item BNT: average score SuperAgers = 28.7 ± 1.1 middle-aged controls = 28.9 ± 1.0, elderly controls = 28.0 ± 2.5). Post hoc tests revealed the elderly controls were significantly slower than the middle-aged controls on Trails B, but the SuperAgers, as a group, did not differ from the middle-aged controls on non-memory performance.

The goal of the imaging analysis was to determine whether SuperAgers' cortical thickness more closely

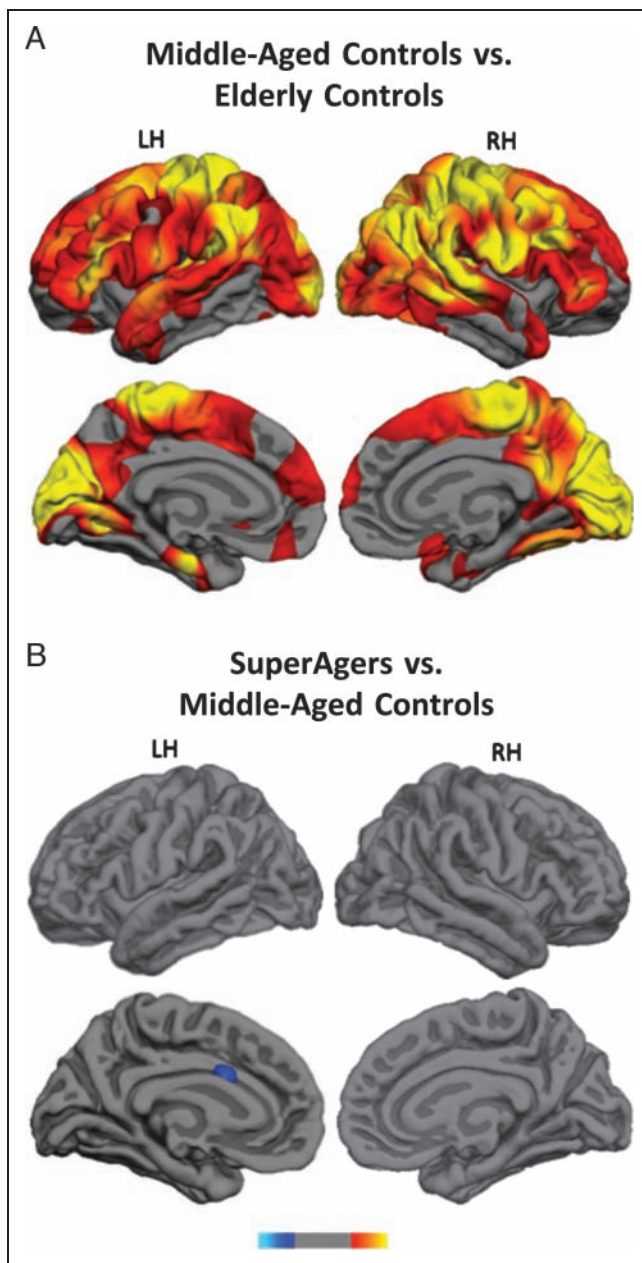
resembled their *age-matched* (but cognitively inferior) or *cognitively-matched* (but younger) peers. Statistical surface maps were generated using a general linear model that displays differences in cortical thickness between two groups for each vertex along the surface representations. Compared with the middle-aged controls, the group of cognitively average elderly showed significant atrophy in multiple regions across the frontal, parietal and occipital lobes (Figure 2A; Harrison et al., 2012). In contrast, the SuperAgers showed no statistically significant atrophy compared with the middle-aged control group (Figure 2B; Harrison et al., 2012). In addition, an area located in the left anterior cingulate shown in blue on Figure 2B was significantly thicker in SuperAgers than in the middle-aged control group by nearly 0.8 mm on average (Harrison et al., 2012). Although the area of increased thickness looks small on the whole-brain images, it has a surface area of 80 mm<sup>2</sup> on average and has a significance level of  $p < .000001$  using a false discovery rate of 0.05 (Genovese, Lazar, & Nichols, 2002). Cortical volume was measured in addition to cortical thickness and revealed complimentary results to the thickness analysis, showing no significant differences between the SuperAgers and middle-aged controls, and both groups had significantly larger cortical volumes than the elderly control group (Harrison et al., 2012).

