Research Partnership in Cognitive Aging

A report to the McKnight Brain Research Foundation
April 17, 2025

Foundation for the National Institutes of Health
The National Institute on Aging

REPORT SUMMARY

The Foundation for the National Institutes of Health (FNIH) is pleased to present the following Research Partnership in Cognitive Aging 2024 report to the McKnight Brain Research Foundation (MBRF). The report provides an update from the National Institute on Aging (NIA) on the Cognitive SuperAgers Networks, both supported through the Research Partnership in Cognitive Aging.

The current centerpiece of the Research Partnership in Cognitive Aging between the NIA and MBRF, coordinated by the FNIH, is the research supported through the funding opportunity "Network for Identification, Evaluation, and Tracking of Older Persons with Superior Cognitive Performance for Their Chronological Age," RFA-21-015 (https://grants.nih.gov/grants/guide/rfa-files/RFA-AG-21-015.html). Updates to this research are provided below.

Network for Identification, Evaluation, and Tracking of Older Persons with Superior Cognitive Performance for Their Chronological Age (U19 Clinical Trial Not Allowed)

Resilience/Resistance to Alzheimer's Disease in Centenarians and Offspring (RADCO) U19AG073172

The RADCO cooperative agreement (U19AG073172), awarded to Drs. Thomas Perls (Boston University Medical Campus), Stacy Andersen (Boston University Medical Campus), and Susan Bookheimer (UCLA) is in the fourth year of award. The NIA continues to support a multi-year administrative supplement, in the form of a fourth phenotyping and biospecimen core and neuroimaging core site at Georgia State University (GSU). The addition of the GSU site has increased the number of centenarian cognitive Superagers in the network and should increase the Black participant proportion of the RADCO sample from 7.2% to 22.2%. Current enrollment in this network is 290 individuals, 173 of which are cognitive superagers. The website for the project may be found at https://www.bumc.bu.edu/centenarian/radco/.

The abstract for U19AG073172:

DESCRIPTION (provided by applicant): Centenarians delay age-related diseases and disabilities into their mid-nineties. Some remain cognitively intact despite extreme exposure to the strongest risk factor for cognitive impairment and Alzheimer's disease (AD), aging. The overall hypothesis of this study, titled "Resilience/Resistance to AD in Centenarians and Offspring" (RADCO), is: centenarian cognitive SuperAgers and some of their offspring have protective factors that confer such resilience or, in some cases, even resistance against cognitive decline and dementia. RADCO assembles an unprecedentedly large sample of prospectively studied centenarian cognitive SuperAgers (n=495, essentially, centenarians with cognitive function that falls within the norms of septuagenarians) along with offspring (n=600) and offspring spouses (n=120), who, via RADCO cores, undergo careful, comprehensive, and cutting-edge neuropsychological, biomarker, neuroimaging, and neuropathological phenotyping. These data are used by two projects with the overall scientific objective of gauging cognitive resilience in this sample, understanding the underlying protective biology and translating that into therapeutic targets. The Cognitive Resilience and Resistance Phenotypes Project (Project 1) gauges resilience by neuroimaging, plasma AD biomarkers risk and neuropathology, and therefore generates a range of resilience endophenotypes. The Protective Factors and Mechanisms Project (Project 2) is the translation arm of RADCO; it discovers genes, candidate biological pathways and sets of mi-RNA regulators associated with the resilience endophenotypes characterized in

Project 1. In-vitro models of AD incorporate cortical neurons, microglial cells, and astrocytes created from centenarian cognitive superager induced pluripotent stem cell (iPSC) lines are used to test the candidate pathways for how they cause resilience against AD.

PUBLIC HEALTH RELEVANCE: Centenarian cognitive SuperAgers have exceptional cognitive function despite extreme exposure to the strongest risk factor for cognitive impairment and Alzheimer's disease, aging. The RADCO Study gauges cognitive resilience among centenarian cognitive SuperAgers and their offspring using cognitive testing, neuroimaging, blood biomarkers, and neuropathology. Translational studies will identify protective factors and underlying mechanisms that confer resilience or in some cases, even resistance against cognitive decline and dementia.

Study to Uncover Pathways to Exceptional Cognitive Resilience in Aging (SUPERAging) U19AG073153

The SUPERAging cooperative agreement (U19AG073153) awarded to Drs. Emily Rogalski, Marsel Mesulam, and Changiz Geula is in the fourth year of award. Of note, last year saw a change in the locus of the parent award. Dr. Rogalski has transferred from Northwestern University to the University of Chicago. Dr. Mesulam stepped down as one of the Multi-Principal Investigators (MPI) last year but has rejoined as an MPI this year. Both Drs. Geula and Mesulam remain on faculty at Northwestern. Enrollment in the study to date is 300 participants, all of whom are cognitive superagers. The website for this project may be found at https://haarc.center.uchicago.edu/superaging/.

The team published findings in *Brain Communications* in 2024 regarding the relationship between functional connectivity and age-related cognitive decline. Decreases in functional connectivity have been associated with the cognitive impairment seen in individuals with Alzheimer's disease. However, there are inconsistent findings in the literature about this relationship. Using optimized MRI methods, the team sought to explore this relationship in cognitive superagers. They found that functional connectivity within or between brain networks did not appear to drive the exceptional memory performance seen in cognitive superagers. These findings could have relevance for differentiating the role of functional connectivity changes associated with age-related cognitive change from those associated with AD. This publication is attached to this report.

The abstract for U19AG073153:

DESCRIPTION (provided by applicant): The primary goal is to establish a multicenter SuperAging Consortium to identify behavioral, health, biologic, genetic, environmental, socioeconomic, psychosocial, anatomic and neuropathologic factors associated with SuperAging. These goals will be achieved through an organizational structure with 3 Cores (Administrative/Biostatistics, Clinical/Imaging, and Biospecimen/ Neuropathology) and 2 Research Projects. The Consortium will enroll 500 participants across 4 US Sites located in Illinois, Wisconsin, Michigan and Georgia, and the Canadian Site in Southwest, Ontario, with a focus on the enrollment of Black SuperAgers and Cognitively Average Elderly Controls with similar demographics (Controls). The Administrative/Biostatistics Core will provide governance and fiscal oversight, maintain scientific integrity, and create a centralized biostatistics and database infrastructure to harmonize the goals and activities of the Cores, Sites, and Projects, with each other, with the NIA, and with extramural collaborators. The Clinical/Imaging Core will standardize criteria for the uniform cross- site and multidisciplinary characterization of SuperAgers, streamline recruitment including that of Black participants, enter relevant information in the comprehensive database, support co-enrollment into Project 1, and encourage collaborative ventures aiming to understand the factors that promote SuperAging. The

Biospecimen/Neuropathology Core will collect and bank brain tissue and blood products from SuperAging and Control cases, according to optimized procedures. It will render pathological diagnoses, quantitate selected markers of neurodegeneration and neuronal structure, coordinate the analyses of plasma biomarkers for Alzheimer's disease, and make specimens available for collaborative investigations. Project 1 will use state-of-the-art wearable technology to obtain real-time measurements in the course of everyday life to characterize quantitative parameters related to sleep, physical activity, autonomic responsivity, and social engagement to determine whether SuperAgers have relatively preserved and quantitatively determined physiologic and behavioral "complexity" compared to Controls. Project 2 will use transcriptomic, genetic, and protein profiling approaches to test the hypothesis that SuperAgers will demonstrate significant molecular differences in their central and peripheral immune and inflammatory system parameters compared to matched Control and Alzheimer's disease participants. By identifying neurobiologic features that contribute to superior memory performance in old age, outcomes from this Consortium will help isolate factors that promote successful cognitive aging and perhaps also prevent age-related brain diseases such as Alzheimer's disease.

PUBLIC HEALTH RELEVANCE: The proposed Consortium offers optimal organization for the accelerated recruitment of a racially diverse cohort of SuperAgers so that they can be more fully characterized neuropsychologically, neuropathologically, psychophysiologically, and molecularly. The planned activities of the Consortium will help isolate factors important for promoting successful cognitive aging and potentially also for avoiding age-related brain diseases such as Alzheimer's disease.

Update on findings from the MEDEX Clinical Trial (R01AG049369)

Findings continue to be published from the MEDEX ("Remediating Age-related Cognitive Decline: Mindfulness-based Stress Reduction and Exercise"; R01AG049369) clinical trial that received past support through the Research Partnership in Cognitive Aging. Focusing on those individuals in MEDEX who received the exercise intervention (n = 225) or a nonexercise comparison condition (n = 260), they estimated for each a physiological age of the brain and derived a predicted age difference compared with chronological age, which they termed BrainPAD. The researchers found that for cognitively normal older adults, exercise did not appear to impact BrainPAD but was effective in improving fitness, body composition, and total sleep time. Changes in body composition, but not fitness, physical activity or sleep, impacted BrainPAD. They concluded that a focus on weight control, particularly central obesity, could be an interventional target for healthier brains.

Update on an Additional Initiative Stemming from the Cognitive Aging Summit III

One of the recommendations from the 2017 Summit was to support a longitudinal study of rats that would closely track the animals throughout their lives. NIA's Intramural Research Program (IRP) implemented that recommendation via a longitudinal study in rodents, "Successful Trajectories of Aging: Reserve and Resilience in Rats" (STARRRS). The award was made to Dr. Peter Rapp in the IRP. The study is on track to generate state-of-the-art neuroimaging, along with phenotypic results, non-invasive biological samples, plus other indicators that should yield insights into the mechanisms of healthy neurocognitive aging. The overarching goal of STARRRS is to establish an open resource of longitudinal data from male and female rats, including detailed behavioral characterization and neuroimaging, tissues and other biospecimens, for research on mechanisms of reserve and resilience in aging, and to inform resilience to Alzheimer's disease and related dementias. As of the end of 2024, approximately 200 animals have completed the

longitudinal study. Brain MRI scans and phenotypic data (motor activity, memory, attention, olfaction, frailty, and anxiety assessments), as well as biosamples have been collected on these 200 animals and deposited in the Aging Research Biobank (https://agingresearchbiobank.nia.nih.gov/). Processing is continuing to make data and samples accessible to researchers in the near future.

APPENDIX

- *Medicine & Science in Sports & Exercise*: Fatness but Not Fitness Linked to BrainAge: Longitudinal Changes in Brain Aging during an Exercise Intervention
- *Brain Communications*: SuperAging functional connectomics from resting-state functional MRI
- *New York Times*: A Peek Inside the Brains of ‘Super-Agers’
- *Chicago Sun Times*: 'Enjoy just being here' — At almost 110, she's still baking pie, with a little help
- *Boston Globe*: Who gets to live to 100? The answer may surprise you.
- Additional 2024-2025 Media Coverage
- Example Recruitment Materials
- RADCO Brain Donation Flyer

Fatness but Not Fitness Linked to BrainAge: Longitudinal Changes in Brain Aging during an Exercise Intervention

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ABSTRACT

WING, D., L. T. EYLER, E. J. LENZE, J. L. WETHERELL, J. F. NICHOLS, R. MEEUSEN, J. G. GODINO, J. S. SHIMONY, A. Z. SNYDER, T. NISHINO, G. E. NICOL, G. NAGELS, and B. ROELANDS. Fatness but Not Fitness Linked to BrainAge: Longitudinal Changes in Brain Aging during an Exercise Intervention. *Med. Sci. Sports Exerc.*, Vol. 56, No. 4, pp. 655-662, 2024. Purpose: Fitness, physical activity, body composition, and sleep have all been proposed to explain differences in brain health. We hypothesized that an exercise intervention would result in improved fitness and body composition and would be associated with improved structural brain health. Methods: In a randomized controlled trial, we studied 485 older adults who engaged in an exercise intervention (n = 225) or a nonexercise comparison condition (n = 260). Using magnetic resonance imaging, we estimated the physiological age of the brain (BrainAge) and derived a predicted age difference compared with chronological age (brain-predicted age difference (BrainPAD)). Aerobic capacity, physical activity, sleep, and body composition were assessed and their impact on BrainPAD explored. Results: There were no significant differences between experimental groups for any variable at any time point. The intervention group gained fitness, improved body composition, and increased total sleep time but did not have significant changes in BrainPAD. Analyses of changes in BrainPAD independent of group assignment indicated significant associations with changes in body fat percentage (r(479) = 0.154, P = 0.001), and visceral adipose tissue (VAT) (r(478) = 0.141, P = 0.002), but not fitness (r(406) = −0.075, P = 0.129), sleep (r(467) range, −0.017 to 0.063; P range, 0.171 to 0.710), or physical activity (r(471) = −0.035, P = 0.444). With linear regression, changes in body fat percentage and VAT significantly predicted changes in BrainPAD (β = 0.948, P = 0.003) with 1-kg change in VAT predicting 0.948 yr of change in BrainPAD. Conclusions: In cognitively normal older adults, exercise did not appear to impact BrainPAD, although it was effective in improving fitness and body composition. Changes in body composition, but not fitness, physical activity, or sleep impacted BrainPAD. These findings suggest that focus on weight control, particularly reduction of central obesity, could be an interventional target to promote healthier brains. Key Words: VISCERAL ADIPOSE TISSUE, MAXIMAL CARDIOVASCULAR FITNESS, SUCCESSFUL AGING, EXERCISE INTERVENTION, BRAIN HEALTH

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Submitted for publication May 2023.
Accepted for publication October 2023.

0195-9131/23/5604-0655/0
MEDICINE & SCIENCE IN SPORTS & EXERCISE®

DOI: 10.1249/MSS.0000000000003337

Changes in brain structure are clearly associated with advancing age. These changes include reduced cortical thickness (1), volumetric decline of both gray and white matter (2,3), and an increase in the absolute number and total volume of white matter hyperintensities (4). However, there is substantial individual variability in the prevalence of these declines (5), as well as the rate at which they progress when observed (3). Better understanding of the mechanisms underlying, and the behaviors that contribute to or inhibit, these changes could help inform interventions targeted at slowing brain structural and functional declines.

High levels of physical fitness, regular engagement in formal exercise, and high levels of overall physical activity have all been hypothesized to explain some of the observed individual differences in brain health. Indeed, several large observational studies have found associations between levels of physical activity and both brain volume and the risk of developing cognitive dysfunction (6). Furthermore, systematic reviews of observational studies have observed that both higher levels of fitness and engagement in regular moderate to vigorous physical activity are often associated with higher volume of gray matter across key regions of the brain, including the hippocampus and prefrontal cortex as measured by magnetic resonance imaging (MRI) (7). Longitudinally, multiple studies have found associations between increased physical activity and changes in brain volume in key regions among both healthy individuals (6) and those with mild cognitive impairment (8), Furthermore, meta-analyses of interventional studies suggest that increasing the number of minutes of moderate- to vigorous-intensity physical activity improves cognitive function in older adults (9) particularly in individuals who are cognitively and physically healthy at baseline (10). In general, these observed improvements are further enhanced by the presence of multimodal instruction that includes strength training (10). However, positive associations both cross-sectionally and longitudinally are not universally observed depending upon clinical status and the presence of comorbidities (2), and some studies have found no association between cardiorespiratory fitness and brain volume in healthy (11,12) and cognitively impaired (13) populations.

