UNIVERSITY OF CALIFORNIA,
IRVINE

Neuroimaging Biomarkers of Successful Cognitive Aging

DISSERTATION

submitted in partial satisfaction of the requirements for the degree of

DOCTOR OF PHILOSOPHY

in Biological Sciences

by

Elena Dominguez

Dissertation Committee:
Professor Craig Stark, Chair
Assistant Professor Liz Chrastil
Professor Maria Corrada
Professor Claudia Kawas

2022

DEDICATION

To

my superhero parents, my blessing of a nephew, and loving late uncle

in recognition of their love, warmth, and light they bring to my life.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

3MS	Modified Mini Mental
ADNI	Alzheimer's Disease Neuroimaging Initiatives
ADRC	Alzheimer's Disease Research Centers
ANTs	Advanced Normalization Tools
AUC	Area under the curve
CIND	Cognitively normal - no dementia
CSAD	Cortical Signature of Alzheimer' Disease
CSF	Cerebrospinal fluid
CVLT	California Verbal Learning Test
DKT	Desikan-Killiany-Tourville
IADL	Instrumental activities of daily living
MCI	Mild cognitive impairment
MNI	Montreal Neurological Institute and Hospital
MRI	Magnetic resonance imaging
NACC	National Alzheimer's Coordinating Center
PET	Positron emission tomography
RAVLT	Rey Auditory Verbal Learning Test
RBANS	Repeatable Battery for the Assessment of Neuropsychological Status
ROC	Receiving operating characteristic
ROI	Region of interest
SDTP	Single domain top performer
TCP	Top Cognitive Performers
TIV	Total intercranial volume
Trails-B	Trails Making Test- Part B
WMH	White matter hyperintensities
WMS-R IIA	Wechsler Memory Scale-revised Logical Memory IIA-Delayed Recall

LIST OF FIGURES

LIST OF TABLES

ACKNOWLEDGEMENTS

I thank Frontiers for permission to include Chapter Two of my dissertation, which was originally published in Frontiers in Neuroscience Journal. Financial support was provided by the University of California, Irvine, UC President's Dissertation Fellowship, The Howard Schneiderman Interdisciplinary Training Program (T32MH119049), R01 AG021055 (PIs: Kawas and Corrada), R01AG034613 (PI: Stark), and the UCI ADRC 1P30AG066519 (PI: LaFerla).

To say that this grueling Ph.D. experience has been sprinkled with a gigantic bucket of blessings would be an understatement. To my P.I., Dr. Stark, whom I have quoted to be a "sweet baby angel" in a room full of 200+ SfN attendees, thank you for always being an exemplary mentor. This journey was full of many hiccups and hurdles, each one almost pushing me to become an accountant, but your wisdom and support kept me on the path to becoming the neuroscientist I am today. In the last legs of this process, you went beyond the duties of P.I. and I am forever grateful. There is no batman, though, without Robin, so I also want to thank Shauna Stark (I am not saying who's who, but I can totally see batman as a blonde). Aside from the science and writing skills you've taught me, your immense compassion made the beginning of this journey so much easier, and you taught me how to have an active voice and be an advocate for myself (#NSP).

I am also extremely grateful to my committee members, Dr. Liz Chrastil, Dr. Claudia Kawas, and Dr. Maria Corrada, who have offered me masterful scientific insight and have continuously shown me new ways to think about my data. I never thought I would look forward to a committee meeting (and I usually never did until after the fact), but pages and pages of notes and "OMG I did not think of that"'s later, I am forever thankful for the scientific rigor you've taught me. I want to thank The 90+ Study, in particular, not just for their data, but for all their significant contributions and all that I've learned these past few years. Thank you to Dr. Davis Woodworth, Dr. Ahmad Sajjad, Dr. Zara Melikyan, and others; the feedback I received in Thursday meetings have been pivotal in my research and for that, I am thankful. Thank you to Dr. Claudia Kawas, for always being excited to see new data and making me ask the important questions, and Dr. Maria Corrada, for your extremely thoughtful insight and unknowingly making me want to become an epidemiologist (and being the only fellow caribeña here in the west coast.) They were not kidding when they say it takes a village. I want to thank my lab for listening to my once-a-year presentations, putting up with my video being off then randomly hearing a mysterious voice, and overall non-work related fun. Thank you to Yueqi for being a machine learning wiz and helping my paper come to fruition. I want to especially thank my lab mates Hamsi and Jess in, who helped me learn how to use a vibratome, listened to my talks at 9 PM at night (scientific and not), and who have become like sisters to me. I want to thank Dr. Mike Yassa and Manuella Yassa for their unwavering support, Dr. Danny Mann for being the kindest most flexible human being I have ever met, the Black in Neuro team for being an absolute powerhouse and becoming a second family, Dr. Gillian Hayes for including me in fancy dinners and teaching me how to be a boss, Dana Greenia and Natalie Bryant for being balls of sunshine, Maria Kirkwood for always being one call away, and many more. To my OG New York besties Angel, Lisa, Andrea, Atilano, Yessenia, and Cris, your support and checking in have made being away from home a little less hard. To the little family I have formed here, Liz, Angeline, Janielle &Anjelica, Maria, Julian, Aliza, Freddie, Miguel, Isabella, and many more, you guys were also instrumental in making sure I don't become an accountant and brought immense joy and laughter into my life.

To my sister, brother-in-law, and nephew, thank you for being a constant beam of light and always checking in and being the life of the party. A big thank you to Kimi, who always made sure to send me love, quick texts to check in, and buy me my favorite conditioners from Dominican Republic. Lastly and most importantly, I want to thank my parents, for whom I would not be writing this if it weren't for them (and not just because they birthed me). Thank you for your daily calls (sike), constant support and motivation, and love throughout this journey. I won't be able to buy you a new house because I went into

the wrong field for that, but I am forever grateful for all of the sacrifices you've made to get me where I am today.

VITA

Elena Dominguez

Education

Ph.D. in Biological Sciences, UC Irvine — 2018-2022
GPA: 3.9/4.0

Master Of Science In Biological Sciences, UC Irvine
GPA: 3.8/4.0 — July 2020
Thesis Title: "The Role of The Cingulate Cortex in Various Trajectories of Aging and Disease Progression"

Bachelor Of Science in Psychology, Brooklyn College — September 2015
GPA: 3.6/4.0
Honors: cum laude, Dean's List 2012-2014
Thesis Title: "Attention & the List-Wide Proportion Congruent Effect"

Laboratory experience

Howard Schneiderman Fellow in the Lab of Dr. Craig Stark, UC Irvine — 2018-2022
Topic: The role of imaging biomarkers in predicting Top Cognitive Performance in the elderly

PREP Scholar in the Lab of Dr. Jose Luis Pena, Albert Einstein College Of Medicine — 2015-2017
Topic: The role of Mammalian Target Of Rapamycin Complex 1 and Eukaryotic Translation Initiation Factor 2A in imprinting in the newborn domestic chick

MARC Scholar in the Lab of Dr. Matthew Crump, Brooklyn College — 2013-2015
Topic: The role of the list wide proportion effect found in Eriksen's Flanker task through the use of dual tasks

Research Support

UC President Dissertation year fellow	2022
NIH Howard Schneiderman T32 Fellow in Learning and Memory *T32MH119049*	2020-2022
NIH Diversity Supplement: Clinical, Imaging, and Pathological Studies in the Oldest Old: The 90+ Study *R01AG021055-17*	2018-2020
NIH Postbaccalaureate Research Education (PREP) Fellow *R25GM104547*	2015-2017
NIH Maximizing Access To Research Careers (MARC) Fellow *T34GM008078*	2013-2015
NIH Research Training Initiative For Student Enhancement (RISE) Fellow *R25GM062981*	2011-2013

Awards & Fellowships

UCI Emeriti Association Dissertation Fellowship, UC Irvine	2022
Latino Excellence & Achievement - Excellence in Research Award, UC Irvine	2021
Outstanding Diverse Educational Community and Doctoral Experience Representative, UC Irvine	2021
30th Anniversary Tau Leadership Fellowship, UC Irvine	2021
Division Of Teaching Excellence and Innovation Summer Fellowship, UC Irvine	2021
Department of Neurobiology and Behavior Service Award for work in Diversity Equity and Inclusion, UC Irvine	2020
Neuroscience Scholars Program Fellow, Society for Neuroscience	2019
Trainee Professional Development Award, Society for Neuroscience	2018
School Of Biological Sciences Dean's Graduate Fellowship Award, UC Irvine	2018
Diversity Recruitment Fellowship, UC Irvine	2017
Saul Lyons Memorial Scholarship Recipient, Brooklyn College	2014
George M. Alexis Memorial Scholarship, Brooklyn College	2011,2012

Publications

Dominguez, E. N., Stark, S. M., Ren, Y., Corrada, M. M., Kawas, C. H., & Stark, C. (2021). Regional Cortical Thickness Predicts Top Cognitive Performance in the Elderly. Frontiers in aging neuroscience, 13, 751375. *https://doi.org/10.3389/fnagi.2021.751375*

Singleton KS, Tesfaye R, *Dominguez EN*, Dukes AJ. An open letter to past, current, and future mentors of Black neuroscientists. Nat Rev Neurosci. 2021 Feb;22(2):71-72. PubMed ID: 33349698.

Batista G, Johnson JL, *Dominguez E*, Costa-Mattioli M, Pena JL. Regulation of filial imprinting and structural plasticity by mTORC1 in newborn chickens. Sci Rep. 2018 May 23;8(1):8044. PubMed Central ID: PMC5966437

Batista G, Johnson JL, *Dominguez E*, Costa-Mattioli M, Pena JL. Translational control of auditory imprinting and structural plasticity by eIF2α. Elife. 2016 Dec 23;5 PubMed Central ID: PMC5245967.