### ApoE

Participants in the Northwestern SuperAging project also provided blood samples from which DNA was extracted for genotyping. ApoE was targeted for initial investigation because the  $\epsilon 4$  allele of this gene is the most extensively documented genetic risk factor for AD. Of the 12 SuperAgers included in the cortical thickness analysis above, only one (8%) had an  $\epsilon 4$  allele ( $\epsilon 3, \epsilon 4$ ) and the others had the  $\epsilon 3, \epsilon 3$  pattern, which is the most common genotype in the general population. In contrast, in a sample of 330 nondemented control participants (median age = 70 years) from the Northwestern ADC database, 89 individuals (26%) had at least one  $\epsilon 4$  allele, suggesting that the  $\epsilon 4$  allele may be underrepresented in the SuperAging group.

### Pathology

To date, one member of the SuperAging cohort (SuperAger 3 in Table 1) who was included in the cortical thickness analysis (above) has come to autopsy. The holdings of the Northwestern Brain Bank were surveyed for autopsied cases that had extensive neuropsychological test records. Four additional cases that fulfilled the SuperAger criteria were identified through retrospective chart review. Each of these individuals had a cognitive assessment within 12 months of death and had episodic memory performance that was at least average for individuals in their 50s or 60s, and performance was within normal limits for age on other tested domains (Table 1).



**Figure 2.** Cortical thickness differences in average cognitive agers and cognitive SuperAgers. (A) Red and yellow regions show significant regional cortical thinning across both hemispheres in the cognitively average elderly controls compared with the cognitively average middle-age cohort. (B) There is no significant thinning in the SuperAging group in either hemisphere compared with middle-aged controls. A region within the ACC (blue) is significantly thicker in SuperAgers when compared with middle-aged controls. False discovery rate was set at 0.05. LH = left hemisphere; RH = right hemisphere. Reprinted (with modifications) from Harrison et al. (2012) with the permission of Cambridge University Press. Copyright© 2012 The International Neuropsychological Society.

Although neurofibrillary tangles and amyloid plaques are considered pathognomonic of Alzheimer's disease, they also emerge as part of cognitively average aging in individuals with no known cognitive impairment. Neurofibrillary tangle and amyloid plaque densities in the brains

of the five SuperAgers mentioned above (average age = 88.6 years) were compared with those of five cognitively average normal controls of a similar age (average age = 90.2 years) from the Northwestern Brain Bank (Table 1). Neurofibrillary tangle densities were qualitatively ranked according to the widely used Braak staging system where a Stage 0 or I indicates the lowest density of neurofibrillary tangle and a Stage VI is the highest (Braak & Braak, 1991, 1995). Three of five SuperAging cases were designated at a Braak Stage 0, I, or II while only one of the control specimens was in that low range of neurofibrillary degeneration; four of the five specimens from cognitively average controls had a Braak Stage III or higher while only one SuperAging case was in that range (Table 1).

On the basis of the structural MRI finding of a thicker region of cortex in the cingulate gyrus in SuperAgers (Figure 2B), this region was examined in greater detail for evidence of cellular pathology. Semiquantitative analysis of plaques and tangles in BA 23 and BA 24 using thioflavin-S-stained sections is provided in Table 1. Between two and six sections from each area cut at 40  $\mu$ m were used for analysis. Density of plaques and tangles was determined in the entire cingulate gyrus in each section. There were four measures for each case: tangles in Areas 23 and 24 and plaques in Areas 23 and 24. Density of lesions was assessed on a scale of 0 (*virtually no tangles or plaques in multiple sections*) to ++++ (*high density covering most of the region*) based on a modified version of a published scale (Mirra, Hart, & Terry, 1993). In the five SuperAger cases, 15 of the 20 counts led to the lesions being classified as *virtually absent* (rating of 0), whereas all 20 counts in the cognitively normal elderly controls displayed plaque and tangle counts at intensity levels of + and ++ (*sparse to mild*).