Independent of fitness and activity levels, body composition, particularly body fatness, has also been hypothesized to contribute to changes in brain volume and cognitive function. For example, higher BMI has been associated with decreased gray matter volume across multiple brain regions (14), and links between central adiposity, as measured by waist circumference, and executive function have been observed both in children (15) and older women (16). Recent systematic reviews of cross-sectional studies have indicated that obesity, particularly central obesity, is commonly correlated with reduced cortical thickness and gray matter volume (17) and with cognitive impairment in older adults (18). However, prospective longitudinal studies in both children (15) and midlife adults (19) have observed a bidirectional predictive relationship between cognition and central obesity indicating that there may be a common causal pathway contributing to the development of both conditions. Kullmann et al. (20) may have identified at least some portion of this shared pathway, noting that insulin sensitivity in the brain is strongly associated with volume of visceral fat, and insulin (in)sensitivity is associated with cognitive capacity. Beginning in the early 2010s, tools utilizing the capabilities of machine learning algorithms to provide a comprehensive assessment of structural changes within the brain have emerged. These algorithms are applied to MRI images to use volumetric measures of multiple brain regions drawn from large samples that range widely in age to provide an estimation of the *physiological* age of the brain (commonly termed BrainAge). The difference between this BrainAge and chronological age can be calculated to provide a brain-predicted age difference (BrainPAD). Using this, we can determine if an individual's brain structure is younger (negative BrainPAD) or older (positive BrainPAD) than expected. These tools have successfully predicted age across the human lifespan, including in healthy adolescents (21) and older adults (22). In addition, these algorithms show very good test/retest reliability (23) and have correctly identified larger BrainPAD (i.e., higher values/older brains) in populations with expected negative changes in brain structure and/or with evident cognitive decline including multiple sclerosis (24), stroke (25), and Traumatic Brain Injury (26). As such, BrainAge (and the associated BrainPAD) may offer meaningful public health research applications, although there has been little longitudinal research into predictors of BrainPAD or the likelihood of changes in BrainPAD in response to changes in modifiable behaviors.

Our research question(s) centered on how BrainPAD was affected by an exercise intervention and associated changes in fitness, fatness, activity, and sleep. We hypothesized that a 6-month moderately intense multimodal exercise intervention focused on a combination of aerobic exercise, traditional resistance training, and functional movements would result in improved physical fitness and body composition (i.e., greater aerobic capacity, less body fat and visceral adipose tissue (VAT), and greater lean mass). We further hypothesized that this intervention would improve BrainPAD, and that those improvements would be associated with changes in the metrics of interest. As a secondary but associated research question, we explored changes in fitness and/or body composition independent of their experimental grouping, with a hypothesis that beneficial changes over 6 months (i.e., greater fitness, less fat) would be associated with changes in BrainPAD indicating brains that are growing "younger" compared with chronological age. We had a final hypothesis that changes in sleep would be associated with changes in BrainPAD (with more sleep leading to a more negative/younger BrainPAD value), although likely minimally affected by the intervention.

METHODS

Participants. Data were drawn from a multicenter randomized interventional clinical trial approved by Institutional Review Boards at both the University of California, San Diego, and Washington University in St. Louis, and informed consent to participate in the research study was obtained from all participants. This group has been described in depth

elsewhere (27). In brief, participants were sedentary adults aged 65 to 84 yr, not currently using glucocorticoid or diabetes medications, and without diagnosed cognitive impairment or neurodegenerative or cardiovascular disease.

Exercise intervention. The exercise intervention was designed with the goal of integrating progressive aerobic and resistance training with functional movement and balance training and has been described in detail previously (28). In short, minimal heart rate targets during aerobic training were generated, personalized resistance training goals were established, and a comprehensive manual was developed to ensure consistency across sites and cohorts. All sessions were led by a trainer licensed by a nationally accredited organization (either The American College of Sports Medicine, The American Council on Exercise, or The National Academy of Sports Medicine) with extensive (>2 yr) on-the-job experience working with older adults. In addition to demonstrated experience working with the target population, trainers went through a 12-h training specific to the intervention during which the goals of the intervention, the exercise prescription and progression plans, and the specific exercises to be utilized were discussed and practiced in detail using team members and "friends and family" as example participants. Across the course of the intervention, a total of five (three at one location and two at the other) trainers were engaged, with one "lead" trainer at each location leading ~60% of all classes at that intervention site. Classes were 90 min and were held twice weekly for 6 months. Classes started with a 30-min warm-up period that included integrated movement designed to warm the body and raise the heart rate to a level at (or above) 55% of heart rate reserve. After the warm-up, classes were split roughly in half, with one group beginning aerobic exercise and the other beginning strength training. After 30 min, the groups switched training positions.

It is worth noting that the larger study was designed with a 2 × 2 factorial design in which approximately half of the individuals within the exercise intervention also received a mindfulness-based stress reduction (MBSR) intervention. Similarly, approximately half of the individuals within the control condition also received MBSR training, whereas the other half received a series of lectures aimed at health promotion. These lectures specifically avoided topics related to exercise and/or mindfulness. All individuals were included in these analyses without differentiation between those receiving or not receiving MBSR.

Neuroimaging acquisition. Neuroimaging was gathered at baseline and following the 6-month intervention period. All baseline scans were acquired >1 d, but <30 d before intervention initiation and ±2 weeks from intervention completion. For individuals involved in the exercise intervention, neuroimage scanning was completed on a nonexercise day (i.e., not on a day where formal training occurred), and participants were asked to report to the scanning location well rested. Although all scans were acquired during standard operating hours (8 AM to 5 PM), time of day and day of the week were not controlled.

MRI scanners (3 T) were used to acquire high-resolution (1 × 1 × 1 mm) T1-weighted sagittal, magnetization-prepared rapid gradient echo with one scanner used at one site (GE, Signa—MP-RAGE; repetition time (TR) = 2300 ms; inversion time (TI) = 900 ms, echo time (TE) = 2.95 ms, flip angle = 9°; acquisition time = 5 min) and two used at another (Siemens Prisma and Tim Trio—MP-RAGE TR = 2400 ms, TI = 1000 ms TE = 3.16 ms, flip angle = 8°). Both used real-time motion correction (PROMO). Scans were processed using FreeSurfer (version 6.0) to provide quantitative measures of image quality. All images were reviewed for incidental findings or excessive head movement by the study neurologist(s).

BrainAge processing of T1-weighted MRI images. The BrainAge model developed by James Cole, commonly called BrainAgeR, was used for these analyses (22). This model was deemed to be the most appropriate available model as the algorithm training was done on a group that contained a comparatively large number of individuals over the age of 65 yr. To derive the BrainAge score, T1-weighted MRI scans were segmented and normalized using SPM12. Vectors with mutually exclusive compartments for Grey Matter, White Matter, and Cerebral Spinal Fluid were established using the Rnifti package in R. The Kernlab package was then applied to provide a BrainAge score using the 435 established input variables. To provide visual quality control beyond the point-of-acquisition review described below, multiple slices of the brain were provided as visual images in .html format using an FMRIB Software Library program. These images were reviewed for obvious object or movement artifact by a specially trained researcher. BrainPAD scores were calculated by subtracting chronological age from the BrainAge score provided by the algorithmic scoring. Positive values reflect brains that are older than chronologically expected, whereas negative scores indicate brains that are younger than the chronological age of the individual.

Assessment of BrainAge values and images for inclusion. Study neurologist's recommendations regarding image usability were applied so that individuals who had uninterpretable findings were not analyzed. The Euler number, which is derived from the FreeSurfer algorithm and provides a quantified description of the number of holes in an image, was applied to further exclude individuals whose scans were poorly visualized and likely to be subject to error. In addition, individuals who had a change in BrainPAD from baseline to the end of the intervention >3 SD from the group change calculated in absolute values were excluded on the presumption that one (or both) of their scans had features that led to inaccurate scoring.

Physical measures (graded exercise test, dual x-ray absorptiometry, accelerometry). These physical measures have been presented in greater detail by Wing et al. (28) and Wetherell et al. (29). However, we have provided key elements of the physical measures below.

A graded exercise test to 85% of age-predicted maximal heart rate (220-age—APMHR) was conducted on either a treadmill (Quinton QStress; Cardiac Science, Chelmsford, MA) or a cycle ergometer (LODE Excalibur Sport, the Netherlands) using 2-min stages that increased by 2.5% elevation (treadmill) or 0.33 $W \cdot kg^{-1}$ (cycle) per stage and continued until the participant reached the predetermined 85% value or the study physiologist ended the test based on physiological changes. Exercise capacity was

calculated in metabolic equivalents of task (METs) using formulas published by the American College of Sports Medicine based upon speed and grade. METs were chosen as the metric of interest based on its common usage in clinical contexts, but changes in estimated oxygen uptake ($\dot{V}O_2$) normalized for body weight at 85% of APMHR could be calculated by multiplying the METs value by 3.5 $mL \cdot kg^{-1} \cdot min^{-1}$.

Body composition was assessed by dual x-ray absorptiometry (DXA) images gathered using a GE Lunar Prodigy densitometer at one site and an iDXA (GE/Lunar, Madison, WI) at the other. Both scanners utilized EnCore software (versions 14.1 and 16.1, respectively) for estimation of body composition. Values of body fat, lean tissue, bone, and VAT were generated. Body fat percentage was derived by dividing the total body fat by the sum of fat, lean, and bone components. Appendicular lean muscle index (ALMI) was derived to control for differences in lean tissue attributable to differences in height. This variable was derived using the sum of the lean tissue (in kilograms) in the arms and legs divided by the participant's height in meters squared.

A triaxial accelerometer, the Actigraph GT9X+ Link (Actigraph Inc., Pensacola, FL), was used to objectively measure physical activity and sleep. Participants were asked to wear the device on their nondominant wrist continuously for 10 d except while bathing or swimming. This location and duration of wear are consistent with best practice as they result in a high degree of wear compliance and have been shown to capture sufficient wear time to be indicative of normal activity (30). After participant wear, devices were downloaded and screened for sufficient wear and potential device malfunction using commonly accepted methods (30) and algorithms (31) with acceleration data process into vector magnitude counts per minute (VM CPM). This metric incorporates intensity, frequency, and duration of movement and has been recognized as a reliable method to assess total volume of physical activity across 24-h (or longer) periods of observation (32) as well as being able to distinguish between sleep and wakefulness (33). Participants were asked to maintain sleep journals recording the time they tried to fall asleep and the time that they first woke during the period(s) of accelerometer wear. These time windows were analyzed on a minute-by-minute basis to determine sleep time using an algorithm designed for use in healthy adults (33). In addition to total sleep time, sleep efficiency and wake after sleep onset (WASO) (both in terms of number of events and total time of events) were calculated.

Statistical analysis. Power calculations were conducted *a priori* to answer the primary research questions of the larger study that these data are drawn from. Specifically, based upon prior investigations completed by the primary investigators of the larger study, power calculations were completed to detect changes in performance-based assessments of cognition and hippocampal volume. Further analysis of power was not conducted for the specific outcomes analyzed here as these data were drawn from the available participant pool. Participants were excluded from any analysis for which they had missing values. SPSS version 27 was used to complete all statistical analysis. Descriptive statistics (percentages, means, and SD) were used to characterize demographic variables and identify potential outliers. Change scores were derived by subtracting baseline values from follow-up values on an individual level. Independent *t*-tests were conducted to assess differences across groups at baseline, and 2 × 2 (time × group) mixed measures ANOVAs were conducted to evaluate the effects of the intervention on BrainPAD, aerobic fitness, body composition, activity levels, and sleep. When there were significant effects for both the interaction and time, groups were split with the effect of time evaluated independently using paired sample *t*-tests.

Independent of the intervention group, associations between changes in BrainPAD and changes in fitness, body composition, activity, and sleep were examined using Pearson's correlation without controlling for any covariates. When associations between change scores were observed, univariate linear modeling was conducted with sex, site, and chronological age included as covariates. These were included based on the known systematic bias in BrainAge estimation toward younger-appearing brains in older individuals, the possibility of systematic differences across sites, and the substantial differences in absolute values for body composition and fitness associated with sex. Years of education were also initially included as a covariate, but excluded when it did not contribute at all to model fit.

RESULTS

After excluding individuals without sufficient imaging (n =1 at baseline, and n = 47 at follow-up), those with suboptimal scans (n =8 at baseline and n = 1 at follow-up), individuals with BrainPAD changes >3 SD of absolute change (n = 10; 5 positive and 5 negative), and those missing all comparator values for aerobic capacity, accelerometry, and body composition (n = 1), a total of 485 participants were included. Because of partially missing data, an additional 77 participants were excluded from analysis of fitness, 4 from body composition, 12 from accelerometry-based physical activity, and 16 from accelerometer-based sleep. Overall, the sample was 72.6% female and showed some racial diversity (365 (75.3%) non-Hispanic White, 54 (11.1%) Black, 33 (6.8%) Hispanic, and 23 (4.7%) Asian, with the remaining 10 (2.1%) claiming either more than one category or declining to answer). Descriptive data and results of 2 × 2 (intervention group × time) mixed measures ANOVA are detailed in Table 1.

There were no significant differences at baseline between those randomized to exercise versus nonexercise conditions for any variables (P range = 0.075 to 0.947), nor were there any cross-sectional group differences at 6 months (P = between 0.118 and 0.944). Variables that were the closest to significant at baseline were total body percentage fat (P = 0.075) with those in the intervention group having an average body fat percentage of 40.5% versus 39.3%, and BrainPAD (P = 0.119) with those in the exercise group having a BrainPAD of −2.5 yr versus −1.6 yr in the nonexercise group.

Changes over time were significant, and the degree of change also differed significantly between the exercise and nonexercise intervention groups for cardiovascular fitness

TABLE 1. Descriptive of key variables at baseline and 6 months.

	Total Group		Exercise Group		Nonexercise Group		
Variable	Baseline Mean (SD)	6-Month Mean (SD)	Mean (SD)	6-Month Mean (SD)	Mean (SD)	6-Month Mean (SD)	*P* for Time by Group Interaction
BrainAge (yr)	69.2 (7.6)	70.0 (7.4)	69.1 (8.1)	69.8 (8.0)	69.4 (7.0)	70.1 (6.9)	0.959
n	485	485	225	225	260	260	
BrainPAD (yr)	−2.0 (6.3)	−1.9 (6.2)	−2.5 (6.6)	−2.4 (6.6)	−1.6 (5.9)	−1.5 (5.9)	0.996
n	485	485	225	225	260	260	
Fitness (METs)	4.7 (1.5)	5.2 (1.5)	4.6 (1.4)	5.3 (1.4)	4.8 (1.6)	5.1 (1.5)	0.001
n	471	414	216	192	255	222	
Body fat (%)	39.8 (7.6)	39.2 (7.8)	40.5 (7.0)	39.0 (7.5)	39.3 (8.0)	39.4 (8.1)	0.001
n	485	481	225	224	260	257	
Lean tissue (kg)	43.7 (9.2)	43.8 (9.0)	43.0 (8.8)	43.6 (8.8)	44.2 (9.6)	43.9 (9.2)	0.001
n	485	481	225	224	260	257	
ALMI (kg·m^{-2})	6.97 (1.24)	6.93 (1.35)	6.94 (1.18)	7.01 (1.26)	6.99 (1.30)	6.86 (1.43)	0.004
n	484	481	224	224	260	257	
VAT (kg)	1.32 (0.93)	1.28 (0.88)	1.32 (0.91)	1.24 (0.83)	1.33 (0.95)	1.32 (0.92)	0.001
n	480	476	224	223	256	253	
Sleep efficiency (%)	84.2 (6.8)	84.2 (6.5)	84.1 (6.6)	84.1 (6.7)	84.3 (6.9)	84.3 (6.4)	0.806
n	483	471	225	221	258	250	
Time asleep (min)	384.6 (56.3)	384.9 (58.8)	382.9 (59.9)	388.9 (60.6)	386.1 (53.1)	381.4 (57.0)	0.011
n	483	471	225	221	258	250	
WASO (min)	72.5 (33.2)	71.8 (30.4)	72.4 (31.4)	72.7 (31.0)	72.6 (34.8)	71.1 (29.8)	0.608
n	483	471	225	221	258	250	
VM (CPM)	1937 (506)	1952 (539)	1935 (484)	1964 (533)	1938 (525)	1941 (545)	0.385
n	483	475	225	222	258	253	

BL, baseline.