Invited Talks

Speaker, "The role of cortical thickness in SuperAging", UCI Graduate Division Dean's Leadership Council, UC Irvine	2021
Speaker, "The role of cortical thickness in SuperAging", Orange County Latinx Alliance Conference, UC Irvine	2021

Speaker, “Cortical Thickness as a predictor of successful aging in the oldest-old”, Society for Neuroscience, Neuroscholars Program Dinner — 2019

Speaker, “Can the brain distinguish SuperAgers in The 90+ Study?”, Mesa Verde Branch Library, Costa Mesa, CA — 2019

Teaching Record

Research Methods in Psychology, Xavier University of Louisiana — Fall 2022
Guest Lecture, Title: From Psychology and Neuroscience: My Path to Data Science
Course Instructor: Angeline Dukes, PhD

N123L: Human Neuroimaging Lab, UC Irvine — Fall 2022
Guest Lecture, Title: “Tissue Type Segmentation”
Course Instructor: Craig Stark, PhD

N131: Human Neurodegenerative Diseases, UC Irvine — Spring 2021
Guest Lecture, Title: Early-Onset Familial Alzheimer’s Disease in Medellin, Colombia
Course Instructor: Claudia Kawas, MD

BIOSCI 41: Aspects of Mood Disorders, UC Irvine — Winter 2020
Guest Lecturer, Title: Genetic and Environmental Contributions to Mood Disorders
Course Instructor: Andrea Nicholas, PhD

PHRMSCI 42: Life 101, UC Irvine — Fall 2020
Guest Lecture, Title: Anti-Racism Module: Becoming Anti-Racist Course Instructor: Mahtab Jafari, PhD

BIOSCI N113L Neurobiology Lab, UC Irvine — Fall 2019
Lab Lecturer
Course Instructor: Audrey Chen Lew, PhD

CITIZEN NEUROSCIENCE TEACHER — 2017-2018
Teacher, Citizen Schools at Bronx Writing Academy (K-12)

Leadership Positions

Black In Neuro: Co-Founder & Organizer — 2020-Present
Mentorship Program co-lead, Conference event organizer

Diverse Educational Community and Doctoral Experience (DECADE) Student Representative – Department Of Neurobiology & Behavior — 2020-2021
Student event organizer, Student-Faculty liaison

Center For The Neurobiology Of Learning And Memory (CNLM): Older Adults Committee Chair *Community event organizer*	2018-2020
DECADE Student Council: Recruitment Co-Chair *Undergraduate/Graduate student event organizer, Panelist and Workshop leader, Recruiter*	2017-2018

Professional Service

CNLM Research Experience for Undergraduates (REU) Program Selection Committee	2021
Biological Sciences Climate Council Inclusive Excellence Grant Review Committee	2021
CNLM Research Experience for Undergraduates Program Mentor	2021
Black in Neuro Week - #BlackJourneytoNeuro Committee Lead	2021
UCI School of Biological Sciences Inclusive Excellence Task Force	2020
Black in Neuro Week Organizer	2020
Black in Neuro Conference Organizer	2020

Community Talks & Outreach

Session Moderator, "Neuroscience Mentoring Club", Diversity and Disparities Professional Interest Area	2022
Panelist, "PREP Symposium: Preparing for Ph.D. and M.D./Ph.D.", University of Pennsylvania, Pennsylvania	2022
Speaker, "Careers to STEM: My Journey to Neuroscience", Girls Inc. New York, New York	2021
Speaker, "How to be Anti-Racist", DECADE School of Medicine, University of California Irvine, Irvine, CA	2021
Speaker, "Becoming Anti-Racist: Being a Better Advisor, Lab Mate and Friend to Black Colleagues", University of California, Irvine	2020
Panelist, "Diversity in OPAM", Virtual Object Perception, visual Attention, and visual Memory Conference	2020
Panelist, "The First-Generation Graduate Student Experience", Graduate Division, University of California Irvine, Irvine CA	2019
Speaker, "The brain as a predictor of successful aging in the 90+, Brews and Brains,	2018

Irvine, CA

ABSTRACT OF THE DISSERTATION

Neuroimaging Biomarkers in Cognitive Aging

by

Elena Dominguez

Doctor of Philosophy in Biological Sciences

University of California, Irvine, 2022

Professor Craig Stark, Chair

While aging is typically associated with cognitive decline, some individuals are able to diverge from the characteristic downward slope and maintain very high levels of cognitive performance. By examining morphological characteristics of the brain using structural neuroimaging, several studies have attempted to understand these trajectories and elucidate what neurobiological factors contribute to preserved cognition throughout advanced aging. Using data from the National Alzheimer's Coordinating Center (NACC) and Alzheimer's Disease Neuroimaging Initiative (ADNI), I examined individuals aged 60 and above who demonstrated a combined performance at or above the top 50th percentile in memory and executive function, deemed as Top Cognitive Performers (TCP). In this thesis, we aimed to understand how well structural (cortical thickness, cortical volume, and white matter hyperintensity volume) and pathological (amyloid and tau burden) characteristics can be used to model TCP. As these relationships are sparsely studied in the oldest segment of our population, those 90 and above, we also utilized existing structural magnetic resonance imaging (MRI) and neuropsychological assessment data collected by The 90+ Study. Results showed that regional network-style cortical thickness both outperformed localist cingulate models and was sufficient in predicting TCP. Additionally, we were able to show that while both cortical thickness and volume models preformed similarly, cortical thickness did slightly better at predicting TCP. Though we were able to see group differences in white matter intensities in some age groups, this measure did not independently perform as well as cortical thickness. Lastly, unlike differences seen in structural correlates, TCP individuals did not exhibit group differences in PET measures of amyloid or tau. Taken together, this shows that neuroimaging biomarkers are useful in the identification of successfully aging cohorts, particularly when examining structural correlates of aging.

These relationships were seen in younger and older datasets, further suggesting that MRI biomarkers are useful across the full adult lifespan.

INTRODUCTION

Aging is a physiological process associated with increased risk in many debilitating diseases such as heart disease, stroke, and dementia. Despite this, advancements in health care and modern technology have led to an increase in life expectancy, and, by 2030, individuals 65 and older will outnumber those under the age of 18 (US Census Bureau, 2010, 2018). With this dramatic increase in the elderly population, it is important to better understand the various cognitive trajectories associated with aging, a well-studied but multifarious path. Disease-related aging, such as those living with Alzheimer's disease, is sometimes met with a precipitous drop in the ability to complete everyday cognitive tasks such as accessing memories and navigating the world. Even cognitively normal individuals who are able to avoid the deleterious effects of dementia may experience subtle changes in cognition. A third aging trajectory, represented by successful aging, includes individuals who are able to retain their cognitive faculties throughout advanced aging. It is widely proposed that the spectrum of these trajectories is the consequence of various neurobiological processes. Thus, this thesis covers 3 aims designed to answer some major questions around this idea and are outlined as follows:

Chapter 1: What does normal and successful aging look like throughout in the elderly? This chapter describes normal and "super" cognitive aging throughout the older-adult lifespan and how it is represented in the brain, as seen on neuroimaging. It briefly describes the contributions of structural characteristics of the whole brain, and how the cingulate cortex may partly explain those who exhibit superior cognitive performance. Additionally, it covers why other networks may also equally contribute to successful aging.

Chapter 2: Is cortical thickness of the cingulate cortex key in predicting successful aging? This chapter assesses the role of regional cortical thickness, both in the *a priori* cingulate cortex and whole-brain, network-level models, in predicting Top Cognitive Performance (TCP), measured by performance in the top 50th percentile of memory & executive function. Additionally, we wanted to observe if such relationships between cortical thickness and TCP persists in rising age groups by examining individuals 70-100.

A version of this chapter was first published in Frontiers in Aging Neuroscience (Dominguez et al., 2021). The chapter has been edited for clarity and relevance to this thesis.

Chapter 3: What factors other than cortical thickness can predict Top Cognitive Performance? This chapter expands upon Chapter 2 and assesses additional structural features that may contribute to Top Cognitive Performance such as cortical volume and white matter hyperintensities and positron. Moreover, this chapter addresses top performance in other cognitive domains (memory, executive function, language, and attention).

Chapter 4: Do Top Cognitive Performers exhibit lower levels of Alzheimer's disease related pathology throughout the lifespan? This chapter aims to assess TCP group differences in Alzheimer's disease related pathologies: amyloid and tau. These goals are studied across the full elderly lifespan and support the theory of resilience in successful aging individuals.

Chapter 5: Discussion and Conclusions

Chapter 1

1.1 COGNITIVE TRAJECTORIES IN THE ELDERLY AND *THE 90+ STUDY*

COGNITION AFTER 60

Though there is general decline in most areas of cognition, studies have consistently shown that not every cognitive domain follows the same trajectory across the lifespan in magnitude or rate (Anstey & Low, 2004; Christensen, 2001; Wilson et al., 2002). For example, some abilities, such as crystallized knowledge, or knowledge from one's past experiences, tend to remain relatively stable throughout adulthood (Christensen, 2001; Craik, 1990), even up to the age of 90 (Singer et al., 2003). Other domains, such as verbal ability, or our ability to use our semantic memory to identify objects, express ideas, and respond to verbal instructions, follow similar stable trajectories throughout our lifespan (Deary et al., 2009; Harvey, 2019; Hedden & Gabrieli, 2004).