Figure 3 shows sections from the anterior aspects of the cingulate cortex (BA 24) of SuperAger Case 3 in Table 1 who was 90 years old at the time of death. Nissl-stained sections showed no evidence of cellular abnormalities and the maintenance of normal cortical architecture (Figure 3A). Coronal sections from the structural MRI scan (Figure 4) of Case 3 also indicate that the cortical ribbon is relatively persevered and that there are no obvious signs of atrophy in the entorhinal cortex and hippocampus. Thioflavin-S-stained sections did not show any mature or neuritic plaques in the cingulate cortex. Phosphorylated tau (PHF-1) and thioflavin-S-positive tangles were scarce (less than one per section; Figure 3B,C). Only isolated A $\beta$ -positive plaques were present, with a density of 1–2 per section (Figure 3D). Occasional clusters of A $\beta$ -positive plaques were seen only in the posterior cingulate and then only in the depths of the cingulate sulcus.

### von Economo Neurons

While examining the postmortem material of the SuperAgers, we were struck by the prominence of von Economo neurons, especially in the anterior cingulate area, which

**Table 1.** Semiquantitative Analysis of Thioflavin-S-stained AD Pathology in SuperAgers and Cognitively Normal Controls

	Age at Death (years)	Sex	Ed.	Cognitive Score	BA 24		BA23		Braak Tangle Staging
					Plaques	Tangles	Plaques	Tangles	
SuperAger 1	87	F	18	13/15 <sup>a</sup>	++	0	++	0	III
SuperAger 2	90	F	14	11/15 <sup>a</sup>	0	0	0	0	II
SuperAger 3	90	F	18	12/15 <sup>a</sup>	0	0	0	0	III
SuperAger 4	81	F	18	10/10 <sup>b</sup>	++	0	–	–	0-I
SuperAger 5	95	F	18	49/50 <sup>c</sup>	0	0	0	0	0
Control 1	89	F	16	8/15 <sup>a</sup>	++	+	++	+	III-IV
Control 2	89	F	16	8/10 <sup>b</sup>	++	+	++	+	II
Control 3	95	F	12	7/10 <sup>b</sup>	++	+	++	+	III
Control 4	88	M	12	5/10 <sup>b</sup>	++	+	++	+	III-IV
Control 5	90	M	16	6/10 <sup>b</sup>	++	+	++	+	III

There were no significant differences in age, sex, or education between the groups. Ed = Education, in years. Cognitive measures were not identical for all participants. Cognitive scores are provided as actual/possible score. Key for thioflavin-S counts in BA 24 and BA 23: 0 = *none* (0–5 total tangles or plaques in multiple sections); + = *sparse and isolated plaques and tangles* (~6–10 total in multiple sections); ++ = *mild*; +++ = *moderate*; ++++ = *severe* (high density covering most of the region); – = section was not available. Braak staging followed published guidelines (Braak & Braak, 1991, 1995).

<sup>a</sup>Delayed recall score from the RAVLT (Schmidt, 2004).

<sup>b</sup>Delayed recall score from the Consortium to Establish a Registry for Alzheimer’s Disease word list (Morris et al., 1989).

<sup>c</sup>Total score from the telephone interview for cognitive status (Brandt, Spencer, & Folstein, 1988), which includes immediate and delayed recall of a 10-word list.