(METs, $P \le 0.001$ for both time and group × time interaction), body fat percentage ($P \le 0.001$ for both time and group × time interaction), total lean tissue ($P = 0.003$ for time and <0.001 for group × time interaction), and VAT ($P = 0.002$ for time and <0.001 for group × time interaction). Follow-up tests indicated that the intervention group gained fitness and improved body composition by lowering body fat percentage and visceral adiposity and increasing lean tissue, whereas the nonexercise group had a significant decrease in lean tissue and nonsignificant changes in body fat and VAT. Somewhat unexpectedly, the nonexercise group also evidenced increased fitness, although not by as large a margin as the exercise group. There was also a significant effect of the intervention on total sleep time (group × time interaction, $P = 0.011$), with small increases in the exercise group and nonsignificant decrease in the nonexercise group; the main effect of time was not significant ($P = 0.485$). Specific results and confidence intervals of follow-up tests are shown in Table 2.

As would be expected with over an approximately 6-month period, there was a significant effect of time for BrainAge ($P = 0.001$) with BrainAge increasing 0.709 yr on average (CI, 0.502 to 0.916). However, there was no significant group by time interaction ($P = 0.959$). In addition, there was no significant effect for time or group by time interaction for BrainPAD ($P = 0.345$ for time and $P = 0.996$ for interaction), nor for sleep efficiency ($P = 0.870$ for time and 0.806 for interaction), number of minutes awake during sleep periods (WASO, $P = 0.096$ for time and 0.608 for interaction), or overall daily physical activity (VM, $P = 0.503$ for time and 0.385 for interaction).

As with many interventions, changes in the metrics of interest were not universal, and some individuals within the nonexercise group also experienced meaningful changes, particularly in fitness. With this in mind, we explored the correlations between changes in BrainPAD and changes in fitness, fatness, activity, and sleep without consideration of the group. These analyses revealed that changes in BrainPAD were significantly associated with changes in body fat percentage ($r(479) = 0.154$, $P = 0.001$) and VAT ($r(478) = 0.141$, $P = 0.002$), but not fitness ($r(406) = -0.075$, $P = 0.129$), metrics of sleep ($r(467)$ range, −0.017 to 0.063; P range, 0.171 to 0.710), or physical activity ($r(471) = -0.035$, $P = 0.444$).

When significant associations were explored independently (while controlling for chronological age at baseline, gender, and location) via linear regression, changes in both body fat percentage and VAT significantly predicted changes in BrainPAD ($P = 0.002$ and 0.003, respectively), although when both are included in the model, neither remains significant ($P = 0.054$ and 0.089, respectively), likely because of a moderate amount of collinearity. The regression model including changes in VAT is included in Table 3, which indicates

TABLE 2. Significant interaction effects from the exercise intervention.

Variable	Units	Exercise		No Exercise	
		Estimate (CI)	*P*	Estimate (CI)	*P*
CRF	METs	0.695 (0.571 to 0.820)	<0.001	0.313 (0.189 to 0.437)	<0.001
Body fat	%	−1.433 (−1.158 to − 1.709)	0.001	−0.095 (−0.331 to 0.142)	0.432
Lean tissue	kg	0.584 (0.418 to 0.751)	<0.001	−0.237 (−0.397 to −0.077)	0.004
ALMI	kg·m^{-2}	0.72 (0.004 to 0.140)	0.039	0.133 (−0.019 to −0.247)	0.022
VAT	g	−84 (−46 to − 123)	0.001	4 (38 to -30)	0.803
TST	min	6.4 (0.7 to 12.1)	0.028	-3.7 (-8.9 to 1.6)	0.171

Significant results in bold.
ALMI, Appendicular Lean Mass Index; CRF, cardiorespiratory fitness; TST, Total Sleep Time; VAT, Visceral Adipose Tissue.

TABLE 3. Linear regression analysis of the association between changes in VAT and changes in BrainPAD.

Model Summary	*R*	R^2	Adjusted R^2	SEE	*P*
	0.203	0.041	0.033	2.258	<0.001

Predictors	Unstandardized *B*	SE	Standardized *B* Coefficient	*T*	*P*
Constant	4.388	1.639		2.677	0.008
VAT mass[a]	0.948	0.316	0.137	2.996	0.003
Covariates					
Chronological age at baseline	−0.054	0.022	−0.110	−2.424	0.016
Sex[b]	0.258	0.237	0.050	1.087	0.278
Site[c]	−0.468	0.208	−0.102	−2.246	0.025

Values for VAT and BrainPAD are change scores based on the difference between values gathered at the 6-month visit minus values gathered at baseline.
[a]VAT derived from DXA measured in kilograms.
[b]Female = 1, male = 2.
[c]UCSD = 1, WUSTL = 2.
UCSD, University of California, San Diego; WUSTL, Washington University of St. Louis.

that for each 1-kg change in VAT, there is a corresponding change of 0.948 yr in BrainPAD when chronological age at baseline, sex, and location are controlled for.

DISCUSSION

As expected, it appears that the multimodal exercise intervention was successful in increasing the cardiovascular fitness of the participants, as well as improving body composition by both decreasing fat and increasing lean tissue. Furthermore, the intervention appeared to have a small but potentially meaningful effect on visceral fat, which is strongly negatively implicated in several chronic disease states common among older adults (34). However, this 6-month exercise intervention did not appear to have a meaningful impact on BrainPAD. In addition, the increased fitness experienced in the nonexercise group suggests that there may have been larger factors at play in this population that encouraged a focus on fitness regardless of the intervention. We have previously observed cross-sectional associations between visceral adiposity, but not fitness and/or physical activity, and BrainPAD (29) in this sample of older adults, and now we show that, when changes in metrics of fitness, fatness, and sleep and their relationship(s) to changes in BrainPAD are explored independent of group assignment, there is a clear association between increased/faster aging brains and increased fatness, particularly increased VAT. However, there was no association between changes in BrainPAD and changes in either fitness or overall physical activity. Given the recent evidence presented by Vidal-Pineiro et al. (35) suggesting that early life behaviors have a strong(er) influence on brain structure, and consequently, BrainPAD, with only minimal contributions from behaviors during middle and older adulthood, it is notable that we found links between BrainPAD change and fatness, but not fitness, change later in life in the context of an intervention study.

These data contrast with published evidence linking fitness and brain health, both in terms of the volume of various brain structures (6) and cognitive performance (10). A possible explanation for this may be that the relatively modest changes in fitness observed in this study (increase of 0.5 METs at 85% of Age Predicted Maximal Heart Rate) were too small to elicit meaningful changes in brain structure (and thus, BrainPAD), and that an intervention that was either longer or more intense might elicit significant changes. Similarly, the combination of strength and aerobic training within the same intervention may have reduced the effectiveness of structural changes that have been observed with interventions more focused on aerobic training exclusively (6,8,9). However, it is worth noting that many of the studies that have found positive associations between fitness and brain structure have looked at individual segments of the brain (i.e., the hippocampus or frontal lobe exclusively); when the whole brain is examined, data have indicated variable levels of association and have generally had small effect sizes (8,36). Furthermore, the data here extend cross-sectional data showing no association between fitness and/or physical activity and BrainPAD in a nearly identical population (29). Given the large number of brain regions/features contributing to the BrainAge score, it is possible that subtle changes to small regions within the brain are not sufficient to meaningfully impact the score. Thus, although BrainAge has proven itself potentially useful in a number of clinical populations (i.e., Traumatic Brain Injury, multiple sclerosis, etc.) to provide a relatively easily understood metric of brain health, it may not be sufficiently sensitive to be useful in evaluating changes that are expected to affect localized regions within the brain, particularly if those regions are ones that are not particularly age related and thus contribute less to the prediction of BrainAge. Interestingly, the observed relationship between body fatness and BrainPAD does offer some evidence to suggest that BrainAge (and the associated BrainPAD) may have utility in evaluating interventional changes in brain health, provided that those changes are occurring across a number of age-related brain regions. Indeed, the results from these analyses match recent research that has identified links between high levels of body fatness and reduced brain health (17,18). Combined with recent scholarship indicating associations between central obesity and declines in whole brain structure (29) and cognitive function (37), these data offer additional evidence to suggest that VAT is particularly deleterious to health and has downstream effects across multiple systems.

Several mechanisms have been proposed to explain the detrimental impact of VAT. For instance, VAT has been linked to reduced immunity secondary to increased levels of inflammation (38) and to increased oxidative stress resulting from upregulated cytokine activation (39). However, potentially most compelling

given the observed links between brain insulin resistance and decreased cognitive function and brain structure (32) is the fact that increased VAT contributes to decreased insulin sensitivity *systemwide* (40). Although these data do not confirm a causal relationship between VAT and insulin (in)sensitivity in the brain, and there is a possibility of shared etiology that affects both independently, they do suggest the possibility of a causal pathway in which increased insulin resistance and visceral adiposity are linked both to each other and to structural brain health.

Although total sleep time was modestly affected by the intervention, neither changes in sleep time nor changes in sleep efficiency were associated with changes in BrainPAD. Because this population was nearly exclusively composed of normal sleepers, both in terms of time and efficiency, and the changes over the observation window were quite small, it is possible that the modest changes in sleep time did not elicit structural changes, or that there was no sufficient variation within the group to detect meaningful differences in brain structure. Furthermore, the lack of association is supported by evidence that suggests that it is only with an amount of sleep substantially above or below the recommended amount (for instance, <4 or >10 h per night) that structural and functional decline is observed (41).

Given the many important positive health outcomes associated with increased fitness and larger volumes of physical activity (particularly moderate to vigorous physical activity), it is tempting to see it as a panacea that can promote good health across all organ systems, including the brain. Interestingly, the role of exercise in weight control is also often overstated (42), further suggesting a desire for one mechanism of intervention to work to promote health in all areas. Unfortunately, likely even more than weight control, brain health is made up of many complementary and interconnected factors that are affected both independently and in coordination with each other. Although these data do not preclude the possibility of positive adaptation in the brain with increased exercise, they do suggest that the physiological aging of the brain as a whole cannot be slowed/changed simply by increasing exercise levels by a moderate amount over a short period. However, these findings do contribute to a substantial literature that suggest that a focus on weight control, particularly reduction/prevention of central obesity, even in the short term, may be a useful target to promote healthier/younger brains, as well as benefiting other physiological systems.

Strengths of this study include the use of high-quality measurement tools in a large population of (presumptively) healthy older adults. Specifically, the use of whole brain MRI imaging for BrainAge calculation, graded exercise testing to estimate aerobic capacity, accelerometry to provide objective measures of physical activity and sleep, and DXA to estimate body composition and visceral adiposity mean that there are likely fewer sources of error compared with proxy measures, self-report, or epidemiologically derived estimation algorithms. However, there are some limitations that should be considered when applying these findings to intervention development or as a guide for future research. In particular is the possibility of a (n unmeasured) shared etiology that accounts for the observed changes in visceral adiposity, and BrainPAD. Furthermore, it is possible that BrainAge, and consequently BrainPAD, is affected not just by the amount of VAT and body fatness, but also by the length of time those metrics are above "safe" levels. In addition, because the BrainAgeR algorithm uses a large number of structural features drawn from multiple brain regions, it is possible that it is insensitive to isolated changes in areas that are less age related and yet make meaningful contributions to cognition and/or function. Furthermore, although 6 months is a reasonably long intervention period, it may be that it was not long enough with an intervention of the intensity used in this investigation to elicit changes in fitness sufficient to manifest as changes in brain structure. Similarly, a 6-month window for observation may not be long enough to see changes in BrainPAD that might be associated with small changes in fitness, fatness, or sleep that are maintained over time. Finally, the degree to which changes in BrainPAD are explained by changes in VAT is small, accounting for less than 4% of the total variance. However, given the potentially modifiable nature of VAT, and the possibility of benefiting multiple other systems through systematic reduction in VAT levels, further research is warranted. In particular, research that better elucidates the causal pathways linking VAT and brain health, or that identifies novel or particularly effective ways to reduce VAT, has the potential to lead to substantial public health benefit, likely including improved structural brain health.

CONCLUSIONS

Brain health as described by the difference between the biological age of the brain versus the chronological age of the individual appears to be modifiable with changes in body composition. Specifically, reducing body fatness in general, and visceral adiposity in particular, is associated with positive changes in BrainPAD consistent with brains growing younger compared with chronological age over time. However, changes in fitness levels, volume of physical activity, and sleep are not associated with changes in BrainPAD. This contributes to the body of evidence that suggests that body composition should be a primary target for behavioral interventions aimed at promoting brain health.

We would like to thank and recognize our funder, the National Institutes of Health (#R01AG049369-01).

We would like to thank the many members of the MEDEX measurement and intervention delivery teams. In particular, we would like to recognize Mr. Michael Higgins, Ms. Mia Green, Ms. Mary Ulrich, Mr. Andrew Scott, Mr. Zachary Bellicini, Ms. Michelle Voegtle, and Dr. David Sinacore for their key contributions to data collection and intervention delivery.

Bart Roelands is a Collen-Francqui research professor. Bart Roelands and Romain Meeusen are members of the Strategic Research Program Exercise and the Brain in Health and Disease: The Added Value of Human-Centered Robotics (SRP17 and SRP77).

The results of this study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation. The results of the present study do not constitute endorsement by the American College of Sports Medicine. The authors have no conflicts of interest to disclose.

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BRAIN COMMUNICATIONS

SuperAging functional connectomics from resting-state functional MRI

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Understanding the relationship between functional connectivity (FC) of higher-order neurocognitive networks and age-related cognitive decline is a complex and evolving field of research. Decreases in FC have been associated with cognitive decline in persons with Alzheimer's disease and related dementias (ADRD). However, the contributions of FC have been less straightforward in typical cognitive aging. Some investigations suggest relatively robust FC within neurocognitive networks differentiates unusually successful cognitive aging from average aging, while others do not. Methodologic limitations in data processing and varying definitions of 'successful aging' may have contributed to the inconsistent results to date. The current study seeks to address previous limitations by optimized MRI methods to examine FC in the well-established SuperAging phenotype, defined by age and cognitive performance as individuals 80 and older with episodic memory performance equal to or better than 50-to-60-year-olds. Within- and between-network FC of large-scale neurocognitive networks were compared between 24 SuperAgers and 16 cognitively average older-aged control (OACs) with stable cognitive profiles using resting-state functional MRI (rs-fMRI) from a single visit. Group classification was determined based on measures of episodic memory, executive functioning, verbal fluency and picture naming. Inclusion criteria required stable cognitive status across two visits. First, we investigated the FC within and between seven resting-state networks from a common atlas parcellation. A separate index of network segregation was also compared between groups. Second, we investigated the FC between six subcomponents of the default mode network (DMN), the neurocognitive network commonly associated with memory performance and disrupted in persons with ADRD. For each analysis, FCs were compared across groups using two-sample independent *t*-tests and corrected for multiple comparisons. There were no significant between-group differences in demographic characteristics including age, sex and education. At the group-level, within-network FC, between-network FC, and segregation measurements of seven large-scale networks, including subcomponents of the DMN, were not a primary differentiator between cognitively average aging and SuperAging phenotypes. Thus, FC within or between large-scale networks does not appear to be a primary driver of the exceptional memory performance observed in SuperAgers. These results have relevance for differentiating the role of FC changes associated with cognitive aging from those associated with ADRD.