Memory, a domain that is most notably susceptible to early subjective complaints in older adults, has been shown to follow a heterogeneous pattern of decline (Christensen, 2001; Grady, 2012; Hultsch et al., 1992), with some aspects declining faster than others. Episodic memory, defined by a process of encoding, maintaining, and retrieving information pertaining to specific events, has frequently been cited to decline sharply with age (Christensen, 2001; Daselaar et al., 2007; Grady, 2012; Harvey, 2019). As shown in Figure 1.1a, cross-sectional performance in measures of episodic memory from The Betula Study drastically decreased as a function of age (Nilsson, 2003). Moreover, when examining 6-year longitudinal changes in the Berlin Aging Study, individuals 70 and above

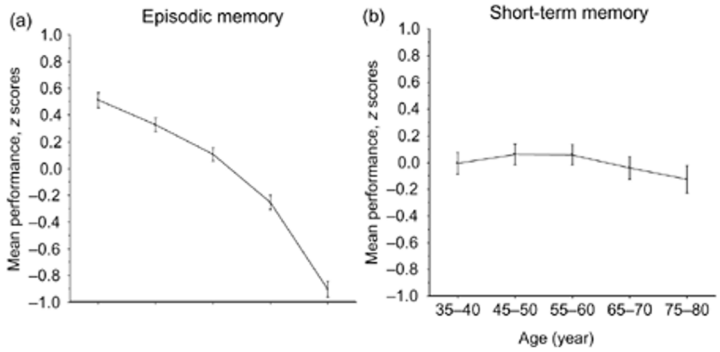


Figure 1.1: **Aspects of memory decline more than Others (Adapted from Nilsson et al., 2003)**- Cross□sectional data from the first wave of data collection from The Betula Study revealed that episodic memory performance dramatically decreased as a function of age in episodic memory, while short-term memory remained relatively stable.

exhibited a decrease in episodic memory performance, with older (mean age= 83.04 years) participants exhibiting a more negative slope than their somewhat younger counterparts (mean age=73.77), suggesting a steeper decline with increasing age (Singer et al., 2003). Alternatively, short-term memory is known to be relatively preserved and shows little to no decline across the adult lifespan (Nilsson, 2003), as depicted in Figure 1.1b. Likewise, procedural memory, or our 'memory for motor actions or skills', (Churchill et al., 2003; Harvey, 2019; Mitchell et al., 1990; Nilsson, 2003) is similarly conserved.

Other cognitive domains, such as processing speed, attention, and executive functioning also deteriorate as we age. Moreover, some have even suggested that cognitive abilities such as speed and executive function may account for or mediate various kinds of memory and fluid abilities (Finkel et al., 2007; Salthouse, 1996; Schretlen et al., 2000). Processing speed, defined by the time it takes to perform mental tasks and to process information, is often cited as a core feature of normal cognitive decline, and is linked to many functional aspects of our life, such as driving cessation in older adults (Edwards et al., 2010; Harvey, 2019). For example, a meta-analysis of 91 early aging studies showed that both working memory and processing speed acted as strong mediators for other age-related differences in other domains such as episodic memory and general fluid intelligence (Verhaeghen & Salthouse, 1997). Unsurprisingly, speed has shown both longitudinal and cross-sectional declines as a function of age (Ebaid et al., 2017; Perbal et al., 2002; Singer et al., 2003). Attention, defined as the process of attending to relevant information and ignoring all else, can be further broken down into subtypes of which are differentially affected by age. Madden (2007) stated that, when compared to younger adults, older adults exhibit slower and less accurate performance in visual-search tasks (Madden, 2007). This finding is also highlighted by Commodari & Guarnera (2008), who demonstrated that participants in their 50's outperformed individuals in their 60's in immediate attention span, attention shifting, and ability to ignore interference, but not in reaction time, suggesting a deficit in some attentional abilities but not others (Commodari & Guarnera, 2008). Executive function, a domain that is closely related to daily living functional status (Cahn-Weiner et al., 2002; Johnson et al., 2007), accounts for decision making, task switching, reasoning,

strategizing, and problem solving (Harvey, 2019). Research has shown that the elderly exhibit worse performance in planning (Allain et al., 2005; Andrés & Van der Linden, 2000; H. Lin et al., 2007), and inhibition (Andrés & Van der Linden, 2000) when compared to younger groups, while other aspects such as cognitive flexibility and reasoning have shown to be preserved (Treitz et al., 2007).

COGNITION IN THE OLDEST OLD AND THE 90+ STUDY

Individuals in their 90's display a more marked and rapid decline than those in their 70's in cognitive domains such as memory, perceptual speed, knowledge, and fluency (Singer et al., 2003). Moreover, people aged 95 and older exhibit significantly increased daily living difficulties than those aged 75-84 years old (Cohen-Mansfield et al., 2013). Given that these aging trends persist and are exacerbated in the oldest-old, defined here as those aged 90 and above, they are of particular interest in the examination of cognition, disease progression, and longevity. The continued growth of those that are able to reach their ninth decade and beyond has prompted considerable interest in the study of nonagenarians and centenarians, one chief population-based cohort being *The 90+ Study*.

The 90+ Study, established in 2003, is an ongoing longitudinal investigation of aging and dementia in individuals aged 90 and above, consisting of the survivors of the *Leisure World Cohort Study* (Kawas, 2008). As one of the largest and longest studies of oldest-old, *The 90+ Study* has contributed seminal findings related to cognition, disease progression, as well as lifestyle and risk factors of disease. In line with other studies, the prevalence of having difficulty in one or more activities of daily living dramatically increased with age in *The 90+ Study* (Berlau et al., 2009). Further, the incidence of dementia persists into the oldest old, nearly doubling in rate percentage every 5 years and reaching 40.7% per year in centenarians (Corrada et al., 2010).

Studies of 90+ participants without dementia (i.e., cognitively normal and cognitively impaired-no dementia (CIND)) revealed that neuropsychological performance assessing attention, language, verbal memory, and construction continuously decline with increasing age (Whittle et al., 2007). Further studies

in *The 90+ Study* examining normative data in *only* cognitively normal participants revealed similar results, though, contrary to Whittle and colleagues (2007), performance on Trails Making Test Part-B and Digit Span Backwards, measurements of working memory and executive function, were not sensitive to increasing age (Melikyan et al., 2019a). Melikyan and colleagues that the variance seen in Whittle et al. (2007) may have been better explained by CIND rather than age. Thus, given their wide-ranging spectrum of cognitive abilities, high risk for developing dementia (Corrada et al., 2010), large well-characterized cognitively normal sample size (Melikyan et al., 2019a), and availability of multi-modal in vivo and post mortem imaging, *The 90+ Study* cohort presents an excellent opportunity to study the neural correlates of age-related cognition.

1.2 DEFINING SUCCESSFUL AGING AND EXAMINING ITS NEURAL CORRELATES

DEFINITIONS OF SUCCESSFUL AGING

While a declining trajectory in cognitive performance is typically expected in the aging population, many individuals are able to diverge from this characteristic downward slope. This phenomenon reflects one of the many operational definitions of successful aging, in which an individual retains optimal cognitive abilities throughout advanced aging in key domains such as memory and processing speed (Rowe & Kahn, 1997). Individuals in these specialized groups are typically identified based on their higher-than-normal performance on various neuropsychological tests, often chosen due to their challenging nature and sensitivity to neurodegenerative processes.

The growing interest in successful aging has resulted in various definitions or labels for specialized cohorts, including SuperAgers, Supernormals, High Performing Elderly, and more, briefly described in Table 1.1. It is important to note that the literature is not limited to those in Table 1.1, and though each of these studies reflect the concept of successful aging in some capacity, they vary in criteria and inclusion for group membership. For example, 70 year old successful agers derived from the Berkeley Aging Cohort Study were required to have a score at or above the mean gender-adjusted value

for young adults (18 –32) on the California Verbal Learning Test (CVLT), a measure of episodic memory, and age adjusted performance on Trails-B, a test of executive function (Harrison et al., 2018). The Health, Aging, and Body Composition Study's longitudinal cognitive maintainers, on the other hand, were described as 70+ year old's that maintained global cognition, measured by a slope greater than zero on the Modified Mini Mental (3MS) test (Rosano et al., 2012; Yaffe et al., 2009). Importantly, although these groups employ different methods of classification, they all offer insight into preserved cognitive functioning late into life "successful" aging and share common threads in their classification methods.

Table 1.1: Definitions of Successful Aging examining structural and functional correlates

Name	Age Range	Participants	Definition	Citations
High Performing Groups				
High Performing Elderly (High Fluid Performers)	60+	Community dwellers	Participant were classified as "high" or "average" on fluid ability based on Wechsler Abbreviated Scale of Intelligence performance.	(Fjell et al., 2006)
Successful Older/ Cognitive Maintainer	60+	Betula Study	Participants were classified based on a moderate to high baseline episodic memory composite score and a better than average rate of change in performance.	(Pudas et al., 2013)
Supernormals	70+	Alzheimer's Disease Neuroimaging Initiative	Participant were classified based on constantly high and stable episodic memory and executive function composite scores over a 5-year period.	(Baran et al., 2018; F. Lin et al., 2017; Wang et al., 2019)
SuperAger	60-93	Australian Imaging, Biomarkers and Lifestyle study	Participant were classified by a score above the sex-adjusted normative average for younger adults (age range, 30-44) in episodic memory and performance above −1 *SD* on non-memory tests.	(Dang, Harrington, et al., 2019a)
	60+	Recruitment from the greater Boston area	Participant were classified by a score at or above the mean gender-adjusted value for young adults (age range, 18 –32) in episodic memory and a score no lower than 1 SD below the mean	(Sun et al., 2016a; Zhang et al., 2020)

			for their age group in executive function.	
	80+	Northwestern University SuperAging Study	Participant were classified by a score at or above average normative values for younger individuals (age, 50s and 60s) in episodic memory and a score within one standard deviation of the average range for their age and education on non-memory tests.	(Gefen et al., 2015; Harrison et al., 2012)
	80+	Northwestern University	Participant were classified by a score at or above average normative values for younger adults (age range, 50-65) on a test of episodic memory and at least average-for-age normative values on tests in other cognitive domains.	(Cook et al., 2017)
Optimal Performers and Maintainers	75+	Harvard Aging Brain Study	Optimal Performers: A score in the top 20% of a memory composite score. Maintainers: A score ≥ 0.5 SD above the mean for the memory composite at a three-year follow-up.	(Dekhtyar et al., 2017)
Successful Agers	70+	Berkeley Aging Cohort Study	Participant were classified by a score at or above the mean gender-adjusted value for young adults (age range, 18 –32) episodic memory and normal-for-age performance in executive function.	(Harrison et al., 2018)
Maintained Cognition				
Cognitive Maintainers	70+	The Health, Aging, and Body Composition Study	"Participants were classified as having shown either maintenance (3MS slope > 0) or decline (3MS slope < 1 SD below the mean) of cognition using linear mixed models."	(Rosano et al., 2012; Yaffe et al., 2009)