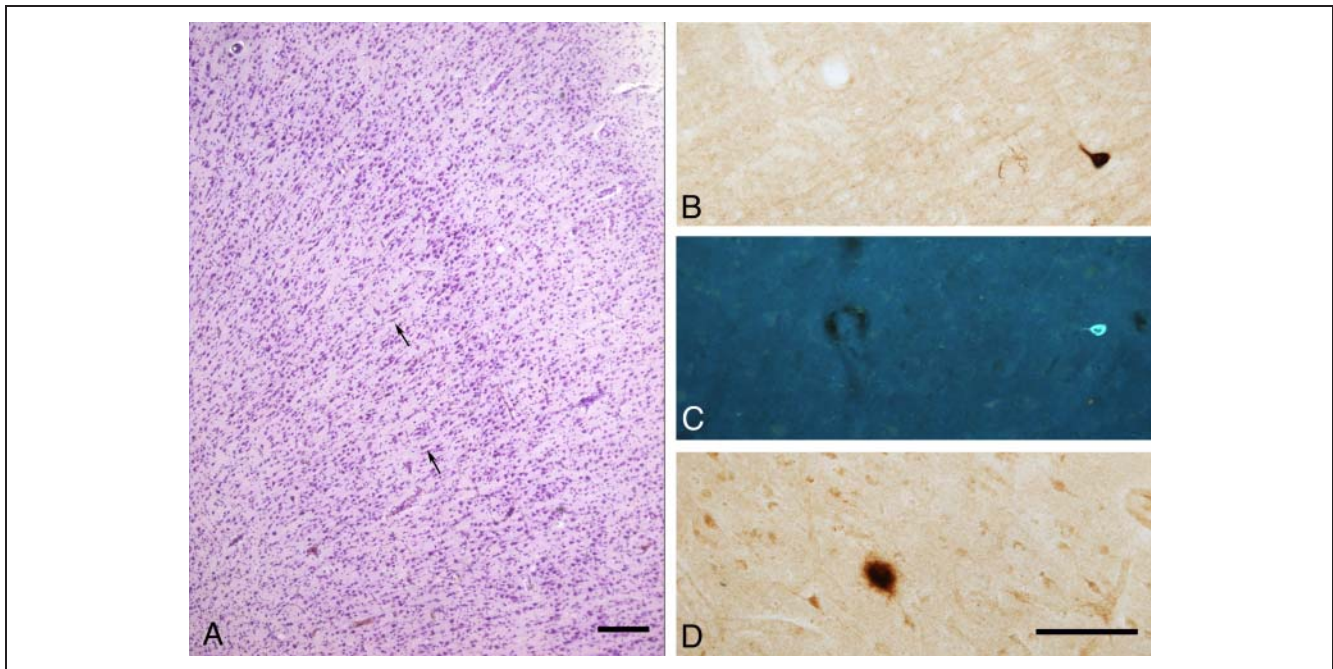
also displayed a region of higher than average thickness on structural neuroimaging (Figure 3A). These large spindle neurons are known to be prominent in the anterior paralimbic areas such as the anterior cingulate and insular cortex, specifically in humans and in a few other phylogenetically advanced species. We therefore initiated a preliminary unbiased stereological quantitative investigation of von Economo neurons in the cingulate cortex of two SuperAgers (SuperAger 2 and SuperAger 3 in Table 1), two cognitively normal elderly controls (Control 2 and Control 3 in Table 1), and two individuals who died at the amnesic mild cognitive impairment stage of Alzheimer’s disease. SuperAgers showed a significantly higher density of von Economo neurons in the ACC compared with the cognitively normal elderly control and amnesic mild cognitive impairment stage cases ( $p < .05$ ). This difference was particularly striking in region BA 24, where von Economo neuron density was approximately fourfold higher in SuperAgers than in comparison groups (Gefen, Rogalski, Weintraub, Mesulam, & Geula, 2012). Whether this feature will emerge as a consistent finding in SuperAgers remains to be seen.

## DISCUSSION

The possibility that cognitive changes of late life may not be inevitable has been raised in numerous contexts. For example, one study focused on more than 1000 physicians

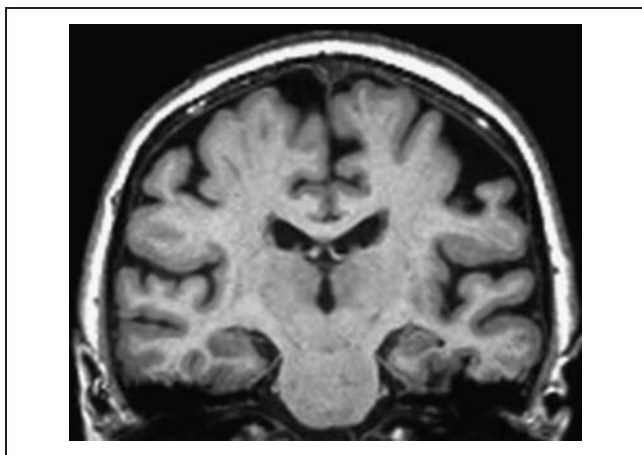
ranging in age from 28 to 92 years (Weintraub, Powell, & Whitla, 1994). As expected, the mean scores for the group of physicians above 75 years were significantly lower than the mean scores for physicians under 35 years in all cognitive tasks. The top and bottom 10 performers were then identified in both groups. The top- and bottom-performing subgroups of young physicians did not vary significantly in their scores. The situation was quite different among the older physicians where the bottom ten obtained significantly lower scores than the young physicians in all tasks. The top 10 elderly physicians, however, displayed performance levels that were identical to those of the young physicians in nearly all areas of cognition that were assessed. This study, in keeping with the results illustrated in Figure 1, leads to two potential conclusions. First, as has been demonstrated in virtually all cross-sectional and longitudinal studies, not only of cognition but of other biological, social, and behavioral variables, aging appears to be characterized by increased interindividual variability (Nelson & Dannefer, 1992). Second, there may be a subgroup of individuals who, because of either good fortune or genetic makeup, may manage to age without major changes of mental acuity. This is the group that is targeted by the SuperAging project.