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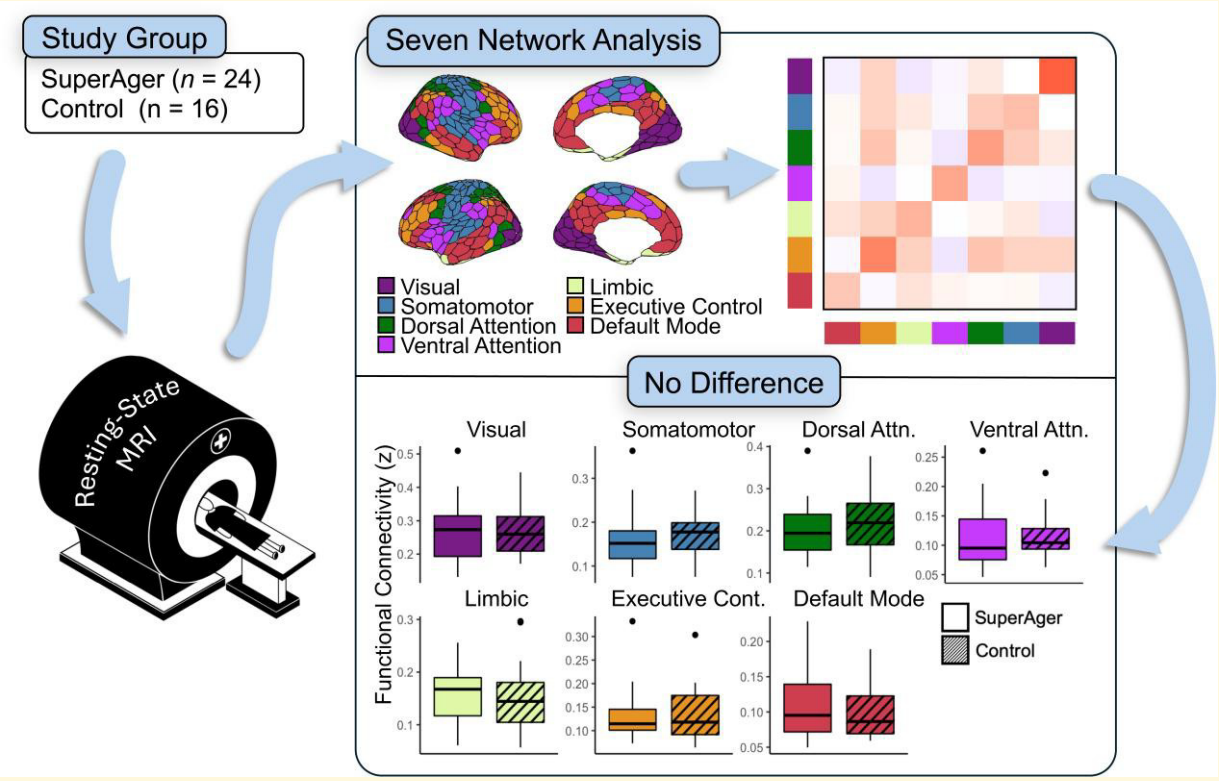
Keywords: neuroimaging; successful aging; memory; neuropsychology

Received December 17, 2023. Revised April 12, 2024. Accepted June 17, 2024. Advance access publication June 11, 2024

Graphical Abstract



Introduction

The global population is rapidly aging and the proportion of adults aged 85 or older is growing faster than younger generations.[1] These adults are at the highest risk for both age-related memory decline[2] and the onset of amnestic dementia due to Alzheimer's disease (AD).[3] However, significant memory decline is not inevitable. A growing literature on 'successful aging'[4,5] has aimed to describe and investigate older adults with unusually high physical,[6-8] social,[7,9] or cognitive functioning.[6,8] Understanding mechanisms of successful cognitive aging promises to inform the development of interventions to prevent or slow cognitive decline.

One well-established phenotype of successful cognitive aging is *SuperAging,* defined by age and cognitive performance as individuals 80 years and older with episodic memory performance equal to or better than 50− to 60-year-olds.[10] The multicenter SuperAging Research Initiative (R01AG045571, R01AG067781, and U19AG073153) was launched to understand what factors underlie this memory-specific phenotype and, by comparison, to inform our understanding of normal cognitive decline and AD. Initial results show that SuperAgers share unique neuropsychological,[11,12] psychosocial,[13] genetic,[10,14] and biologic[15-19] features. Post-mortem studies have identified neurobiological features of the SuperAger phenotype, such as relatively large neurons in the entorhinal cortex,[15] a lower AD neuropathologic burden, and a greater density of von Economo neurons in the anterior cingulate cortex.[16] Structural MRI studies have found brain features of the SuperAging phenotype that appear more like middle-aged-controls than older-aged-controls (OACs), such as relatively slow atrophy rates[20] and thick cingulate cortices.[18] To date, studies of the SuperAger phenotype have focused on brain morphometry. Less is known about the brain functional connectivity (FC) that supports their extraordinary memory abilities.

The brain is thought to be subdivided into distinct brain networks composed of highly interconnected neural regions that communicate to manifest complex behaviours and cognitive abilities.[21] Resting-state functional MRI (rs-fMRI) has emerged as a proxy method for exploring the FC of these distributed neurocognitive networks[22] by capturing intrinsic temporal correlations in neural activity[23] indirectly measured from blood-oxygen-level-dependent (BOLD) signal. Exploratory rs-fMRI studies have identified resting-state networks that correspond to major networks previously established by neuroanatomical experiments[21,24] and others with unclear neural connections.[25] Some resting-state networks are thought to be involved in unimodal sensory processing, such as the visual[26] and somatomotor networks.[23] Other resting-state networks are thought to modulate indistinct higher-order cognitive functions, such as the frontoparietal,[27] ventral attention,[28-30] dorsal attention,[28] and default mode networks (DMN).[31]

Resting-state networks have become a focus of cognitive aging research because they undergo a complex

reorganization during development and in older adulthood[32,33] and within-network FC has been directly related to cognitive performance.[29,34-36] An age-related decrease in within-network FC has been demonstrated in regional activation during task-based fMRI comparing young and older adults[37,38] and in cross-sectional studies of rs-fMRI over the normal lifespan as measured by independent component analysis[39] and seed-based connectivity.[40-42] The significance of these age-related changes is unclear. Some have suggested that a gradual shift away from 'youthful' functional patterns indicates progressive dysfunction and signifies or precipitates cognitive decline.[41,42] One rationale for this hypothesis is that the topography of resting-state networks overlaps with regional activation during specific cognitive tasks. For example, commonly identified regions of the DMN, such as the inferior parietal lobe (IPL), posterior cingulate cortex (PCC), medial prefrontal cortex (MPC), parahippocampal cortex (PHC), medial temporal gyrus (MTG), reliably demonstrate greater BOLD activity during task-based fMRI involving episodic memory encoding and retrieval.[43-45] The DMN is also commonly thought to include the hippocampus,[31] the brain region most commonly associated with episodic memory.[46] In some cases, within-network FC has also been related to composites of neurocognitive performances, such as persons with relatively strong within-network FC in the DMN performing better on episodic memory tasks.[34,39,41] Nearly all higher-order resting-state networks display a similar pattern.[32] As such, the overall degradation of within-network FC may be more closely related to the severe cognitive decline associated with ADRD.

The DMN has become a major focus of cognitive aging research because of its high detectability, topographical overlap with memory-related regions, and enigmatic association with AD dementia. The DMN is one of the most commonly studied resting-state networks.[47] It demonstrates unique functional patterns in persons with mild neurocognitive impairments[48] and amnestic dementia due to AD.[49] The pathogenesis of AD amyloidopathy appears to selectively accumulate within regions of the DMN[50,51] early in the disease course. Given these findings, some have argued that preserved DMN integrity in old age supports optimal memory abilities. However, DMN functional anomalies emerge prior to amnestic symptoms of AD.[49,52-55] In addition, decreases in DMN cannot distinguish persons with amnestic AD from persons with non-amnestic variants of AD.[56-58] Furthermore, functional changes in the DMN are also implicated in non-AD diagnoses including depression, autism spectrum disorder and schizophrenia[44] where memory impairments are not core features. As such, the relationship between the DMN and memory decline in AD is complex, with evidence suggesting the network may be vulnerable to change in multiple disease-related states rather than being specific for AD.

Given the age and AD-related findings, it has recently been proposed that relatively robust FC within neurocognitive networks may support successful cognitive aging. Research differs in the terminology and classification of successful cognitive aging,[59,60] specifically the age range of cohorts, which limits the generalizability of findings. Nonetheless, one recent study of adults aged 60 and over with exceptional episodic memory abilities found that these individuals had relatively strong FC within the DMN and ventral attention neurocognitive networks compared to similar aged cognitive controls.[34] They also reported a positive association between FC and performance on a task of episodic memory. However, another recent study using the same methods in a separate but equally sized cohort from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database was unable to replicate their findings.[61] Two recent studies have used machine learning to differentiate rs-fMRI signal from successful cognitive agers and controls in participants 60 and older[62] and 80 and older.[63] However, results are difficult to interpret because neither study has longitudinal data to ensure that participants were free from emergent neurodegenerative disease.

In summary, the role of resting-state networks in memory and aging is not well defined and the SuperAger phenotype provides a unique opportunity to understand its role in memory preservation beyond the eighth decade. The few studies that have investigated rs-fMRI in successful cognitive aging have had mixed results and no study has longitudinally monitored progressive cognitive decline. This study includes carefully characterized groups of cognitively stable SuperAgers and OACs over two or more visits to investigate the baseline functional integrity of seven canonically defined resting-state networks and subregions of the DMN.

Materials and methods

Participants

Retrospective data used in this project were obtained from the SuperAging Research Initiative database. The goal of the SuperAging Research Initiative is to identify factors that contribute to SuperAgers' uniquely youthful memory function. Participants are community-dwelling, English speaking adults 80 years or older and without significant neurological or psychiatric illness. While enrolled, participants returned every two years for follow-up research visits. At each visit, participants receive a neuropsychological evaluation and, when feasible, MRI scans. Participants were recruited through community lectures, advertisements, word of mouth, community engagement and outreach activities, clinician referral and from the healthy control sample in the Clinical Core of the Alzheimer's Disease Research Center (ADRC) at Northwestern University. This study was approved by the Institutional Review Boards of Northwestern University and the University of Chicago and informed consent was provided by all participants at enrolment.

Neuropsychological evaluation

At each visit, we administered a battery of neuropsychological tests sensitive to detect cognitive aging and incipient amnestic AD dementia[64] that capture both episodic memory

Table 1 Participant demographic and cognitive characteristics

	SuperAgers (n = 24)	Older-aged controls (n = 16)	Statistic (t-test or x^2)	P-value
Demographic characteristics				
Age (SD), y	84.7 (2.89)	84.27 (3.67)	−0.4	0.69
Sex (F,M), no.	16, 8	10, 6	0.00	1.00
Handedness (R, L, A)	22, 1, 1	15, 1, 0	0.75	0.69[a]
Education (SD), y	16.79 (2.23)	15.88 (3.7)	−0.89	0.38
Follow-up time (SD), y	1.78 (0.31)	1.65 (0.3)	−1.31	0.2
Neuropsychological measures				
WTAR Est. FSIQ, (SD), SS	116.75 (6.24)	113.81 (8.83)	−1.15	0.26
RAVLT delay (SD), raw	11.25 (1.68)	6.13 (1.09)	−11.85	<0.001
CFT (SD), raw	22.29 (5.18)	18.25 (4.93)	−2.49	0.02
BNT-30 (SD), raw	28.71 (1.3)[b]	26.63 (3.36)	−2.36	0.03
TMT-B (SD), s	85.36 (33.48)	106.47 (53.01)[c]	1.38	0.18
MRI quality checking				
Mean FD (mm)	0.17 (0.05)	0.17 (0.04)	−0.12	0.91
Volumes after scrubbing (%)	94.31 (3.85)	93.55 (4.92)	−0.53	0.6

[a]One SuperAger was ambidextrous and not included in the x^2 analysis. [b]One SuperAger met all SuperAging criteria with the exception of the BNT-30, but scored within expectation in a subsequent visit, 6 months later. [c]One older-aged control was missing the TMT-B at the MRI visit. SD = standard deviation; y = years; F = female; M = male; d = days; R = right; L = left; A = ambidextrous; SS = standard score (mean = 100; SD = 15); WTAR = Wechsler test of adult reading; FSIQ = Full-Scale Intelligence Quotient; RAVLT = Rey Auditory Verbal Learning Test; CFT = Category Fluency Test; TMT-B = Trail Making Test - B; BNT-30 = 30-item Boston Naming Test; FD = Framewise Displacement.

Table 2 Group classification criteria according to neuropsychological test scores

Cognitive domain	Neuropsychological assessment	SuperAger	Older-aged control
Episodic memory	RAVLT	ss ≥ 10[a]	ss = 7–11
Executive Functioning	Trail Making Test: Part B	ss ≥ 7	ss ≥ 7
Verbal fluency	Semantic Fluency: Animals	T ≥ 40	T ≥ 40
Picture naming	BNT-30	ss ≥ 7	ss ≥ 7

[a]Scaled scores for SuperAgers are compared to 56–64-year-olds (midpoint age = 61); all other standardized scores are compared to same-aged peers. Standardize score summary statistics: ss (mean = 10; SD = 3), T (mean = 50; SD = 10). Reference norms: Rey Auditory Verbal Learning Task, Trail Making Test: Part B, Semantic Fluency, Boston Naming Test. SD = standard deviation; ss = Scaled Score; T = T-Score.

and non-memory domains. Tests included the Rey Auditory Verbal Learning Test (RAVLT) for episodic memory, 30-item Boston Naming Test (BNT-30)[65] for picture naming, Trail Making Test Part B (TMT-B)[66] for executive functioning and Category Fluency Test[67] for verbal fluency. Participant neuropsychological performance is summarized in Table 1.

Group criteria

In accordance with the criteria operationally defined for SuperAgers in the study by Harrison *et al.*, 2012, SuperAgers performed above the average range for their peer age normative group on the RAVLT delayed recall (raw score, ≥ 9), at least as good as normative scores for adults in their 50s and 60s,[68] and at least in the average range compared to same-aged peers on the three other tests loading on non-memory cognitive domains (BNT, TMT-B and Category Fluency Test). OAC scored within one standard deviation of average compared to same-aged peers on the memory measure (RAVLT delayed recall score between 3 and 7) and at least in the average range on other cognitive tests. Group classification criteria are summarized in Table 2. Participants maintained group status at consecutive study visits occurring approximately two years apart (mean = 1.7 years; range = 1.16–2.29 years).

Inclusion criteria

Participants with T_1-weighted (T1w) scans and rs-fMRI scans were considered for this study. Of these participants, we identified those with stable neuropsychological profiles over two visits and excluded those whose group status changed over that interval of time (e.g. participants who developed mild cognitive impairment). MRIs were collected during both visits. Data from the baseline MRI were used in our analysis where possible; data from the second MRI was used only if the baseline scan was unavailable or unusable. We excluded participants with scans containing artefacts in both scans (e.g. magnetic susceptibility, motion, aliasing). In total, 40 participants [mean age (SD): 84.5 (3.2)] were identified for inclusion in the present study. Participant demographics are summarized in Table 1 and a flow chart detailing cohort selection is shown in Fig. 1.

Imaging protocol

MRI scans were acquired for all participants with a standard 12-channel birdcage head coil on a Siemens 3T

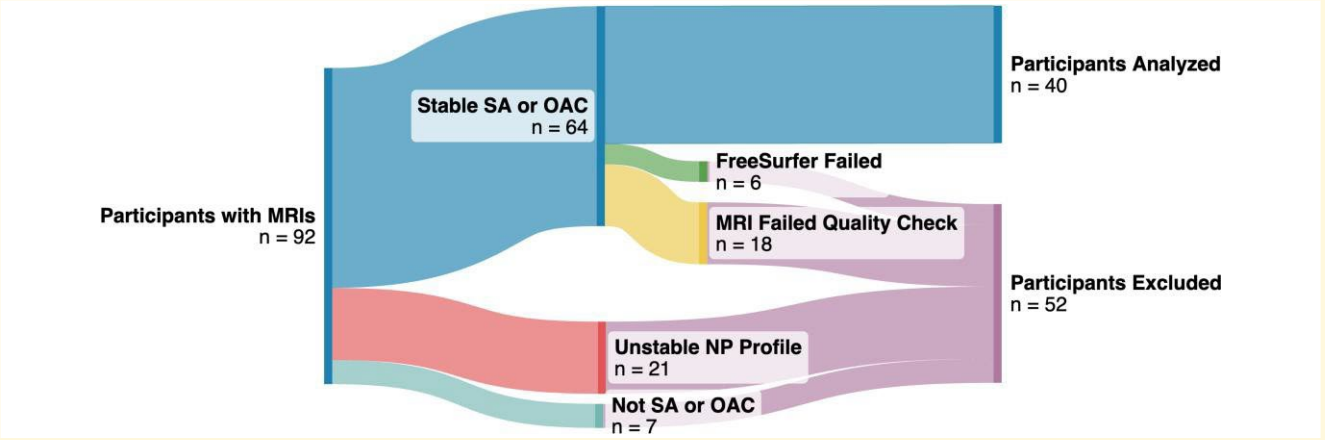


Figure 1 Flow chart of cohort selection. T1w = T1-weighted; rs-fMRI = resting-state functional magnetic resonance imaging; NP = neuropsychological; SA = SuperAger; OAC = older-aged control.