SUCCESSFUL AGING AND THE BRAIN

Two terms that are at the forefront of successful aging literature are resistance and resilience. Though a common core feature of both is the maintenance of stellar cognition in old age, *resistant* individuals exhibit an absence or low frequency of neurodegenerative brain insults, while *resilient* individuals maintain their cognition even in the presence of said neuropathology and brain atrophy (Montine et al., 2019; J. W. Rowe & Kahn, 1997)(Montine et al., 2019; J. W. Rowe & Kahn, 1997). To explore both resistance and resilience, researchers like those mentioned in Table 1.1 have studied the brains of these specialized cohorts compared to normal-for-age individuals to determine what structural and pathological characteristics (measured by structural MRI, PET imaging, etc.) contribute to preserved

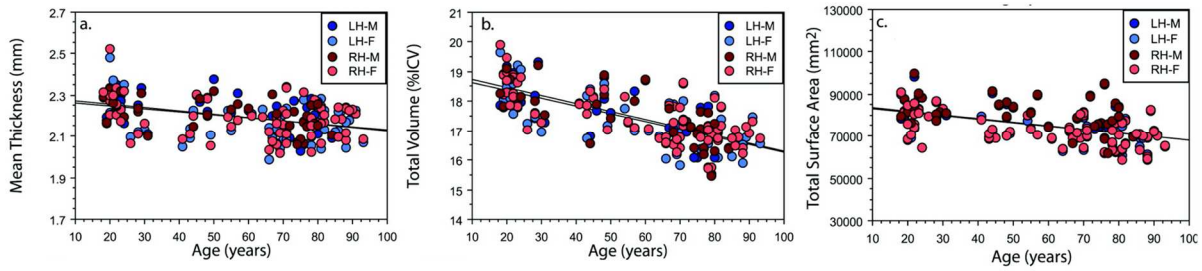


Figure 1.2: Age-related changes in the brain: Total mean cortical thickness (a), total cortical volume (b), and total cortical surface area (c) (adapted from Salat et al., 2004) – Structural T1-weighted magnetic resonance imaging in 106 non-demented participants ranging in age from 18-93. Scatter plots in each hemisphere were regressed by age, separated by sex (F, female; M, male) and cortical hemisphere (lh, left hemisphere; rh, right hemisphere).

cognition in the elderly.

First, to explore its contribution to alternative aging trajectories, it is important to understand characteristic brain changes in normal aging. Typically, normal aging is met with diffuse atrophy throughout the brain. It is important to note, though, that while mean cortical thickness, total intracranial

volume, and total surface area are significantly correlated with age (Figure 1.2), atrophy does not occur uniformly throughout the brain (Salat et al., 2004). Areas of increased age-related atrophy include regions in the frontal (Jernigan et al., 2001; Resnick et al., 2003; Thambisetty et al., 2010; Tisserand et al., 2002), temporal (Fjell et al., 2014; Raz et al., 2010; Yao et al., 2012), and parietal lobes (Fjell et al., 2014; Lemaitre et al., 2012; Resnick et al., 2003), as well as regions of the cingulate cortex (Lemaitre et al., 2012; Mann et al., 2011; Pardo et al., 2007). Atrophy has been reported to be more pronounced in the cingulate cortex (Resnick et al., 2003), with decreases in both volume (Good et al., 2001), and cortical thickness (Hurtz et al., 2014) in aging subjects.

The cingulate cortex has been of particular interest in successful aging due to its diffuse connectivity throughout the brain and involvement in many areas of cognition, including memory, emotional processing, task engagement, and attention (Pearson et al., 2011a; Stanislav et al., 2013a; Vaidya et al., 2007a). The cingulate can be further divided into subregions (e.g., anterior and posterior), with regional specificity in function, cytoarchitecture, and connectivity (Palomero-Gallagher et al., 2019; Torta & Cauda, 2011). The anterior cingulate cortex has been shown to exhibit connectivity to key limbic areas, such as the amygdala and hippocampus, as well as the prefrontal cortex (Etkin et al., 2006, 2011; Margulies et al., 2007). The posterior cingulate, in contrast, is a key node and central hub of the default mode network and is highly metabolically active (Leech & Sharp, 2014). It has been implicated in emotional processing (Maddock et al., 2003), recollection and familiarity (Yonelinas et al., 2005), and autobiographical memory retrieval (Maddock et al., 2001). Thus, the cingulate cortex plays a critical role in the domains of cognition that are sensitive to aging and may represent a key region in resistance to age-related decline.

In the context of successful aging, many have connected structural properties, such as cortical thickness, to successful aging. Areas such as the caudal anterior and posterior cingulate (Fjell et al., 2014; Gefen et al., 2015; Harrison et al., 2012, 2018), the insula (Fjell et al., 2014; Sun et al., 2016a), and the prefrontal cortex (Harrison et al., 2018) were found to exhibit greater cortical thickness in successful

aging individuals, described more in Chapter 2. Interestingly, the cingulate has also been identified in other modes of imaging such as functional MRI (fMRI) and diffusion tensor imaging (DTI). Seventy year old Supernormals, distinguished by a higher episodic memory composite score, exhibited a significantly stronger functional connectivity between the anterior cingulate cortex and right hippocampus, a region heavily involved in memory (F. Lin et al., 2017).

SUMMARY

The goal of this proposal is to understand the neurobiological mechanisms that underly resistance to cognitive decline that plagues our rapidly growing elderly population via neuroimaging biomarkers. Given the various definitions of successful aging and their modeling of a priori networks, the current literature leaves us with the question of what is the central and salient model of successful aging? In other words, is there a true hotspot of regions, key cortical measure, or one definition that identifies super individuals? For example, whether the cortical thickness of the cingulate sufficiently predicts preserved cognition in older adults is still to be determined. Though the cingulate has proven to be important in successful aging, the structural integrity of other regions and networks have also been identified in preserved cognitions. This suggests that structural properties across a wide range of areas may better explain differences in cognitive abilities. Thus, using data driven approaches we assessed established models of cortical thickness and examined multiple structural markers associated with normal decline. Additionally, it is important to consider other age-related biomarkers that are known to be associated with cognitive decline, such as amyloid burden. Identifying neurobiological markers that contribute to cognitive preservation may help us to prolong onset of decline and develop therapies that target these protective features.

Chapter 2

Regional Cortical Thickness Predicts Top Cognitive Performance in the Elderly

Prior studies have found that cortical thickness in the cingulate cortex, a region involved in information processing, memory, and attention, distinguish those with exceptional cognitive abilities when compared to their cognitively more typical elderly peers. Others major areas outside of the cingulate, such as the prefrontal cortex & insula, are also key in successful aging well into late age, suggesting that structural properties across a wide range of areas may better explain differences in cognitive abilities. Here, we aimed to assess the role of regional cortical thickness, both in the cingulate and the whole brain, in modeling Top Cognitive Performance (TCP), measured by performance in the top 50th percentile of memory & executive function. Using data from National Alzheimer's Coordinating Center and The 90+ Study, we examined healthy subjects aged 70-100 years old. We found that, while thickness in cingulate regions can model TCP status with some degree of accuracy, a whole-brain, network-level approach out-performed the localist, cingulate models. These findings suggest a need for more network-style approaches and furthers our understanding of neurobiological factors contributing to preserved cognition.

2.1 Introduction

As previously described, many studies in successful aging have identified the cingulate cortex as a key area in identifying those who are able to maintain their cognition. For example, upon conducting a whole brain analysis, Northwestern University's eighty year old SuperAgers, distinguished by their middle-age-like episodic memory, exhibited a significantly thicker anterior cingulate cortex when compared to their normal-for-age peers (Harrison et al., 2012). Note, however, that the modest sample

sizes (n=12 SuperAgers and n=10 elderly controls) may have impacted their ability to reliably identify a broader range of regions. Following this finding, an *a priori* region-of-interest (ROI)-based analysis revealed that SuperAgers displayed greater cortical thickness in the posterior and caudal anterior cingulate cortex when compared to elderly controls (Gefen et al., 2015).

As shown in Table 1.1, studies of successful aging are not limited to the popularized SuperAger cohort, and many have examined top performing individuals based on varying neuropsychological performance and tests. Despite this variability, one commonality exists in the structural integrity of the cingulate cortex. Seventy-year-old successful agers, defined by high performance in episodic memory, working memory, and processing speed, displayed greater cortical thickness within the right anterior cingulate and prefrontal cortex (Harrison et al., 2018). Additionally, they had greater hippocampal volume and lower white matter hypointensity volumes. Another study, examining optimal cognitive aging assessed by high performance in visuo-constructive abilities and visual reasoning, found that older individuals with high fluid abilities displayed greater cortical thickness in large areas of the cingulate cortex. Interestingly, they did not find this same relationship when comparing high vs. average performers in younger groups (Fjell et al., 2006).

Though the cingulate has proven to be important in successful aging, the structural integrity of other regions and networks have also been identified in preserved cognitions. For example, the above mentioned optimal cognitive aging individuals also displayed greater cortical thickness in areas such as the insula, temporal middle gyrus, and the isthmus cingulate (Fjell et al., 2006). Sun and colleagues (Sun et al., 2016b) found that younger SuperAgers, aged 60-80, exhibited greater cortical thickness in the dorsomedial prefrontal cortex, angular gyrus, and superior frontal gyrus; all key regions in the default mode and salience networks. Whole brain analyses in high functioning individuals, aged 90 and older, revealed structural preservation in prefrontal and insular areas (Yang et al., 2016). Similarly, 70+ year old Successful Agers, distinguished by high memory scores, exhibited greater cortical thickness in the insula, midcingulate cortex, and the medial prefrontal cortex (Harrison et al., 2018). Thus, while the

cingulate appears in each of these studies, several other regions have been implicated as well, suggesting a possible widespread network contributing to the resistance to cognitive decline.