The neuropsychological test results in the SuperAger group show that it is possible for elderly individuals to have memory performance at a level that falls within or even above the normative range of cognitively healthy individuals at least 20–30 years their junior. We cannot



**Figure 3.** Extremely sparse Alzheimer pathology in the anterior aspects of cingulate cortex (BA 24) in a 90-year-old SuperAger (Case 3). (A) Nissl-stained sections revealed high packing density of neurons in the anterior cingulate. Arrows in A point to von Economo neurons. Most of this cortical region was devoid of plaques or tangles. Only isolated phosphorylated tau-stained (B, PHF-1, less than one per section) or thioflavin-S-positive tangles (C, less than one per section) and amyloid- $\beta$ -positive plaques (D, 6E10, two per section) were detected in this region. Scale bars: 1 mm (A) and 100  $\mu$ m (D; also applies to B and C).

tell yet whether this indicates that the SuperAgers had a much higher baseline level of memory capacity or whether they have resisted age-related changes. If the former explanation were to be taken seriously, our subjects would have had to have truly unusual memory capabilities in their earlier lives as young adults. However, detailed life histories provided no evidence of such unusual cognitive strengths as a characteristic feature of the SuperAgers.



**Figure 4.** Coronal section of a T1-weighted MRI scan from a 90-year-old SuperAger (SuperAger 3 in Table 1) who came to autopsy. The cortical ribbon is largely preserved, and the hippocampus and the entorhinal cortex do not show any obvious atrophy.

We therefore favor the interpretation that the SuperAgers are resistant to the age-related involution of memory function. The ongoing longitudinal arm of the SuperAging project will assess this contention more directly.

The quantitative imaging results confirmed the well-known fact that cortical thickness decreases in the course of average aging, from late adulthood to senescence. The SuperAgers did not show this effect; in fact, the anterior cingulate was thicker in SuperAgers than middle-aged controls. As in the case of cognitive performance data, these results cannot determine whether the SuperAgers have resisted age-related atrophy or whether they had an unusually thick cortical surface when younger. At this stage of the study, the quantitative analyses of the imaging data were confined to measurements of the hemispheric surface. Future studies of morphometry will target areas that are more specifically related to memory function, such as the entorhinal cortex and the hippocampal complex.

The role of ApoE in aging and Alzheimer's disease is incompletely understood. Overwhelming evidence supports the conclusion that the  $\epsilon 4$  allele increases the risk of Alzheimer's disease by shifting the age-incidence curve to the left, as if it promoted earlier disease onset (Corder et al., 1993; Poirier et al., 1993). The frequency of the  $\epsilon 4$  allele is approximately twice as high in groups of pathologically proven Alzheimer's disease than in age-matched controls (Roses, 1997). In animal models, the  $\epsilon 4$  allele may interfere with reactive neuroplasticity (Arendt et al., 1997; Nathan et al., 1994). Even in subjects with no known

neurological disease, the  $\epsilon 4$  allele may be associated with reduced hippocampal volume (Lind, 2006) and decreased cortical metabolism (Small et al., 2000; Reiman et al., 1996). Although our sample was too small for any definitive conclusion, the unusually low incidence of the  $\epsilon 4$  allele may provide one potential substrate for the apparent resistance of the SuperAgers to age-related decline of cortical functionality, cortical atrophy, and Alzheimer-type degenerative changes.