MAGNETOM TIM Trio scanner (Erlangen, Germany). For surface reconstruction, we acquired structural T1w MP-RAGE sequences (repetition time [TR] = 2300 ms, echo time [TE] = 2.86 ms and flip angle = 9°, 1 mm^3). The functional scan was un-directed and participants were instructed to stay awake, keep their eyes open and let their minds wander. Runs were 11.5-minute long and consisted of a spin echo/echo planar imaging sequence with 244 volumes (TR = 2800 ms, TE = 20 ms, 1.7 × 1.7 × 3 mm^3).

MRI processing

Structural imaging

T1w images underwent volumetric segmentations and surface reconstruction by FreeSurfer (v7.2). Trained technicians visually inspected and made iterative edits to optimize FreeSurfer processing. Volumetric segmentations and surface reconstructions were used for registration during rs-fMRI processing.

fMRI quality assessment

Motion artefacts in rs-fMRI are concerning for confounds in older populations.[69,70] Quality checking measures were used to censor time series motion artefacts by accounting for deviation in frame-to-frame motion and signal. Respectively, framewise displacement (FD) is a six-dimensional metric of instantaneous head motion calculated from frame-to-frame and DVARS is the relative change in signal from frame-to-frame. We used the eXtensible Connectivity Pipeline[71,72] (XCP; v3.2) to calculate FD using the formula from Power *et al*. (2014), with a head radius of 50 mm. Volumes with filtered FD greater than 0.4 mm were flagged as outliers and excluded from nuisance regression. The filtered versions of the motion traces and FD were not used for denoising. DVARS and the correlation between DVARS and FD decreased following motion scrubbing. Scans with fewer than 80% interpretable frames (total scan-time, ≥ 9 minutes) were excluded. Quality reports produced by fMRIPrep[73] (v22.1.1) and XCP[71,72] were inspected to ensure suitable completion of preprocessing steps. Quality checking metrics are summarized in Table 1.

fMRI processing

Minimal functional MRI preprocessing was performed using fMRIPrep[73] with custom methodologies. fMRIPrep preprocessing included slice-time correction, motion correction using affine registration to the middle time-point, co-registration to the T1w image and resampling into standard space using a single interpolation step. Following minimal MRI preprocessing, XCP[71,72] was used to post-process rs-fMRI. XCP post-processing includes the removal of initial rs-fMRI volumes, outlier detection and filtering, de-spiking and interpolation and a bandpass filter (0.01–0.1 Hz) to reduce low-frequency drift and high-frequency noise in the signal. Global signal, the first principal components from cerebral spinal fluid and white matter, and frame-to-frame motion in six degrees of freedom calculated during motion correction were regressed out to reduce physiologic noise.[74] The use of global signal regression is controversial and may remove real neural signal.[75] Therefore, all analyses were replicated using rs-fMRI without global signal regression. The processed BOLD was smoothed on the surface using Connectome Workbench[76] with a Gaussian kernel size of 3.0 mm in agreement with best practices.[77-80]

To calculate within-network FC of the DMN, executive control, limbic, ventral attention, dorsal attention, somatomotor and visual networks, Connectome Workbench was used to extract residual signal from all parcels of a seven network (see Fig. 2A), 400 region-of-interest (ROI) parcellation (Schaefer *et al*., 2018), of a common group-level resting-state atlas (Yeo *et al*., 2011), resulting in 400 time-series.[25,81] Subsequently, pair-wise FC (i.e. Pearson's r converted to Fisher's z) between all ROI time-series were computed to create connectivity matrices (400 × 400). Within-network FC was defined as the average z-value for all pairs within a given

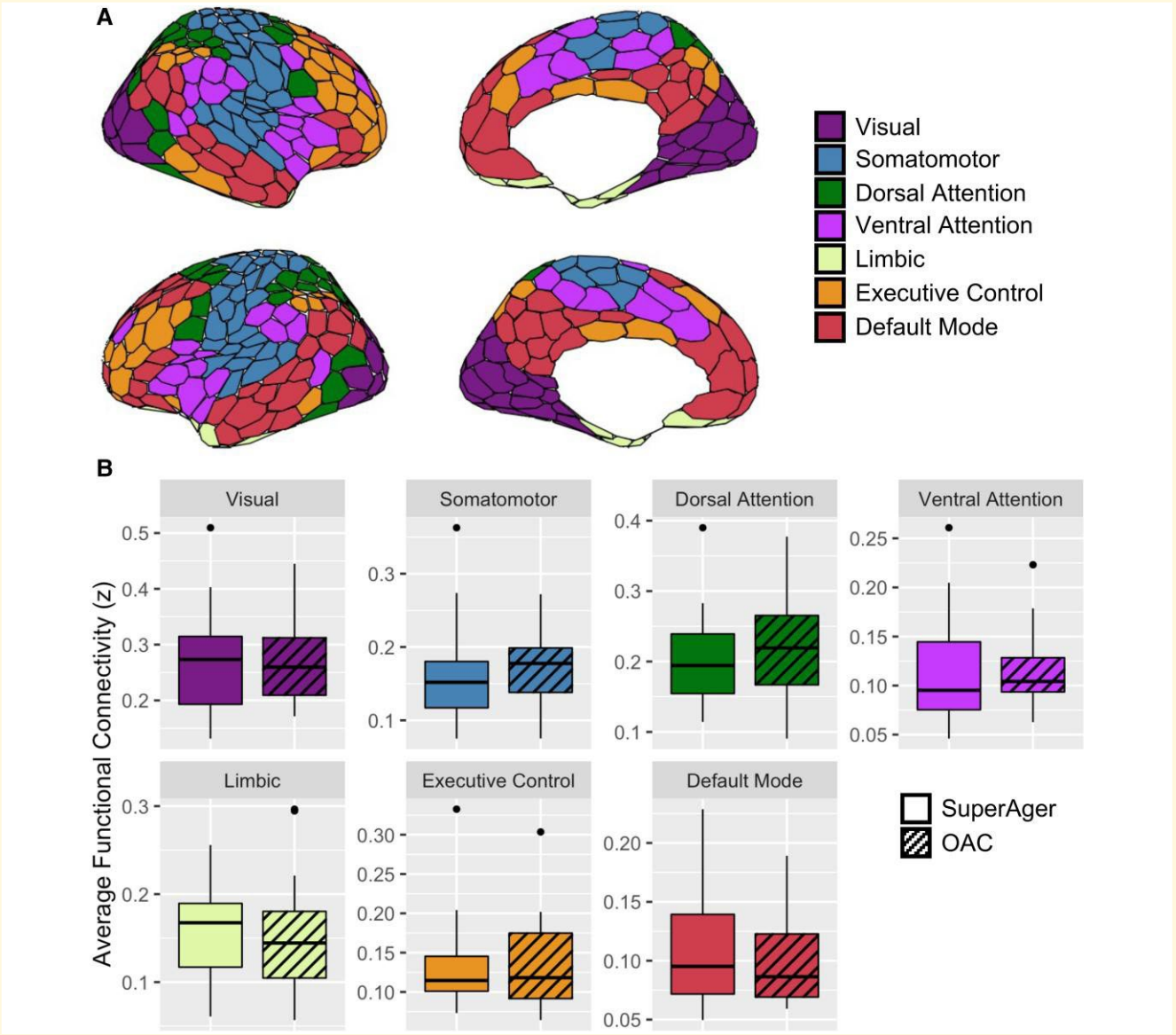


Figure 2 Within-network resting-state functional connectivity does not differ between groups. (**A**) 400-parcel cortical parcellation of seven large-scale resting-state networks from Schaefer *et al.* (2018) used for within-network analysis. (**B**) Average within-network functional connectivity across resting-state networks did not differ between SuperAgers and older-aged controls; OAC = older-aged controls. Wilcoxon signed-rank test; $P > 0.05$ for all comparisons.

network. The seven network parcellation from Schaefer *et al.* (2018) is freely available online.[81]

To calculate the DMN subcomponent FC, ROI-ROI correlation coefficients were calculated from six bilateral DMN canonical regions: the IPL, PCC, MPC, PHC, MTG and hippocampus. Correlations were calculated between each possible pair, for a total of 30 correlations (15 unique correlations) per person. To ensure that ROIs were completely confined to their predefined regions, cortical areas of interest were defined as the central polygon for each DMN region from the seventeen network parcellations subdivided into 600 parcels[81] (Supplemental Fig. 1). The hippocampal ROI was taken from the Human Connectome Project (HCP) subcortical CIFTI atlas.[78] All ROIs were chosen to include homologous regions on both hemispheres. ROI placement is shown in Fig. 3A and cortical ROI identification values (corresponding to the atlas CIFTI metadata) are provided in Supplemental Table 1. Code to generate the custom CIFTI parcellation of cortical ROIs used in the DMN analysis is provided in the Supplemental Material.

Statistical analysis

Independent sample two-tailed *t*-tests and x^2 tests were used to examine group differences in demographic factors, MRI quality metrics and neuropsychological measures. One ambidextrous SuperAging participant was excluded from

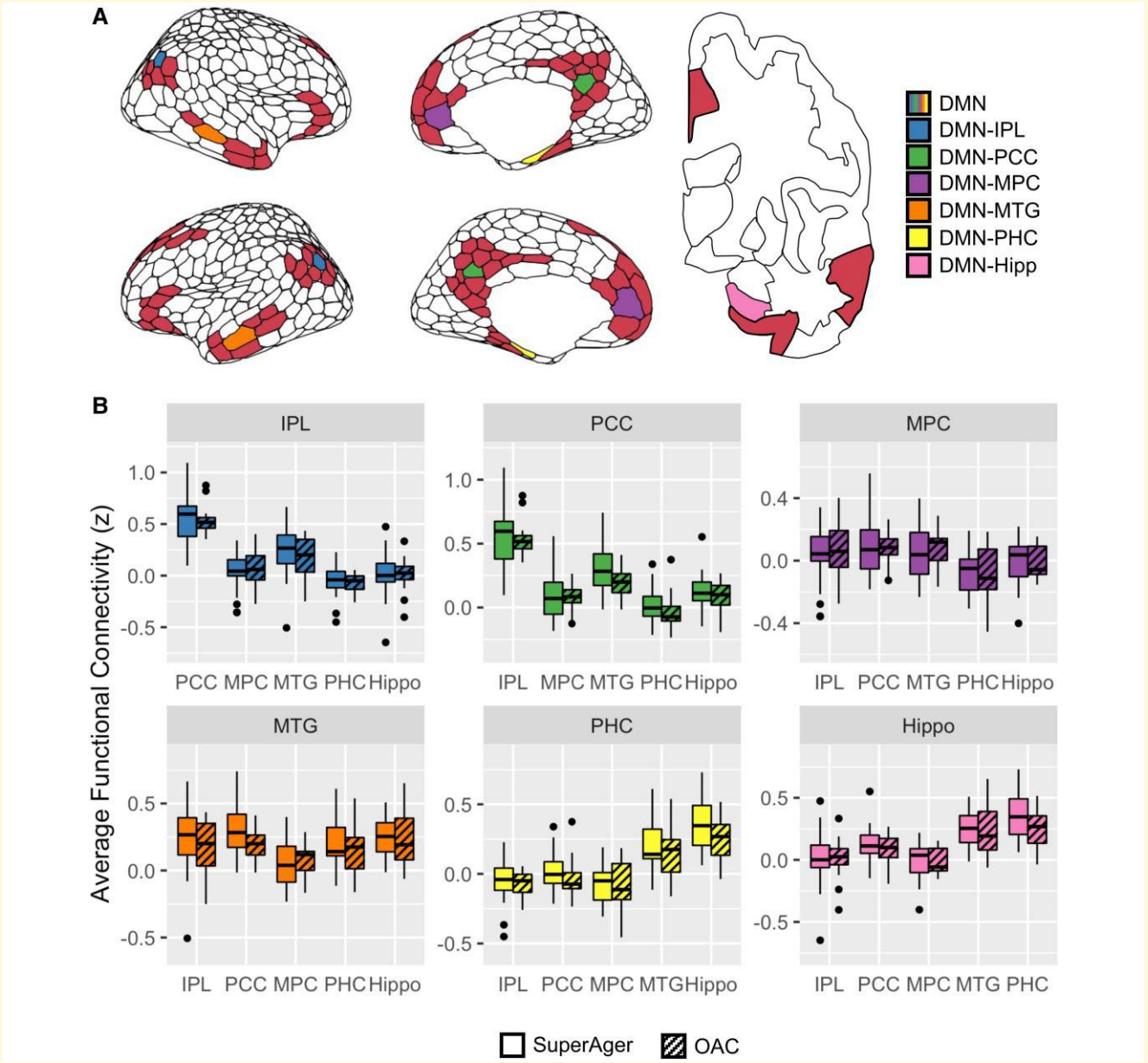


Figure 3 Functional connectivity between subcomponents of the DMN do not differ between SuperAgers and controls.
(A) Regions-of-interest (ROIs) used for functional connectivity of the default mode network (DMN); Left: Five central polygons from DMN clusters of the 600-parcel cortical parcellation from Schaefer *et al.*, 2018; Right: Hippocampus (Hipp) seed from Glasser *et al.*, 2013.
(B) Two-sample independent *t*-tests found no significant between-group difference in functional connectivity; IPL = inferior parietal lobe; PCC = posterior cingulate cortex; MPC = medial prefrontal cortex; PHC = parahippocampal cortex; MTG = middle temporal gyrus. Wilcoxon signed-rank test; $P > 0.05$ for all comparisons.

the handedness x^2 analysis because no OACs were ambidextrous. The Pearson correlation was calculated between the time-series for each possible pair of ROI. For the 400-parcel atlas, this generated 79 800 unique coefficients which were averaged within-network to create seven average within-network coefficients for every participant. Average between-network connectivity was also computed for each participant (Supplemental Fig. 2). Average within-network FC was defined for each participant as the average of all coefficients between two ROIs of the same network (2618 coefficients per participant). For each participant, average between-network FC was defined as the average FC of all ROIs belonging to separate networks (77 182 coefficients per participant). Finally, system segregation was defined for each participant as the difference between within-network FC and between-network FC divided by within-network FC.

For subcomponents of the DMN, we generated 15 unique coefficients for every participant. Pearson's coefficients were converted to Fisher's z-transformed values for all analyses.

After ensuring normality within groups,[82] each within-network coefficient and DMN subcomponent z-value was compared across groups using two-sample independent t-tests with α's adjusted for multiple comparisons using the Benjamini–Hochberg false discovery rate (FDR) at $q = 0.05$.[83] All statistical analyses were performed within RStudio (version 2023.06.1 + 524).