It is important to note that our goal here is not to identify a set of specific cortical biomarkers of successful aging. Rather, the goal of the present study is a more generalized one. Here, we aim to understand how well cortical thickness can be used to model a behavioral outcome like successful aging, whether certain regions are disproportionately involved in this, and whether the cingulate cortex in particular is disproportionately involved. Thus, one hypothesis is that there is a set of specific regions, such as the cingulate regions, where thickness is able to predict cognitive status, while other regions have little or no predictive value (i.e., the cingulate is particularly informative when trying to model cognitive status). A second hypothesis is that the predictive power is distributed as a relatively smooth gradient across regions, with some more predictive than others, but no clear-cut differentiation between predictive and non-predictive regions. Finally, a third, "null" hypothesis is that all regions are equally predictive (or non-predictive) of cognitive status. Using structural and neuropsychological data from the National Alzheimer's Coordinating center (NACC), we evaluated these hypotheses by examining the relationship between cortical thickness the brain and high cognitive performance in measures of episodic memory and executive function; two abilities that are otherwise known as hallmark domains of cognitive impairment and disease progression. We examined individuals aged 70-89, who demonstrated a combined performance at or above the top 50th percentile in both domains, deemed as Top Cognitive Performers (TCP) and we compared logistic regression performance using the cingulate ROIs relative to using the whole brain. To assess reliability of our models and the overall informativeness of individual regions, we performed Monte Carlo sampling of the population, creating logistic regression models for each sample. Finally, we examined the efficacy of these approaches as a function of age as by breaking them down by decade and including data from *The 90+ Study*. Individuals in their 90's display a more marked and rapid decline than those in their 70's in cognitive domains such as memory, perceptual speed, knowledge, and

fluency (Singer et al., 2003), making it valuable to understand how the informativeness of these metrics persists into very advanced stages of aging.

2.2 Experimental Design And Methods

The National Alzheimer's Coordinating Center

Participants

Three hundred and forty-seven individuals were selected from the larger NACC cohort (Figure 2.1A). NACC is a database of patient information collected from multiple Alzheimer disease centers funded by the National Institute on Aging (Beekly et al., 2004). For this analysis, participants were required to be seventy years old and above (70-89 years old) and have at least one T1 MRI scan available within 2 years of their initial UDS visit. Additionally, participants were required to have a NACC status indicating normal cognition and behavior (NORMCOG and NACCUDSD), as determined by a clinician

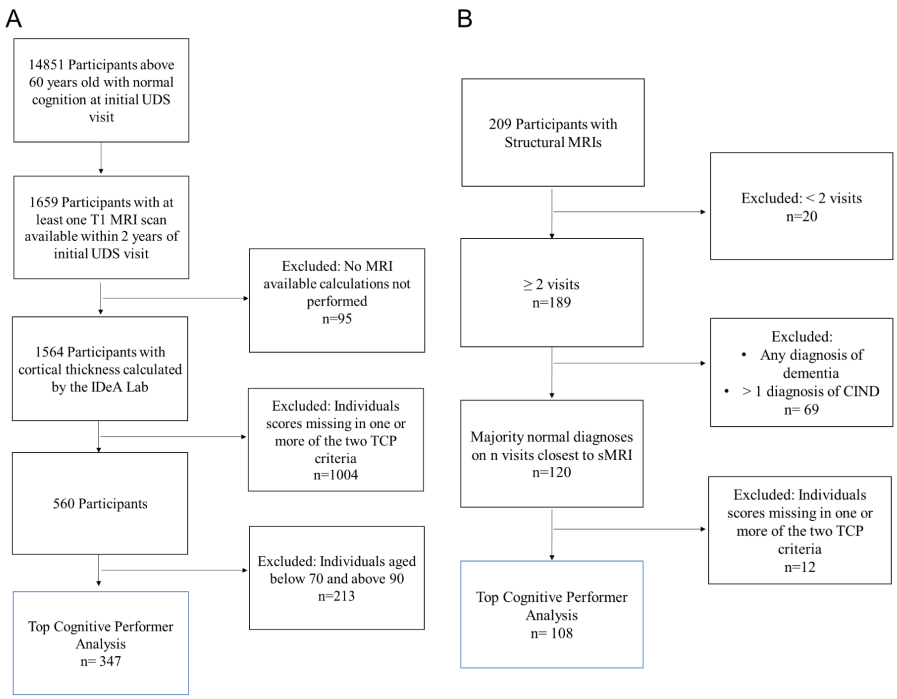


Figure 2.1: Inclusion flow chart for (A) NACC and (B) The 90+ Study Participants. Blue box reflects the participants included in the final analysis of top cognitive performers (TCP).

or panel of clinicians based on neuropsychological test scores, CDR, Form B9 (Clinician Judgement of Symptoms), and center specific tests. Individuals who contained missing data in any of the criteria variables, described below, were excluded from the analyses.

Neuropsychological criteria for group inclusion

Previous studies of successfully aging cohorts have used neuropsychological tests with specific criteria based either on performance being consistent with a younger population or with performance being atypically high for their age group. Following the latter, TCPs were required to be in the top 50th percentile for both the Wechsler Memory Scale-revised Logical Memory IIA-Delayed Recall (WMS-R IIA) and Trails Making Test- Part B (Trails-B). The WMS-R IIA tests verbal and visual modalities and asks participants to recall units of a story after a 15 minute delay (Wechsler, 1987). Trails-B engages executive function and processing speed by asking the participant to draw a line that connects an ordered progression of alternating letters and numbers (e.g. 1 – A – 2 – B – 3 – C…) as quickly as possible (Tombaugh, 2004). All individuals that did not fit these criteria were classified as non-Top Cognitive Performers (non-TCP).

Image Data

Pre-calculated regional cortical thickness data for NACC MRIs were provided by the IDeA Lab at University of California, Davis. T1-weighted structural MRI (sMRI) scans were obtained from multiple centers using 3.0 and 1.5 Tesla scanners (GE, Siemens, and Phillips). sMRI data from the date closest to the initial UDS visit were processed based on the Advanced Normalization Tools (ANTs) toolkit and thickness pipeline (Das et al., 2009). Modifications to that pipeline for improving grey/white matter segmentation used to generate the numbers in NACC are described by Fletcher et al. (2012).

The 90+ Study

Participants

One hundred and eight individuals from the larger *The 90+ Study* cohort were included (Figure 2.1B)**.** The 90+ Study, established in 2003, is an ongoing longitudinal investigation of aging and dementia in individuals aged 90 and above, consisting of the survivors of the Leisure World Cohort Study (Kawas, 2008). Participants were selected based on the availability of a sMRI, two or more neuropsychological visits, and a cognitively normal diagnosis at a majority of their visits (i.e., 2 out of 3 visits or 3 out of 4 visits). Cognitively normal was determined by *The 90+ Study* and refers to a primary diagnosis, determined by neurological examiners, where an individual is deemed as normal, absent of impairment in any cognitive domains, and able to complete Instrumental activities of daily living (IADL). Individuals who contained missing data in any of the criteria variables were excluded from the analyses.

Neuropsychological criteria for group inclusion

While participants in *The 90+ Study* are visited every six months by researchers who perform neuropsychological tests, the number of visits for each individual at the time of these analyses varied from one visit to twenty three. Thus, based on the available data, median cognitive scores from up to four visits closest to sMRI scan date were chosen as a more robust measure of cognition that would account possible variance in individual session performance. Following NACC TCP criteria, The 90+ TCP individuals were required to perform at or above the top 50th percentile for their age group on the long-delay recognition portion of the California Verbal Learning Test – short form (CVLT) and at or above the top 50th percentile on completion time for their age group in the Trails-B. All other individuals that did not fit these criteria were classified as non-Top Cognitive Performers (non-TCP).

Image Data

T1-weighted structural MRI scans were collected on a 3.0 Tesla GE Discovery MR750w scanner (1 mm isotropic resolution, TE=3ms, TR=7.2ms, flip angle = 11°). Images were processed using Mindboggle (Klein et al., 2017), which performs atlas registration to the Desikan-Killiany-Tourville (DKT) atlas (Desikan et al., 2006) and cortical thickness estimation using Advanced Normalization Tools (ANTs; its additional FreeSurfer estimates were not used here). ANTs calculates cortical thickness by measuring the distance between gray/white matter boundaries and grey/cerebrospinal fluid (CSF) boundaries by quantifying the amount of registration needed to bring these surfaces together. Thickness was calculated in the original native subject space before being transformed into Montreal Neurological Institute and Hospital (MNI) space. Using DKT regions of interest as masks, we computed the average cortical thickness within each ROI. To reduce edge effects that will be present in these masks (thickness is computed in the cortical sheet and the ROIs will cover voxels not in a particular subject's sheet), thickness maps were clipped at 1 mm and the average computed across all resulting non-zero voxels. The average cortical thickness of three bilateral cingulate regions from the DKT atlas (posterior cingulate cortex, caudal anterior cingulate cortex, rostral anterior cingulate cortex) was examined as *a priori* regions based on their previously shown involvement in successful aging (Figure 2.2).

Statistical analysis of MRI study participants and cortical thickness

For both datasets, statistical analyses were performed using SAS and both the Statsmodels (https://www.statsmodels.org/) and skikit-learn (https://scikit-learn.org/) libraries in Python. To evaluate the influence of cortical thickness on top cognitive performance, two logistic regression model were used to model TCP status as a function of regions of interest as follows: (1) 6 bilateral *a priori* cingulate ROIs (rostral anterior, caudal anterior, and posterior segments), and (2) a forward-selection model with 62 whole brain cortical ROIs (cutoff p-value for the F statistic, p=0.25). Receiving Operating Characteristic (ROC) curves were created to assess the accuracy of TCP status as a diagnostic marker. Additionally, unpaired t-tests were used to evaluate differences in continuous variables (age, education-NACC, and neuropsychological performance) and Fisher's exact test to evaluate gender distribution, across the two subject groups.