The diagnosis of Alzheimer's disease requires the post-mortem detection of amyloid plaques and neurofibrillary tangles in specific densities and distributions. However, lesser quantities of both of these markers of Alzheimer pathology are common in elderly individuals with no known cognitive or neurological impairment (Thal, Tredici, & Braak, 2004; Price & Morris, 1999). Moreover, the density of these features has been shown to correlate with age-related memory loss (Mesulam, Shaw, Mash, & Weintraub, 2004; Guillozet, Weintraub, Mash, & Mesulam, 2003). It appears, therefore, that aging increases the vulnerability to the emergence of Alzheimer pathology and that these degenerative changes may be responsible, at least in part, for age-related alterations of cognitive function. The few autopsies we have completed show that Alzheimer changes are less prominent in the SuperAgers, especially in the cingulate cortex, which is thicker in SuperAgers than in younger adults. Thus, the lower frequency of Alzheimer pathology in SuperAgers, conceivably related to the lower prevalence of the  $\epsilon 4$  allele of apolipoprotein E, may underlie their resistance to involuntional changes of memory capacity and cortical volume. Such resistance to markers of Alzheimer pathology has been reported in a 115-year-old woman whose performance on neuropsychological tests was above average for healthy adults of 60–75 years (den Dunnen et al., 2008).

One influential account of successful aging has revolved around the theme of cognitive reserve. This concept has been invoked to explain the preservation of cognitive strength despite the presence of brain atrophy or other forms of cellular neuropathology. The cognitive reserve account does not appear to be particularly relevant to our group of SuperAgers because their above-average performance was associated with greater cortical thickness and a tendency for less Alzheimer pathology than peers of average memory capability. However, this may not be the rule for all successful agers. Successful aging may reflect resistance to the emergence of involuntional changes of brain structure in some individuals and resistance to the cognitive consequences of such changes in others.

von Economo neurons have recently captured interest in the context of frontotemporal dementia, where they display particularly severe degeneration (Seeley et al., 2007). von Economo neurons, also known as spindle neurons, are particularly prominent in the anterior paralimbic cortices of the cingulate gyrus and insulo-orbitofrontal complex. They are thought to be present only in hominids

and other phylogenetically advanced species (Nimchinsky et al., 1999). These considerations have led to the speculation that the von Economo neurons may have a special role in advanced affiliative behaviors and that their loss may be related to at least some of the comportmental abnormalities that characterize the behavioral variant of frontotemporal degeneration. The fate of von Economo neurons in aging is unknown. Our preliminary finding that these neurons may be more numerous in SuperAgers may be related to the equally puzzling finding of increased thickness of cingulate cortex in this group. The cingulate gyrus is a critical site for the transmodal integration of multiple limbic and neocortical functions including attention and motivation, which are essential for proper memory function (Mesulam, 1998, 2009). One possibility is that the prominence of cingulate circuitry in the SuperAgers may somehow promote unusually efficient memory performance.

These results in an initial cohort of SuperAgers show that excellent memory capacity in late life is a biological possibility. They also show that SuperAgers have larger cortical volumes, less ApoE4, and perhaps also more von Economo neurons and fewer instances of Alzheimer pathology than their cognitively average peers. Longitudinal investigation of larger groups of subjects will be needed to consolidate these findings and to disentangle cause from effect as we try to identify factors that promote successful aging.

### **On Suzanne Corkin's Festschrift**

Just as classic voyages of discovery enabled the map of the world to take its current shape, explorations of patients with focal brain lesions allowed the functional cartography of the human brain to emerge from total obscurity. Gage, Leborgne, and H.M. generated fundamental insights that remain relevant to contemporary thinking. Although modern methodology has introduced dazzling refinements to the classic map of functional localization, principled investigations of patients with focal lesions continue to provide the conceptual scaffolding of cognitive neuroscience. Suzanne Corkin's distinguished career exemplifies this outlook. Her methodical investigations of H.M. and her subsequent work on Alzheimer's disease introduced lasting neurobiological insights into the fractionation of memory impairments caused by focal lesions, neurodegeneration, and aging. As homage to her work, we are offering this preliminary communication on the converse phenomenon of preserved memory in advanced age. Sue has always had a flair for new ideas, especially those related to memory and its neuroanatomy. We hope that she will find this contribution to her festschrift interesting and, perhaps, also reassuring.

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