Results

Data inclusion

At the time of our analysis, the SuperAging Research database included 92 participants with T1w scans and rs-fMRI scans from a Siemens 3T MAGNETOM TIM Trio scanner. Of those, 28 were excluded from our analysis due to unstable neuropsychological profiles across two research visits ($n = 21$) or unclear neuropsychological group profile ($n = 7$). An additional 24 were excluded due to artefacts in T1w data that made FreeSurfer segmentation fail ($n = 6$), contained rs-fMRI motion that surpassed FD thresholds ($n = 17$), or had insufficient useable imaging data ($n = 1$). Twenty-four SuperAgers and 16 OACs ($n = 40$) had MRI data and longitudinal neuropsychological profiles that met inclusion criteria for analysis in the present study (Fig. 1).

Demographic and neuropsychological profiles

There were no significant between-group differences in demographic characteristics (all P-values > 0.05) including age, sex, handedness, education or time between research visits. Performance on neuropsychological measures was significantly different between SuperAgers and OACs for episodic memory as measured by the RAVLT delay ($t = -11.85$; $P < 0.01$), generative fluencies as measured by category fluency test ($t = -2.49$; $P = 0.02$) and confrontation naming as measured by the BNT-30 ($t = -2.36$; $P = 0.03$). The between-group difference in RAVLT delay performance is expected due to predefined group classification criteria. There were no significant between-group differences in the overall premorbid functional abilities as measured by the WTAR estimated Full-Scale Intelligence Quotient [FSIQ ($t = -1.15$; $P = 0.26$)] or executive functioning as measured by TMT-B ($t = 1.38$; $P = 0.18$). Statistical tests for group differences in demographic and neuropsychological profiles are summarized in Table 1.

Functional connectivity analysis

After motion scrubbing, there were no significant between-group differences in mean FD or scan length. Group summary values are included in Table 1.

Average within-network FC of seven resting-state networks were compared between SuperAgers and OACs. There were no significant differences between SuperAgers and OACs in within-network FC of the resting-state networks, including the DMN, executive control, limbic, ventral attention, dorsal attention, somatomotor and visual networks (P-values > FDR adjusted α; Fig. 2B). Similarly, there were no significant group differences in between-network FC (Supplemental Fig. 3). Additionally, broader measures of FC compared between SuperAgers and OACs, including average within-network FC from all networks, average between-network FC from all networks, and system segregation, did not differ significantly between groups (P-values > 0.05; Fig. 4).

FC between subregions of the DMN, including the IPL, PCC, MPC, PHC, MTG and hippocampus, were compared between SuperAgers and OACs. There were no significant between-group differences in FC of the four DMN ROIs after adjusting for FDR (P-values > FDR adjusted α; Fig. 3B). Notably, even before adjusting for FDR, we were unable to find significant between-group differences. Replication of all analyses without global signal regression similarly did not reveal significant group differences. Figures contain results from analyses with global signal regression.

Discussion

The present study compared FC within seven canonical resting-state networks and between major regions of the DMN in SuperAgers and OACs. Results showed no significant group differences in FC between groups for any networks or regions of the DMN. The relationship between the large-scale resting-state networks and the spectrum of cognitive aging is complex and group-based average measurements of FC do not appear to explain the exceptional memory performance observed in SuperAgers. Potential contributors to these results, including the discrepancy between our findings and those that have found relatively strong within-network FC of successful cognitive agers,[34] are likely multifactorial.

One possible contributor to the difference between our results and those of previous studies is our longitudinal inclusion criteria to reduce the risk of undiagnosed neurodegenerative processes among our participants. Of the 92 participants from the SuperAging Research Program with MRI considered for our study, 21 exhibited unstable neurocognitive profiles and were excluded. Participants with unstable neurocognitive profiles are not commonly accounted for in alternate successful cognitive aging rs-fMRI studies[59] in part because the studies only have access to cognitive data from a single time-point. Participants with declining neurocognitive profiles could inadvertently drive differences in within- or between-network FC due to underlying ADRD. As such, group differences observed in prior studies may have been driven by ADRD. This highlights the importance of careful consideration of participant profiles in future studies aiming to elucidate the role of FC in cognitive aging.

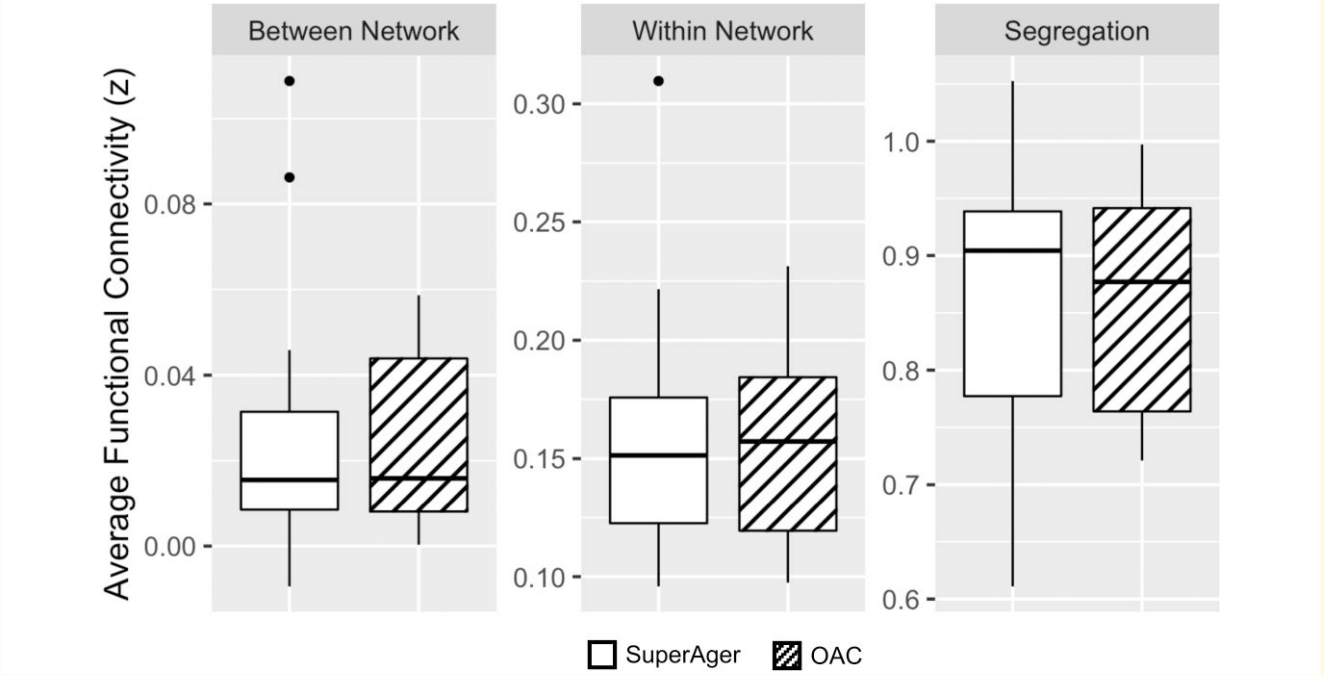


Figure 4 Whole-brain measures of functional connectivity do not differ between SuperAgers and controls. Network-wide average within-network functional connectivity and between-network connectivity did not differ between groups. A measure of network segregation (the difference between within-network FC and between-network FC divided by within-network FC) also did not differ between groups; OAC = older-aged controls. Wilcoxon signed-rank test; $P > 0.05$ for all comparisons.

It is also plausible that differences in rs-fMRI between SuperAgers and OACs are subtle and require highly precise measurements to detect. Subtle differences may be confounded by the relatively superior health of our OACs. Nonetheless, high-precision instruments are capable of identifying even the most nuanced group differences.[84,85] For example, recent machine learning studies have successfully differentiated SuperAgers from OACs, albeit with limited generalizability due to sample overlap. Leveraging similar machine learning techniques in expanded datasets with more robust methods could potentially unveil significant and reliable findings. Furthermore, additional high-precision methods, such as adopting person-specific approaches for rs-fMRI metrics, may help capture subtle nuances that may differentiate SuperAgers from OACs.[35,86,87]

The present study of SuperAgers applies advanced neuroimaging methods, is the first to ensure participants maintain stable cognitive profiles and includes a cohort matched in size to similar studies[34,61,88]; however, it is limited in participant size. Nonetheless, at least one study[61] was recently unable to detect previously reported group differences in FC of successful cognitive agers and controls observed with equivocal group size.[34] Given the publication bias,[89] there may also be unpublished studies with similar null results. Looking forward, the recent expansion of SuperAging Research Initiative (U19AG073153) into a multisite initiative will provide increased enrollment and greater power for future analyses. Future research may also make use of MRI scanners with higher magnetic field strength (e.g., 7 Tesla) or employ high-precision machine learning methods, both of which have been demonstrated to improve sensitivity[90,91] and detect subtle group differences and have shown promise in recent studies.[62,63]

In conclusion, this study serves as a foundational step in exploring the complexity of large-scale neurocognitive networks and their relationship to cognitive aging. At the group-level, within-network FC of large-scale networks and between subcomponents of the DMN were not a primary differentiator between cognitively average aging and SuperAging phenotypes. Recognizing the complexity of this field, future research may benefit from considering the role of undiagnosed neurodegenerative processes and employing high-precision rs-fMRI measurements including those that allow for consideration of individual rather than group-based statistics. These efforts will undoubtedly enhance our understanding of the contributions of resting-state network integrity to cognitive aging trajectories and the factors that underlie the exceptional cognitive abilities of SuperAgers.

Supplementary material

Supplementary material is available at *Brain Communications* online.

Acknowledgements

We would like to thank Dr Todd Parrish and Dr Yu Fen Chen for MR imaging, performed at the Northwestern University Department of Radiology Center for Translational Imaging. Image processing was supported by the Quest high performance computing cluster provided by Northwestern University, Department of Information Technology, Office for Research, and Office of the Provost.

Funding

This project is supported by the following National Institutes of Health Research Grants U19AG073153, R01AG045571, R56AG045571, R01AG067781, P30AG13854, P30AG072977, T32AG020506 and by the McKnight Brain Research Foundation (MBRF).

Competing interests

The authors report no competing interests.

Data availability

All codes used to conduct analyses are made available in the Supplemental Material. Atlases used for analyses are open source and publicly available: Schaefer cortical atlases (https://github.com/ThomasYeoLab/CBIG/) and HCP subcortical atlas (https://github.com/Washington-University/HCPpipelines/blob/master/global/templates/91282_Greyordinates/Atlas_ROIs.2.nii.gz). Data are available through a collaborative request to the SuperAging Research Initiative (superagingdata@uchicago.edu or emily.rogalski@bsd.uchicago.edu).

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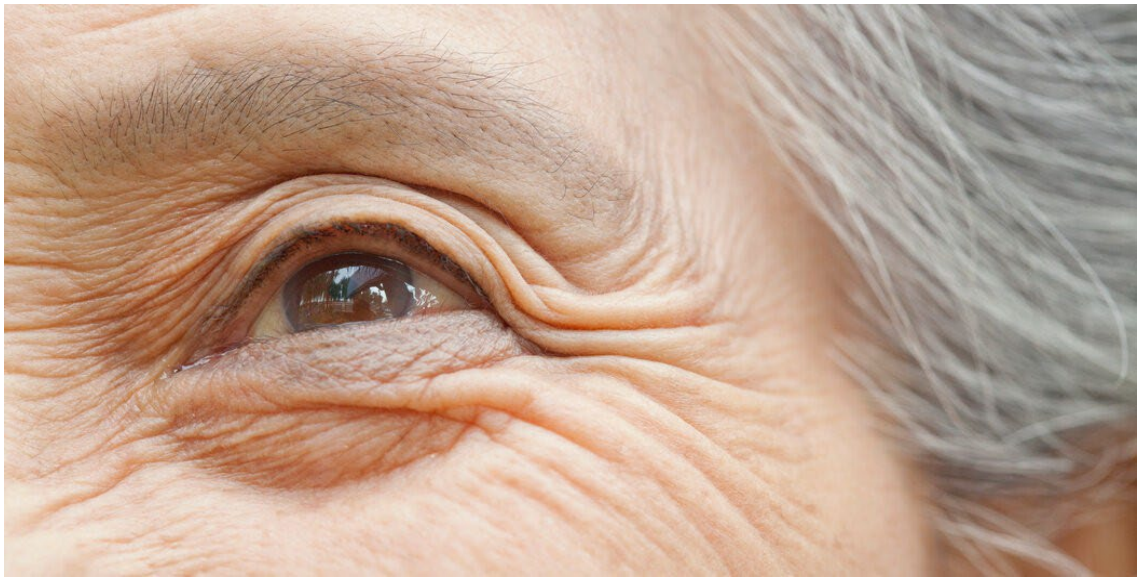
A Peek Inside the Brains of ‘Super-Agers’

nytimes.com/2024/04/29/well/mind/super-agers-study.html



When it comes to aging, we tend to assume that cognition gets worse as we get older. Our thoughts may slow down or become confused, or we may start to forget things, like the name of our high school English teacher or what we meant to buy at the grocery store.

But that’s not the case for everyone.

For a little over a decade, scientists have been studying a subset of people they call “super-agers.” These individuals are age 80 and up, but they have the memory ability of a person 20 to 30 years younger.

Most research on aging and memory focuses on the other side of the equation — people who develop dementia in their later years. But, “if we’re constantly talking about what’s going wrong in aging, it’s not capturing the full spectrum of what’s happening in the older adult population,” said Emily Rogalski, a professor of neurology at the University of Chicago, who published one of the first studies on super-agers in 2012.

A paper published Monday in the Journal of Neuroscience helps shed light on what’s so special about the brains of super-agers. The biggest takeaway, in combination with a companion study that came out last year on the same group of individuals, is that their brains have less atrophy than their peers’ do.

The research was conducted on 119 octogenarians from Spain: 64 super-agers and 55 older adults with normal memory abilities for their age. The participants completed multiple tests assessing their memory, motor and verbal skills; underwent brain scans and blood draws; and answered questions about their lifestyle and behaviors.

The scientists found that the super-agers had more volume in areas of the brain important for memory, most notably the hippocampus and entorhinal cortex. They also had better

preserved connectivity between regions in the front of the brain that are involved in cognition. Both the super-agers and the control group showed minimal signs of Alzheimer's disease in their brains.

"By having two groups that have low levels of Alzheimer's markers, but striking cognitive differences and striking differences in their brain, then we're really speaking to a resistance to age-related decline," said Dr. Bryan Strange, a professor of clinical neuroscience at the Polytechnic University of Madrid, who led the studies.

These findings are backed up by Dr. Rogalski's research, initially conducted when she was at Northwestern University, which showed that super-agers' brains looked more like 50- or 60-year-olds' brains than their 80-year-old peers. When followed over several years, the super-agers' brains atrophied at a slower rate than average.

No precise numbers exist on how many super-agers there are among us, but Dr. Rogalski said they're "relatively rare," noting that "far less than 10 percent" of the people she sees end up meeting the criteria.

But when you meet a super-ager, you know it, Dr. Strange said. "They are really quite energetic people, you can see. Motivated, on the ball, elderly individuals."

Experts don't know how someone becomes a super-ager, though there were a few differences in health and lifestyle behaviors between the two groups in the Spanish study. Most notably, the super-agers had slightly better physical health, both in terms of blood pressure and glucose metabolism, and they performed better on a test of mobility. The super-agers didn't report doing more exercise at their current age than the typical older adults, but they were more active in middle age. They also reported better mental health.

But overall, Dr. Strange said, there were a lot of similarities between the super-agers and the regular agers. "There are a lot of things that are not particularly striking about them," he said. And, he added, "we see some surprising omissions, things that you would expect to be associated with super-agers that weren't really there." For example, there were no differences between the groups in terms of their diets, the amount of sleep they got, their professional backgrounds or their alcohol and tobacco use.

The behaviors of some of the Chicago super-agers were similarly a surprise. Some exercised regularly, but some never had; some stuck to a Mediterranean diet, others subsisted off TV dinners; and a few of them still smoked cigarettes. However, one consistency among the group was that they tended to have strong social relationships, Dr. Rogalski said.