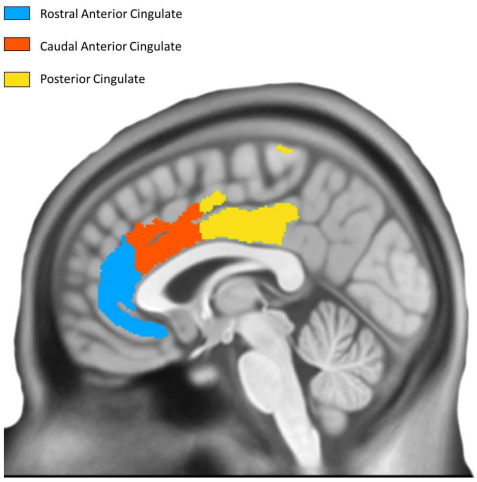


Figure 2.2: Desikan Killiany Tourville Atlas Three bilateral a priori cingulate regions derived from DKT atlas; left hemisphere is shown

2.3 Results

Demographics and neuropsychological performance at baseline

NACC analyses used data from 11 Alzheimer's Disease Research Centers (ADRCs) for UDS visits conducted between September 2005 and December 2020. The average time between initial neuropsychological visit and MRI was 133.3 (189.6) and 138.7 (185.1) days for non-TCP and TCP, respectively. The 347 NACC participants had an average of 15 years of education and were 60.81% female (Table 2.1). TCP and Non-TCP groups did not differ in age in either the 70 ($t(24)=0.71$, $p=0.48$) or 80 year old subgroups ($t(1)=0.98$, $p=0.33$). They did, however, differ in education ($t(242)=5.02$,

p<0.0001) and gender distribution (Fisher's exact p=0.04) in the 70 year-olds and education (t(101)=2.72, p=.01) in the 80 year-olds. The 108 90+ Study participants were 63.89% female and 47% had a college education (Table 2.2). TCP and Non-TCP did not differ in age (t(106)=0.58, p=0.57), gender distribution (Fisher's exact p=>0.999), or education level at a baseline visit (X^2 (2, n = 108) = 1.88, p = .39).

Cortical thickness in the NACC sample: a priori cingulate regions

When considered in isolation, logistic regressions modeling TCP status based on the *a priori* cingulate regions' thickness (Table 2.3) failed to robustly model TCP status. When examining the full NACC 70-89 sample, no cingulate ROI could reliably model TCP status (p's > .1, uncorrected for multiple comparisons). When restricted to only those in their 70s, the right caudal anterior (p= 0.04, uncorrected), and rostral anterior (p= 0.01, uncorrected) cingulate showed some predictive power, but this was not the case in the NACC participants in their 80s (p= 0.15 & p= 0.29, respectively).

Table 2.1: NACC Demographics									
	All	**70 Year Old's**	**TCP**	**Non-TCP**	**T-Test/ Fisher's Exact Test**	**80 Year Old's**	**TCP**	**Non-TCP**	**T-Test/ Fisher's Exact Test**
n	347	244	83	161		103	22	81	
Age (SD)	75.94 (4.95)	74.25 (2.72)	74.07 (2.68)	74.34 (2.75)	0.476	83.31 (2.67)	82.82 (2.56)	83.44 (2.70)	0.331
Female (%)	211 (60.81%)	150 (61%)	59 (71%)	91 (56%)	**0.037**	61 (59.22%)	13 (59.09%)	48 (59.26%)	> 0.999
Education (SD)	15.00 (3.38)	15.07 (3.35)	16.49(2.37)	14.33(3.54)	**< 0.0001**	14.82 (3.47)	16.55 (2.54)	14.35 (3.55)	**.008**

Table 2.2: The 90+ Study Demographics				
	All	**TCP**	**Non-TCP**	**T-Test/ Fisher's Exact Test or Chi Square Test**
n	108	35	73	
Age (SD)	93.85 (2.60)	94.06 (2.60)	93.75 (2.62)	.565
Female (%)	69 (63.89)	22 (62.86)	47 (64.38)	> 0.999
Education (SD) High-school graduate or less (%) Some college to college graduate(%) Some graduate school or higher (%)	15 (13.89) 47 (43.52) 46 (42.59)	3 (8.57) 18 (51.43) 14 (40)	12 (16.44) 29 (39.73) 32 (43.84)	0.391

Table 2.3: Fitted Logistic Regression Models		
Age Group	**ROI**	**Fitted Model**
70-89	Left Caudal Anterior Cingulate, Left Posterior Cingulate, Left Rostral Anterior Cingulate, Right Caudal Anterior Cingulate, Right	$\text{Logit}(TCP) = -4.13 + 0.48\, x_{L\ Caudal\ Anterior\ Cingulate} + 0.48\, x_{L\ Posterior\ Cingulate} + 0.28\, x_{L\ Rostral\ Anterior\ Cingulate} + 0.43\, x_{R\ Caudal\ Anterior}$

	Posterior Cingulate, Right Rostral Anterior Cingulate	$Cingulate + 0.33\ x_{R\ Posterior\ Cingulate} - 0.61\ x_{R\ Rostral\ Anterior\ Cingulate}$
	Left Caudal Anterior Cingulate, Left Caudal Middle Frontal, Left Entorhinal, Left Medial Orbitofrontal, Left Paracentral, Right Cuneus, Right Superior Frontal	$Logit(TCP) = -2.36 + 0.66\ x_{L\ Caudal\ Anterior\ Cingulate} + 1.72\ x_{L\ Caudal\ Middle\ Frontal} - 0.62\ x_{L\ Entorhinal} + 1.28\ x_{L\ Medial\ Orbitofrontal} + 1.37\ x_{L\ Paracentral} - 1.00\ x_{R\ Cuneus} - 2.23\ x_{R\ Superior\ Frontal}$
70s	Left Caudal Anterior Cingulate, Left Posterior Cingulate, Left Rostral Anterior Cingulate, Right Caudal Anterior Cingulate, Right Posterior Cingulate, Right Rostral Anterior Cingulate	$Logit(TCP) = -3.95 + 0.73\ x_{L\ Caudal\ Anterior\ Cingulate} + 0.28\ x_{L\ Posterior\ Cingulate} + 0.51\ x_{L\ Rostral\ Anterior\ Cingulate} + 1.05\ x_{R\ Caudal\ Anterior\ Cingulate} + 0.10\ x_{R\ Posterior\ Cingulate} - 1.28\ x_{R\ Rostral\ Anterior\ Cingulate}$
	Left Entorhinal, Left Inferior Temporal, Left Paracentral, **Left Rostral Anterior Cingulate, Right Caudal Anterior Cingulate**, Right Lingual, **Right Rostral Anterior Cingulate**	$Logit(TCP) = -4.19 - 0.64\ x_{L\ Entorhinal} + 1.01\ x_{L\ Inferior\ Temporal} + 1.62\ x_{L\ Paracentral} + 1.19\ x_{L\ Rostral\ Anterior\ Cingulate} + 1.33\ x_{R\ Caudal\ Anterior\ Cingulate} - 1.50\ x_{R\ Lingual} - 1.39\ x_{R\ Rostral\ Anterior\ Cingulate}$
80s	Left Caudal Anterior Cingulate, Left Posterior Cingulate, Left Rostral Anterior Cingulate, Right Caudal Anterior Cingulate, Right Posterior Cingulate, Right Rostral Anterior Cingulate	$Logit(TCP) = -5.37 - 0.30\ x_{L\ Caudal\ Anterior\ Cingulate} + 1.91\ x_{L\ Posterior\ Cingulate} - 0.24x_{L\ Rostral\ Anterior\ Cingulate} - 1.06\ x_{R\ Caudal\ Anterior\ Cingulate} + 0.74\ x_{R\ Posterior\ Cingulate} + 0.77\ x_{R\ Rostral\ Anterior\ Cingulate}$
	Left Pericalcarine, Left Postcentral, Left Superior Temporal, Left Supramarginal, Right Isthmus Cingulate, Right Parahippocampal, Right Superior Parietal	$Logit(TCP) = -9.94 + 3.49\ x_{L\ Pericalcarine} + 9.14\ x_{L\ Postcentral} - 5.33\ x_{L\ Superior\ Temporal} + 3.95\ x_{L\ Supramarginal} + 5.76\ x_{R\ Isthmus\ Cingulate} - 3.72\ x_{R\ Parahippocampal} - 7.79\ x_{R\ Superior\ Parietal}$
90s	Left Caudal Anterior Cingulate, Left Posterior Cingulate, Left Rostral Anterior Cingulate, Right Caudal Anterior Cingulate, Right Posterior Cingulate, Right Rostral Anterior Cingulate	$Logit(TCP) = -2.67 + 1.51\ x_{L\ Caudal\ Anterior\ Cingulate} + 0.55\ x_{L\ Posterior\ Cingulate} - 0.11x_{L\ Rostral\ Anterior\ Cingulate} - 1.28\ x_{R\ Caudal\ Anterior\ Cingulate} + 0.71\ x_{R\ Posterior\ Cingulate} - 0.43\ x_{R\ Rostral\ Anterior\ Cingulate}$
	Left Isthmus Cingulate, Left Lateral Orbitofrontal, Left Pars Opercularis, Left Transverse Temporal, **Right Caudal Anterior Cingulate**, Right Medial Orbitofrontal, Right Insula	$Logit(TCP) = -4.21 + 2.31\ x_{L\ Isthmus\ Cingulate} + 5.41\ x_{L\ Lateral\ Orbitofrontal} - 6.94\ x_{L\ Pars\ Opercularis} + 2.25\ x_{L\ Transverse\ Temporal} - 2.63\ x_{R\ Caudal\ Anterior\ Cingulate} - 2.77\ x_{R\ Medial\ Orbitofrontal} + 2.33\ x_{R\ Insula}$

We next turned to receiver-operating characteristic (ROC) analysis, using a logistic multiple regression based on all six cingulate ROIs modeling TCP status. Here, we used the area under the curve (AUC) to quantify performance and assess the sensitivity and specificity of the model. Using this, the cingulate regions yielded an estimated AUC of 0.64 across the full age range in NACC (Figure 2.3A). While modest, this AUC was reliably better than chance. Given the combination of the biased base-rate of TCP status and the multiple predictors used (and potential for overfitting), a null value of 0.5 for AUC cannot

be assumed. To assess the null and estimate the true alpha, we conducted a permutation analysis, randomly shuffling the TCP/non-TCP labels 10,000 times and running the same logistic regression and AUC estimation to empirically derive an alpha using the same data and the same proportion of TCP status labels. We found the alpha to be ~0.009, indicating the odds that a large or larger AUC would be generated by chance (Figure 2.3D, blue line).

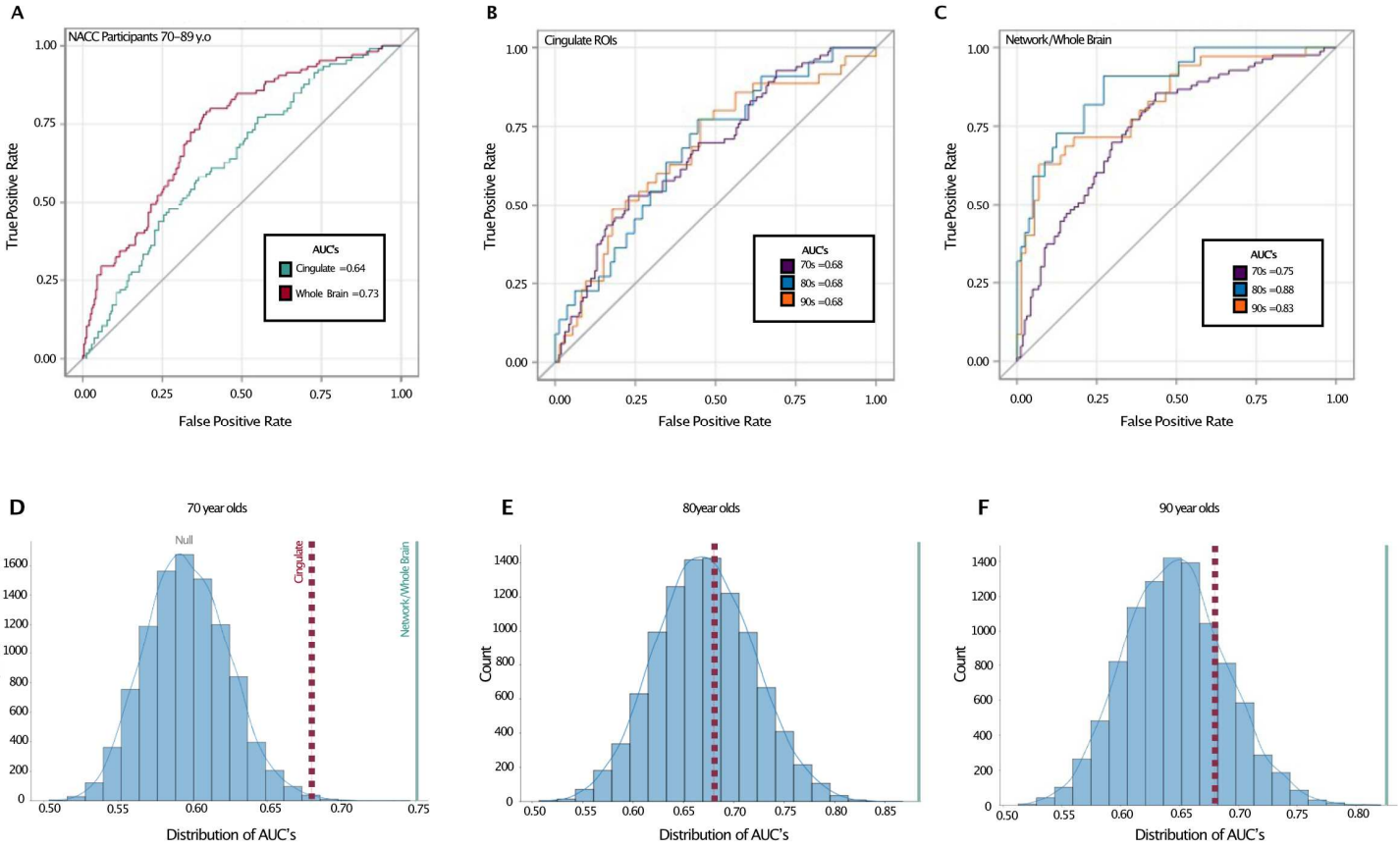


Figure 2.3: Receiver operating characteristic curves show better TCP predictive performance in whole brain model. Top: ROC curves with area under the curves (AUC) displayed for (A) entire NACC sample (ages 70-89), (B) *a priori* cingulate regions in all age groups, and (C) whole-brain forward-selected ROIs across all age groups. Bottom: Permutation analyses where the labeling of TCP vs non-TCP was shuffled 10,000 times in (D) NACC 70 year old's, (E) NACC 80 year olds, and (F) The 90+ Study 90 year olds. Red line represents AUC's for *a priori* cingulate ROIS reflected in panel (B) and blue line represents AUC for whole brain forward-selected ROIs reflected in panel (C). Abbreviations AUC: Area under the curve, 70s: NACC 70 year old's, 80s: NACC 80 year old's, 90s: The 90+ Study 90 year old's

Cortical thickness in the NACC sample: Whole-brain

To determine whether the cingulate ROIs represented the ideal or near-ideal set of regions for this approach, we next performed a whole-brain forward-selection logistic regression (i.e., using all 62 cortical ROIs). This analysis selected the left caudal anterior cingulate, left caudal middle frontal, left entorhinal, left medial orbitofrontal, left paracentral, right cuneus, and right superior frontal regions with a resulting AUC of 0.74 and a permutation-derived alpha of $p<0.0001$. Thus, while one of the cingulate regions was present in this model, the optimal model drew upon regions throughout the brain.

We should note that this is not the result of any global difference in cortical thickness across TCP groups. Estimates of average whole-brain cortical thickness were calculated for each individual by weighted averaging of the thickness from all 62 regions (weighted by region volume). Unpaired t-tests showed no difference in average whole-brain cortical thickness for the whole cohort or for those in their 70s or 80s separately (all t's < 0.8, all p's > 0.4).

Cortical thickness across age groups

We next turned to the question of whether our ability to model TCP status was affected by age. To do so, we shifted from thickness values provided by NACC to thickness values derived from ANTs directly as we wanted to include data from The 90+ Study as well to give a broader age range (note, we found that overall, the estimates provided by NACC yielded slightly higher AUCs than those provided by ANTs.) Here, we found that when restricting ourselves to the *a priori* cingulate regions, all three age groups yielded virtually identical ROC curves and 0.68 AUC values (Figure 2.3B). As with the combined data, however, shifting to a whole brain analysis improved performance considerably. The AUCs rose to 0.75 in the cohort in their 70's, 0.88 in those in their 80's, and 0.83 in the 90+ (alpha < 0.0001 in all). ROC contrast estimations comparing AUCs for cingulate versus forward-selected ROIs revealed a significant difference across all age groups, suggesting a better fit by regional cortical thickness (all $p <$ .02).

Role of age, sex, and education covariates

Our primary question here was whether cortical thickness could be used to model TCP status. As such, we excluded typical covariates such as age, sex and education that might otherwise predict TCP status and therefore inflate our AUC values. To determine their predictive value beyond cortical thickness, we repeated each of these logistic regression models including these factors. There was a slight increase in AUCs across all age groups when age, sex, and education were added to the model (Table 2.4). The 70 year old group showed the largest improvement, moving from 0.75 – 0.8, while the 80 year old group improved from 0.88 to 0.89 and the 90 year old group from 0.83 to 0.85.

Table 2.4: Effects of age, sex, & education on AUC values

Age Group	Forward Selected ROIs	Forward Selected ROIs + Sex	Forward Selected ROIs + Education	Forward Selected ROIs + Sex, Education	Forward Selected ROIs + Age, Sex, & Education
70-89	0.73	0.74	0.77	0.79	0.79
70s	0.75	0.76	0.78	0.80	0.80
80s	0.88	0.89	0.89	0.90	0.89
90s	0.83	0.83	0.84	0.84	0.85

Reliability of selected regions

Finally, we turned to the question of the consistency of the generated models. Informally, Table 2.3, which details fitted models of both the a priori cingulate model and our forward selection models, shows that there is some degree of consistency across models, but that there is significant deviation in the regions chosen as well. These data lead to the hypothesis considered at the outset that, rather than a specific set of ROIs carrying far more predictive value than others, that all ROIs capture some amount of

this variance. In this framework, which ROIs are selected in the model might depend, to a large degree, on the specific sample of brains used rather than purely any prior probability of the predictive value of a given region.

Here, we sought to determine the distribution of the predictive value of each ROI across samplings. To do so, we performed a nonparametric bootstrapping analysis that drew 1000 samples from our 70-89 NACC population. Each sample drew the same number of TCP and non-TCP individuals as our final dataset, drawing samples with replacement to arrive at an estimate of the samples one might have outside of our particular population (Wu & Jia, 2013). Figure 2.4 shows the resulting distribution of how often each region was selected in the forward-selection logistic along with an inset depicting several possible models. This enables us to determine whether a subset of regions is selected more often than others (e.g., inset, orange line), all regions are equally likely to be selected (inset, blue solid or dashed lines), or if some in between gradient of predictive value for regions exists (inset, purple line). Results showed a curvilinear distribution that highlighted the relative importance of some regions, but also demonstrated the broad predictive value across the whole brain. In particular, two regions (left entorhinal and right superior frontal) were selected in almost every iteration with two more (left caudal middle frontal and left medial orbitofrontal) selected over 75% of the time. Notably these four ROIs were also included in our initial forward-selection model. Moving down in frequency of selection, 11 ROIs were selected ~60-70% of the time. This group included three of the *a priori* cingulate ROIs. Note, all of the 62 ROIs were selected at least 22% of the time, although some number of these are at rates expected by chance (determined by 1000 random shufflings of the TCP/non-TCP labels and repeating the entire process to determine the base rate of region selection). When this analysis was repeated in the 70 year-olds separately, the two of the top four ROIs in the whole group were again in the top 4 here, but the overall distribution was quite linear (Supplemental Figure 1A). When repeated in just the 80-year old's, the distribution was again non-linear, but no region was included more than 62% of the iterations and none of the original top four ROIs were present in the top four in this subset (Supplemental Figure 1B).