"In an ideal world, you'd find out that, like, all the super-agers, you know, ate six tomatoes every day and that was the key," said Tessa Harrison, an assistant project scientist at the University of California, Berkeley, who collaborated with Dr. Rogalski on the first Chicago super-ager study.

Instead, Dr. Harrison continued, super-agers probably have "some sort of lucky predisposition

or some resistance mechanism in the brain that's on the molecular level that we don't understand yet," possibly related to their genes.

While there isn't a recipe for becoming a super-ager, scientists do know that, in general, eating healthily, staying physically active, getting enough sleep and maintaining social connections are important for healthy brain aging.

CHICAGO SUN-TIMES

COLUMNISTS HEALTH

'Enjoy just being here' — At almost 110, she's still baking pie, with a little help

Edith Renfrow Smith, Grinnell College class of '37, is a rare "supercentenarian." In the fall her alma mater is naming a new dorm after her.

By Neil Steinberg | Jul 9, 2024, 12:18pm CDT

Edith Renfrow Smith, who will celebrate her 110th birthday on July 14, is the first Black graduate of Grinnell College in Iowa. She's planning to return to her alma mater later this year for the dedication of a dormitory named in her hono[illegible]. Ashlee Rezin/Sun-Times

Edith Renfrow Smith is baking a sour cherry pie.

"I just love sour cherry," she confides. "My father planted a sour cherry tree in the yard. He was a cook ... all the fruit; he had peaches, he had plums, he had gooseberries,

currants and grapes. Everything that momma could can, because we were poor."

That yard was in Grinnell, Iowa, where Smith was born on July 14, 1914, two weeks before the start of World War I. Regular readers might remember meeting her in 2021 for her 107th birthday and learning her down-to-earth world view, "Nobody's better than you." I figured, if 107 was noteworthy, how could 108 not be? Or 109, for that matter? The year she got COVID-19 and weathered the deadly disease so easily she didn't even mention that she'd had it.

For her 110th, this Sunday, I wondered how to shake things up. Such "supercentenarians" are an extreme rarity. Researchers estimate one person in a thousand who reaches age 100 will live to see 110, which makes Smith one woman out of a million, maybe out of 5 million.

I asked her daughter, Alice Smith, 78, if her mother still makes homemade jelly and wine.

She does, Alice said, inviting me to come by and watch production of a cherry pie last Friday, an offer I suspect she had reason to regret.

Edith Renfrow Smith, who turns 110 on July 14, bakes a cherry pie at her North Side home last week.|Ashlee Rezin/Sun-Times

“It takes 45 minutes to pit a quart of cherries,” says Alice, arriving at her mother’s apartment with a bag from a farmer’s market. “I won’t be doing that ever again.”

Alice is late, and perhaps not in the best mood, having had to fight NASCAR traffic from the South Side. “I’m only bringing this stuff,” she says. “I’m not making the cherry pie. That’s not something I want to make.”

But as daughters know, what you want to do, and what you end up doing, are two different things when your mother enters the equation. Alice is pressed unwillingly into the role of de facto pastry sous chef.

“Open the cookbook right there and check,” Edith says, gesturing to a 1960s-era Better Homes &lightttttt Gardens ring binder cookbook on the floor.

“Mother, I don’t need to open the cookbook,” snaps Alice. “I understand how to bake.”

Not easy as pie

The cookbook surprises me — I had anticipated cherished family baking traditions dating back to the 19th century, which is why it's always good to check your imagined notions against the yardstick of reality. Edith sets me right.

"Momma didn't make pies," she explains. "She didn't give us dessert. She said children should have apples and peaches. 'No garbage.' She called cookies and doughnuts and what have you 'garbage' because they were not good for you. She didn't give us cookies. She didn't bake pie. She made bread, three times a week, and she only used graham flour."

A pie needs sugar, and Edith directs her daughter to fetch it.

"The sugar's right there on the counter," she says. "Turn the light on."

"Mother, I don't need the light on," replies Alice. "I'm not blind!"

Edith Renfrow Smith (left), gets a spoon from her daughter, Alice, as they make a pie in Smith's North Side home last week. She turns 110 on July 14| Ashlee Rezin/Sun-Times

Edith flips the switch anyway.

“Mother, turn the light off,” says Alice. “I don’t need the light. I can see perfectly fine without it.”

“Excuse me,” says Edith, with formality.

“I found the sugar. I knew where the sugar was,” Alice says, then, as an aside to me: “This is why we don’t cook together. Or live together.”

I decided to share the sometimes messy process of pie-making, not to embarrass anybody, or because it is in any way unusual, but because it is so ordinary. The relationship between mothers and daughters is often fraught, and if there are daughters in their 20s reading this, thinking about their own mothers in their 50s, wondering if it will be any different half a century hence, the honest answer is: probably not.

“Mother, mother, *mother!*” exclaims Alice. “I will mix it … never mind, I’ll let you dirty up all you want, because I’m not cleaning up.”

Edith stands at a small table, assembling the pie. For maybe 20 minutes. Alice stands in the kitchenette of her one-room apartment. Communication is called back and forth, at a distance.

“It’s better that I walk away, ‘cause I have a bad habit of doing it myself,” says Alice.

“How much sugar?” asks Edith.

“One and a half cups,” calls Alice. “And you need three cups of cherries. That’s barely two cups. So you need one more cup of cherries.”

Edith Renfrow Smith adds sugar to the sour cherry pie she and her daughter Alice were making last week. Ashlee Rezin/Sun-Times

Flour is requested.

“Why are you putting flour in there? You’re already using corn starch?” asks Alice.

“May I have the flour, please?” asks Edith, coolly.

“I’m handing it to you, mother,” Alice says.

‘That’s just how we are’

One of the preconceptions I had was that the pie would be made for others — and the guard at the front desk did say that Mrs. Smith is known to regularly show up with a slice for whomever is on duty. But Edith is making this pie for herself. Why? Aren’t bakery pies adequate?

“‘They don’t make ‘em like I like,” she says.

Alice certainly isn’t touching it.

“It’s her pie,” she says. “I don’t eat that stuff.”

“I need half a cup of sugar,” says Edith, abruptly.

“*Why*?” asks Alice. “I’m asking ‘Why’? You don’t need it.”

“Because they’re sour cherries,” says her mother.

“They’re not that sour,” says Alice.

As the process winds up, credit is given.

“She does a much better job than anybody I know on crimping, making it look pretty,” says Alice. “That looks nice, mom.”

But that doesn’t last long. Cream is requested.

“I will get the cream for you,” says Alice. “I will take the brush and brush cream across the top.”

“No, you will give it to me,” says Edith.

“Why, don’t you trust me?”

“No,” replies Edith, who previously pressed down on each cherry with a spoon, to make sure her daughter hadn’t missed a pit. She shrugs off Alice’s suggestion of a pastry brush and egg white and massages the cream onto the top of the crust with her fingertips. “This will make it a pretty golden brown,” she says.

Alice leaves. A few days later, not wanting to cause anybody any unease by sharing the sticky pie-making process, I phone her to sound her out. She doesn’t mind.

“That’s just how we are,” Alice says. “We still love each other.”

‘Don’t let life pass you by’

Her mother’s 109th year, by the way, was unexceptional — except maybe for the publication of a children’s book about her life, “No One Is Better Than You” by Monique McLay Shore, with illustrations by Erica Lauren Butler.

“I feel great,” Edith says. “Very good. Not sick one day. I’m very, very fortunate.”

She does need a caregiver when she goes out, which she plans to do to mark her 110th

birthday.

“My daughter and I are going to tea,” she adds, with the regal lilt such a sentence demands. “I haven’t been to tea for a good while. The last time we went to tea was at the Peninsula. It’s a very lovely place. It’s very nice to have such nice places to go.”

Who gets to live to 100? The answer may surprise you.

In old age, life expectancy among the races shifts in dramatic ways, a new study shows.

By Kay Lazar Globe Staff, Updated December 4, 2024, 3:01 a.m.

Dr. Tom Perls, a Boston University researcher who runs the largest study of centenarians and their families in the world, sat last year with Herlda Senhouse, who was 112 at the time. Senhouse, who died last month at 113, was the second oldest person in the United States. JESSICA RINALDI/GLOBE STAFF

Imagine two neighbors, both in their mid-to-late 80s. One is Black and the other is white. Which one might have a better chance of reaching 100 years old?

Conventional wisdom would suggest the white octogenarian would have a leg up on that climb to 100, because of the mountains of research showing better access to health care and other opportunities for white Americans. Additionally, Black people in the United States generally have higher death rates at younger ages.

But a new study from Boston and Canadian researchers adds important depth to an unusual reversal of that death equation — that Black octogenarians in the United States have significantly better odds of living to 100 than their white counterparts. And those odds get better with age.

The study, published in the Journal of Internal Medicine, found that white women at 80 years old have a 4 percent chance of living to 100, while the odds are 6 percent for Black women. By the time they hit 90, that stretches to 9 percent for white women — and 13 percent for Black women.

The survival odds are lower for males, but the pattern is the same; a roughly 3 percent chance for Black men at age 80 to make it to 100, but just 2 percent for white men. By age 90, it was 5 percent for white men and 9 percent for Black men.

The researchers also studied survival patterns among Hispanics and Asian Americans and both showed even better longevity odds. They found a roughly 8 percent chance for Hispanic women, and 10 percent for Asian women to make it to 100 from age 80. That expanded to roughly 15 percent for both groups at 90. The researchers did not have sufficient data to analyze survival patterns for American Indian or Alaska Native populations.

“There is a tremendous amount to be learned from these different groups in what they have in common and don’t have in common,” said study coauthor Dr. Tom Perls,

professor of medicine and geriatrics at Boston University's school of medicine and director of the New England Centenarian Study.

"By studying this, we will solve this puzzle, which is, what are the environmental and genetic underpinnings of exceptional longevity and healthy aging," Perls said.

The study also acknowledged the significant disparities between Black and white populations at birth, showing a life expectancy of 78 years in 2019 for Black people, but 81 for whites. Hispanic and Asian American life expectancies were even greater, with Hispanics projected to live to 84 and Asians to 87.

But it also dramatically highlights a long-debated phenomenon known as the Black-white mortality crossover: Up until roughly their mid-80s, Black people have higher mortality rates than whites, but then decline in comparison to whites, and their life expectancy becomes greater.

The phenomenon was first noted by researchers more than a century ago, and it has been debated and investigated ever since. Skeptics have long said that the "crossover" was not real, and that the phenomenon of Black people outliving whites in their later years was merely a reflection of inaccurate birth and death records, especially from decades ago for Black people.

That concern remains but has eased as record-keeping has improved. The data Perls and his coauthor, Nadine Ouellette, an associate demography professor at the University of Montreal, used to calculate survival rates came from the US National Center for Health Statistics and are considered reliable.

Nadine Ouellette, an associate professor of demography at the University of Montreal, and coauthor of the new study on the Black-white crossover. NADINE OUELLETTE

Today, most researchers say the crossover phenomenon likely reflects what they call "select survival," meaning that many Black people die at younger ages because of social, economic, and other disadvantages, leaving the hardiest to live on. Or, as Ouellette puts it: "Those who survived to these great old ages are probably the most robust and this is what we are seeing in terms of survival."

In their study, the Black-white crossover occurred between the ages of 86 and 88, depending on gender, and persisted to age 100 and beyond.

Researchers not involved in the study said it is the first to demonstrate the Black-white crossover continued a decade longer than previous studies have shown.

But it wasn't just the persistent Black-white crossover that was intriguing, they said. The study also demonstrated that at age 100, estimated additional life expectancy for the Black population was similar to that of the Hispanic and Asian populations, and all three were significantly greater than for the white population.

"It's interesting how all the minority groups were together in terms of their probability of survival. They are very similar to each other, and all of them together are very different than the white population, and that's news," said Mark Hayward, a sociology professor at the University of Texas at Austin who studies population health and mortality rates of older adults.

Those greater odds of survival, even at age 100, translated to a life expectancy that was roughly six months longer for Black people compared to white people in 2019, the study showed. And for the Hispanic and Asian populations, it added up to about four to five additional months, compared to the white population.

Perhaps one of the most dramatic illustrations of Black longevity came in the life of Herlda Senhouse of Wellesley, who died last month at age 113. A petite woman with a firecracker personality, she was the second oldest person in the United States whose age was verified. The oldest is Naomi Whitehead, a 114-year-old in Pennsylvania, who is also Black.

The research by Perls and Ouellette did not try to answer the question of why Black, Hispanic, and Asian-American populations have longer life expectancies once they hit old age.

But the researchers noted other ongoing work by Perls at the New England Centenarian Study has demonstrated that combinations of certain genes appear to play an increasingly stronger role in survival to very old ages.

Even so, as the researchers point out, behavariol and environmental factors are the main drivers of mortality rates up to about age 90. For example, studies of Seventh Day

Adventists in California, whose members typically don't smoke, showed their life expectancies were roughly four to seven years longer than the California population as a whole. And Adventists who were vegetarian, did not smoke, engaged in high physical activity, and were not overweight lived roughly 10 years longer than their white California peers.

Lowell Taylor, an economics professor at Carnegie Mellon University who has studied the Black-white crossover phenomenon, said the Perls and Ouellette study will help researchers and the general public focus on similar ways to live better longer.

"Learning about the forces that shape mortality at a very old age would give us really good ideas about what we theoretically can do ourselves to make us have longevity," Taylor said.

Kyriakos Markides, a pioneering sociology professor at the University of Texas Medical Branch, said the new study confirms and adds to the research he has done. Markides is credited with coining the term the 'Hispanic paradox,' where Hispanic people in the United States live longer than white people, despite generally lower socioeconomic levels and health-care access.

Back in 1984, Markides coauthored a study about the Black-white crossover and found the phenomenon in the United States then happened at around age 75 — when overall life expectancies were lower. The study suggested that having a greater proportion of Black people who are more robust at very old ages, compared to white people, might have explained the lower rates of suicide among older Black people and fewer living in nursing homes at that time.

But Markides notes that often overlooked in discussions of the Black-white crossover are the great disadvantages Black populations often face earlier in life, hurdles that often lead to proportionately more deaths at younger ages, compared to white people.

"When you get to be very old," he said, "and you enjoy certain advantages, it's nice to see."

Kay Lazar can be reached at kay.lazar@globe.com Follow her @GlobeKayLazar.

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Additional Media Coverage

1. **Unlocking the Secrets of SuperAgers** – *Michigan Today*, February 2024
2. **Bio and the Brain** – *Wittenberg University – Next Why Witt?,* February 2024
3. **What We Can Learn from SuperAgers** – *BottomLine Inc.*, March 2024
4. **SuperAging Research Initiative** – *Senior Talk Radio*, *Podcast/Video*, April 2024
5. **Maximizing Healthy Aging & Alzheimer's Research Care** – *University of Chicago HAARC Center - Video spotlight at American Academy of Neurology annual conference*, *Video*, April 17, 2024
6. **Why this 110-year old's brain is exciting scientists** – *BBC Sounds*, *Podcast*, June 2024
7. **Is an 80-year-old brain fit for the Presidency?** – *Men's Health Australia*, July 2024
8. **What's happening inside an 80-year-old brain?** - *Fortune Well*, July 2024
9. **How to increase your odds of becoming a 'SuperAger'** – *Fortune*, August 2024
10. **All the right moves: Middle Tennessee woman shares secrets to SuperAging** – *WSMV4*, August 2024
11. **Unlocking the Secrets of 'SuperAgers,' with Emily Rogalski** – *Big Brains Podcast*, October 2024
12. **The Future of Aging** - *AARP*, November 2024
13. **Episode 21: Dr. Emily Rogalski on Neurodegenerative Diseases and Brain SuperAging** – *Backed by Science Podcast*, November 2024
14. **Western researchers unlocking secrets to healthy aging** – *Western News*, November 2024

15. **Unlocking secrets to healthy aging** – *The Globe and Mail*, November 2024
    a. Western University SuperAging Awareness Campaign in partnership with the Globe and Mail

16. **The 10 habits to keep your brain young** – *The Telegraph*, February 9, 2025

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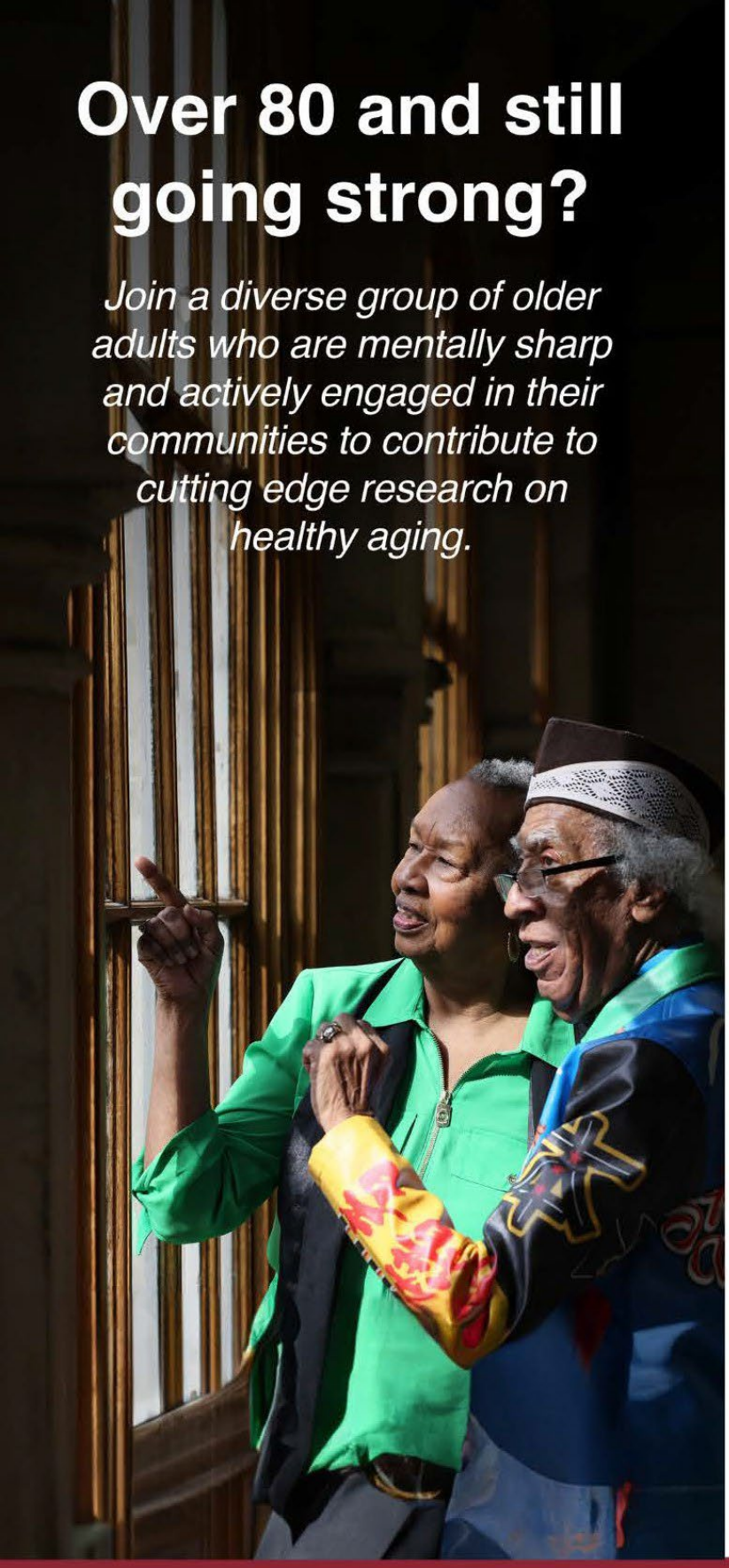
Join a diverse group of older adults who are mentally sharp and actively engaged in their communities to contribute to cutting edge research on healthy aging.



Supe1·Aging
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Please Participate

The SuperAging Research Initiative needs your help to better understand and identify factors that contribute to exceptional aging.

Who are SuperAgers?

SuperAgers are adults who have the memory capacity of someone 20-30 years younger.

What's involved?

About 8 hours of study visits broken up in 2-3 visits every 2 years, including:

- Pen, paper, and computerized memory and thinking tests
- MRI brain scans
- Surveys and questionnaires
- Blood collection

You will receive at least $100 for your time.

If this sounds like you, we would love to hear from you!

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Study funded by: National Institute of Aging and the McKnight Brain Research Foundation
Grant# U19A6073153 R01AG067781 Principal Investigator: Emily Rogalski, PhD

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Albert Einstein College of Medicine
IRB NUMBER: 2021-13250
IRB APPROVAL DATE: 02/22/2023

Be the **Brain** Behind the **Breakthroughs**

Volunteering to donate your brain could help lead to better understanding, treatment, and prevention of brain diseases, such as Alzheimer's disease and related dementias.

Why do people donate their brains to research at the end of life?

- Help researchers better understand the causes and potential treatments for brain diseases that affect millions of people.
- Have a broad, positive impact on public health and future generations.
- Help family members learn more about any diagnosis of brain diseases that may run in the family.

How does brain donation work?

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What do I do next?

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BRAIN DONATION
A GENEROUS GIFT

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Use su **cerebro** para ayudar a las **generaciones futuras**

Ofrecerse como voluntario para donar el cerebro podría ayudar a mejorar la comprensión, el tratamiento y la prevención de trastornos cerebrales, como la enfermedad de Alzheimer y las demencias relacionadas.

¿Por qué donar el cerebro a la investigación al llegar al final de la vida?

- Ayuda a los investigadores a comprender mejor las causas y los posibles tratamientos de las enfermedades cerebrales que afectan a millones de personas.
- Tiene un impacto amplio y positivo en la salud pública y en las generaciones futuras.
- Ayuda a sus familiares a aprender más sobre cualquier enfermedad cerebral hereditaria que puede haber sido diagnosticada en su familia.

Cómo funciona el proceso de donación del cerebro?

Para ser voluntario, regístrese con anticipación en el programa de donación de cerebros de RADCO. En el momento de la muerte, un ser querido designado o un profesional de la salud llamará al centro de donación de cerebros. Un especialista extraerá cuidadosamente el cerebro a través de la parte posterior de la cabeza de manera que no afecte la apariencia de la persona. Luego, el cerebro se envía a un banco de cerebros para su análisis . El cuerpo permanece con la familia o en la casa funeraria para su entierro o cremación y las ceremonias afines.

¿Cuál es el siguiente paso?

Aunque los temas relacionados con la vida y la muerte pueden ser difíciles de abordar, el mejor momento para pensar en ser un donante de cerebro es ahora. Obtenga más información sobre nuestro programa de donación de cerebro. Hable con su familia y amigos al comienzo del proceso de toma de decisiones. Si decide donar, considere registrarse con tiempo en el programa de donación de cerebro de RADCO.

Para convertirse en un donante de cerebro, considere inscribirse en el programa de donación a través del estudio de Resiliencia/Resistencia contra la Enfermedad de Alzheimer en Centenarios y sus descendientes (RADCO, por sus siglas en inglés) . Si tiene dudas o desea más información del programa, contacte al coordinador del estudio RADCO, Cristian Ibarra al **617-353-0919**

BRAIN DONATION · A GENEROUS GIFT

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Resilience/Resistance against Alzheimer's Disease in Centenarians & Offspring

La donación del cerebro: Un regalo para las generaciones futuras

EINSTEIN
Albert Einstein College of Medicine
IRB NUMBER: 2021-13250
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Preguntas Frecuentes

La donación de un cerebro puede generar un gran impacto ya que tiene el potencial de ofrecer información para cientos de estudios de trastornos cerebrales, como la enfermedad de Alzheimer y las demencias relacionadas. Aprenda más sobre el proceso de donar el cerebro y cómo comenzar.

¿Por qué es importante?

La donación del cerebro ayuda a los investigadores a comprender mejor las causas y los posibles tratamientos de los trastornos cerebrales que afectan a millones de personas.

¿Quién puede donar?

Cualquier persona mayor de 18 años, tanto con un trastorno cerebral como con un cerebro sano, puede donar el cerebro. Se necesitan muchos cerebros de diferentes poblaciones y edades.

¿Qué le sucede al cerebro después de la donación?

Cuando el donante fallece, un especialista extrae cuidadosamente el cerebro por la parte posterior de la cabeza de manera que no afecte la apariencia de la persona. El cerebro se envía nuestro banco de cerebros, que distribuye muestras de tejido a investigadores calificados. El cuerpo permanece con la familia o en la casa funeraria para su entierro o cremación y las ceremonias afines.

¿Hay algún costo para mí o para mi familia?

No, cuando se dona un cerebro como parte de un estudio , no hay ningún costo para la familia por el proceso de donación del cerebro.

Cómo puedo donar?

La donación de cerebros es diferente a la donación de otros órganos. Usted puede ser un donador de cerebro inscribiendose en el programa de donación del estudio RADCO.

¿Qué deben hacer mi familia y mis amigos?

Deben decidir quién se comunicará con el centro de donación de cerebros en el momento de su muerte.

¿Cómo puedo hablar con mi familia y amigos sobre la donación del cerebro?

Explíqueles por qué quiere donar el cerebro y comparta lo que ha aprendido sobre este tipo de donación. Hable con ellos desde el inicio de su proceso para tomar una decisión. Si tienen preguntas, comuníquense con nosotros.

¿Listo para dar el siguiente paso?

Para convertirse en un donante, considere inscribirse al programa de donación de cerebro a través del estudio de Resiliencia/Resistencia contra el la Enfermedad de Alzheimer en Centenarios y sus Descendiente (RADCO, por sus siglas en inglés) Si tiene dudas o desea más información del programa, contacte al coordinador del estudio RADCO, Cristian Ibarra al **617-353-0919**

BRAIN DONATION A GENEROUS GIFT
#braindonation

Resilience/Resistance against Alzheimer's Disease in Centenarians & Offspring

McKnight Clinical Translational Research Scholarship in Cognitive Aging and Age-Related Memory Loss

Funded by the McKnight Brain Research Foundation through the American Brain Foundation and the American Academy of Neurology

Application Deadline: September 9, 2025

This award aims to support young investigators in clinical studies relevant to age-related cognitive decline and memory loss. The award also recognizes the importance of rigorous training in clinical research and encourages young investigators to seek opportunities to establish future careers in the area of human cognitive aging. Please note: the focus should NOT be on a neurodegenerative dementia (e.g. Alzheimer's disease); however, proposals that focus on combined study of cognitive aging and neurodegenerative cognitive changes may be considered.

The award will consist of a commitment of $65,000 per year for two years, plus a $10,000 per year stipend to support education and research-related costs for a totalof $150,000. Supplementation of the award with other grants is permissible, but to be eligible to apply for this award, the other grant source(s) cannot exceed $75,000 annually.

The American Academy of Neurology is firmly committed to embracing the diversity among our members, applicants, and reviewers and affirms the importance of equity and inclusiveness within the AAN research program.

HOW TO APPLY

1. Visit AAN.com/view/ResearchProgram
2. Go to "McKnight Clinical Translational Research Scholarship in Cognitive Aging and Age-Related Memory Loss"
3. Select "Apply now"

Please only submit one application - applicants are not allowed to submit applications for more than one award. Your application will also be considered for all relevant clinical research training scholarship awards.

Visit the Frequently Asked Questions portion of the website for more information.

IMPORTANT DATES

September 9, 2025: Application deadline – Note that this is the deadline for all documents, including those from the mentor and chair. Applications will be declined if this information is not submitted by September 9.
January 2026: Notification of recipients
July 1, 2026: Funding begins

ELIGIBILITY

1. For the purpose of this scholarship, research is defined as patient-oriented research conducted with human participants, or translational research specifically designed to develop treatments or enhance identification of age-related cognitive decline and memory changes. These may include epidemiologic or behavioral studies, clinical trials, studies of disease mechanisms, the development of new technologies, and health outcomes research. Disease-related studies not directly involving humans are also encouraged if the primary goal is the development of therapies, diagnostic tests, or tools to mitigate age-related cognitive decline and memory loss.

2. Recipient is interested in an academic career in neurological research who has completed residency or a PhD no more than 5 years prior to the beginning of this award (July 1, 2026). If you have completed both residency and a PhD, your eligibility is based on when you completed residency. If you completed a fellowship of any kind after residency, your eligibility is still based on the date you finished residency. The applicant must hold a post-baccalaureate PhD degree or equivalent, or a doctoral-level clinical degree such as MD, DO, DVM, PharmD, DDS, DrPH, or PhD in nursing, public health or other clinical health science.

3. The proposed program of training and research must be performed entirely within an institution in the United States accredited by the relevant accrediting authority.

4. Research studies at the intersection of age-associated cognitive changes and disease-related cognitive impairment may be considered if a strong case can be made for their relevance to cognitive aging and age-related memory loss. However, research that is primarily focused on neurodegenerative diseases (e.g., Alzheimer's disease) will not be supported. Applicants are encouraged to reference the Opportunities for Action section of the National Academies 2015 Cognitive Aging report for areas of research need.

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A successful application should include the following:

- Well-developed hypothesis: The hypothesis is testable and presented in clear language.
- Detailed statistical plan: Statistical methods are well-designed and detailed.
- Strong mentorship: There is clear demonstration of strong mentorship to support the project.
- Feasible primary outcomes: Each aim is feasible, focused, and logical.
- Innovation: Project concept is original, novel, and will advance the applicant's long-term career goals.
- Well-defined training plan: There is a clear and gap-based career development plan.

EVALUATION AND SELECTION

Applications are evaluated by reviewers based on the following criteria:

- Quality and originality of the research plan
- Applicant's ability and promise as a clinician-scientist based on prior record of achievement and career plan, and NIH Biosketch
- Quality and nature of the training to be provided and the mentor-specific, departmental, and institutional training environment
- Innovation of the research plan approach
- Project significance: the ability to advance the field of cognitive aging

REQUIRED ATTACHMENTS FOR APPLICATION

1. PDF of Three-page Research Plan, including brief statements of aims, background, contemplated approaches to methodology and any supporting preliminary data/figures. References do not count toward the page limit. The research plan should be written by the applicant and should represent their original work. However, the applicant is expected and encouraged to develop this plan based on discussion with the proposed mentor.

2. PDF of Applicant's NIH Biosketch. See this link for the most recent NIH Biosketch template

Once the above information is fully completed and **submitted** by the applicant:

3. The **chair** will receive an email with a link asking them to check a box confirming that the applicant's clinical service responsibilities will be restricted to no more than 30 percent of your time and include a list of applicant's non-research related service. The chair will NOT be asked to submit a letter.

4. The **mentor** will receive an email with a link to submit a letter of reference detailing their support of and commitment to the applicant and the proposed research and training plan. The letter should be 1,000 words or less and specifically indicate the mentor's role in the development and preparation of the applicant's research plan and should include:

   - How the proposed research fits into the mentor's research program
   - Expertise and experience in the area of research proposed and the nature of the mentor's proposed time commitment to the supervision and training of the applicant
   - Mentor's prior experience in the supervision, training, and successful mentoring of clinician scientists
   - Potential for applicant's future research career
   - Institution's commitment to 70 percent protected research time

5. The **mentor** will also be required to upload a NIH Biosketch.

ANNUAL AND FINAL PROGRESS REPORTS

An annual progress report is due in May of the first year. Renewal of the award in year two is contingent upon presentation of a satisfactory progress report. Additionally, a final research report and a final expenditure report are due within 60 days following the close of the grant term. The final expenditure report must be prepared by the institution's financial office.

CONTACT INFORMATION

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Email: research@aan.com