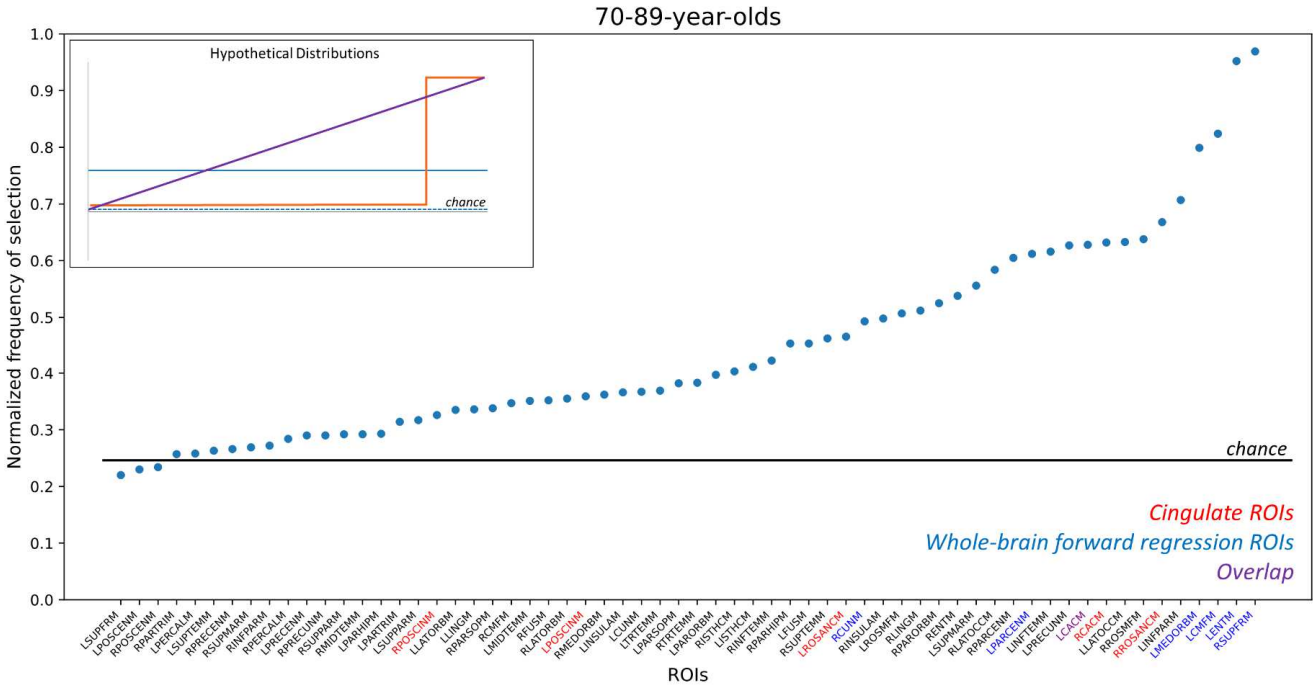


Figure 2.4: **Frequency of ROI selection in bootstrapping analysis**. Random samplings of subjects matching our existing TCP rates were repeatedly drawn and analyzed using the same logistic forward regression to determine how often each ROI was selected by the model. ROIs here are sorted by their frequency of being selected, which was normalized by the number of iterations (n=1000) to scale from 0 to 1, and ROI names are color-coded by whether they are part of the cingulate *(red)*, were in the original whole-brain model *(blue)*, or both *(purple)*. The horizontal line reflects the chance frequency of selection. ROI names are based on NACC labels. Highlighted Abbreviations (in order): RPOSCINM: Right Posterior Cingulate; LPOSCINM: Left Posterior Cingulate; LROSANCM: Left Rostral Anterior Cingulate; RCUNM: Right Cuneus; LPARCENM: Left Paracentral; LCACM: Left Caudal Anterior Cingulate; RCACM: Right Caudal Anterior Cingulate; RROSANCM: Right Rostral Anterior Cingulate; LMEDORBM: Left Medial Orbital; LCMFM: Left Caudal Middle Frontal; LENTM: Left Entorhinal; RSUPFRM; Right Superior Frontal. For full list, please refer to NACC's Imaging Data Researcher's data dictionary: https://files.alz.washington.edu/documentation/rdd-imaging.pdf. **Inset Figure:** Hypothetical distributions that would arise from different underlying models: *(orange)* distribution that would result if only a small subset of regions were highly predictive; *(purple)* distribution that would result if an even gradient of predictive ability existed across regions; *(blue, dashed)* distribution that would result if no regions' cortical thickness could model TCP status; *(blue, solid)* distribution that would result if all regions had some predictive power but there was no differentiation across regions.

2.3 DISCUSSION

The present study aimed to: (1) assess if the cingulate as a localized *a priori* network sufficiently models successful aging, (2) observe if such relationships between cortical thickness and TCP persists in rising age groups, and (3) assess the reliability of various selected networks in the brain in modeling TCP.

We were particularly interested in the cingulate cortex based on it recurring role in successful aging literature, as well its role in cognition; including information processing, memory, emotional processing, task engagement, and attention (Pearson et al., 2011b; Stanislav et al., 2013b; Vaidya et al., 2007b). Here, we were able to replicate the finding that the thickness of cingulate cortex can be used to some degree to model TCP status and that this ability was similar across 70s, 80s, and 90+ cohorts (Figure 2.3B). However, we also found that far stronger models could be made when extending the scope of the analysis to the whole brain. Our AUCs from the ROC analyses revealed that, across all age groups, forward selected ROIs from the logistic regression outperformed *a priori* cingulate regions in modeling TCP status. Furthermore, the regions selected by logistic regressions, either on the complete dataset (Table 2.4) or via random sub-sampling of our data (Figure 2.4) often had representation of the cingulate (typically caudal anterior cingulate), but also included representation across the brain.

Thus, while our results continue to implicate structural characteristics of the cingulate cortex in successfully aging individuals, these results suggest that global-style networks, rather than literature driven localized areas, may be better at modeling preserved cognition in the elderly. This is not to suggest a new subset of regions as a model for studying successful aging, but rather to propose examining a more data-driven set of ROIs as a robust approach in modeling superior cognition in memory and executive function.

Similar relationships can be found in other modes of imaging. Seventy-year-old "supernormals", defined by stringent criteria based on 5-year maintenance of episodic memory and executive functioning, displayed stronger functional connectivity between anterior cingulate and the hippocampus, middle cingulate, posterior cingulate, among other regions when compared to healthy elderly controls and those with mild cognitive impairment (F. Lin et al., 2017). More importantly, these researchers identified a functional "Supernormal map", consisting of the right fusiform gyrus, right middle frontal gyrus, right anterior cingulate cortex, left middle temporal gyrus, left precentral gyrus, and left orbitofrontal cortex, which successfully predicted a 1-year change in global cognition and correlated to Alzheimer's pathology

(Wang et al., 2019). Similar to possible cortical signatures of successful aging, these findings all suggest a pattern of widespread brain regions that may reflect the neurobiological underpinnings that result in preserved cognition.

This widespread pattern is perhaps best illustrated in Figure 2.4 where we aggregated across many random re-samplings of our 70-89 year-old population to determine how frequently different regions were included in our logistic model. Under the null hypothesis of all regions being equally uninformative of TCP status (inset, blue dashed), we would have observed a flat distribution with all regions being included ~25% of the time. Under a localistic hypothesis in which some subsets of regions are informative of TCP status while others are not (inset, orange line), we would have observed a step-function distribution where most regions were uninformative and highly unlikely to be included in the model while others were highly informative and almost always included in the model. Our results were not consistent with either of those hypotheses, instead supporting the view that while cortical thickness is informative of TCP status and while individual regions do vary in their predictive value, there is no specific subset of regions that are the key regions we should use. Instead, the results suggest that many, if not all regions carry the ability to inform modeling of TCP status. Thus, specific set of regions one isolates in a given analysis from a given sample of scans will vary to some degree from what one would arrive at with a different set of scans. However, these results do not arise from simple Type II error as shown by the permutation analyses in Figure 2.3D-F and by the distribution shown in Figure 2.4. Rather, if all regions contain variance that is informative of TCP status to some degree, we would expect that noise and the randomness associated with a particular population (that which we attempted to model in Figure 2.4) will lead to a somewhat different subset of ROIs being chosen in any particular forward selection model, consistent with what we observed in Table 2.4. Therefore, when approaching the problem of modeling TCP status from regional cortical thickness, we must view this as a "brain-wide" problem rather than a "localistic" problem. Rather than approaching a problem such as the relationship between a biomarker like cortical thickness and a behavioral outcome such as TCP status by searching for

a critical region or small set of regions, a richer understanding of this relationship might be had by taking a more "distributed" or network-based approach.

While discussing this network-level view of relating regional thickness to TCP status, we should note that a number of the beta coefficients in our models (Table 2.3) are negative. These negative coefficients should not be interpreted as demonstrating a thinner cortex in these regions in TCP individuals. For example, in our 70-89 group, while approximately half of the coefficients in Table 2.3 are negative in both the cingulate and the whole-brain analyses, TCP individuals are numerically thicker in all these regions (see also Figure 2.3). The negative coefficients are merely the byproduct of this multiple regression approach.

Finally, we should note that the group analyses in NACC revealed significant differences in sex and education. TCP subjects in their 70s tended to have a higher education and female distribution, while those in their 80s tended to only be more highly educated. All AUCs increased when both sex and education were added into the model, but the gains in AUC appeared quite modest. This is not to say that sex and education are not informative of cognitive status. When examining a cohort of SuperAgers from the Personality and Total Health Through Life (PATH) study, researchers found that SuperAging was both more prevalent in woman and associated to education (Maccora et al., 2021). It is possible that the significant differences in demographics are attributed to TCP group inclusion, which is reflected higher scores in both memory and executive function. Previous studies examining the role of age, sex, and education in elderly cognition revealed that (1) individuals with higher levels of education performed better on cognitive tests and (2) women performed better than men on verbal memory tasks (van Hooren et al., 2007). Additionally, despite there being no group differences in the oldest-old TCP, The 90+ Study previously showed that higher education is associated with lower prevalence rates of dementia in women (Corrada et al., 2008). For example, if education and sex alone are used to model TCP status in the 70-89 group, performance is at least as good as the *a priori* cingulate-only models (AUC=0.7 vs. the cingulate's AUC of 0.64). However, it is not the case that thickness is merely a very expensive way of determining

age and education, as in other groups, performance is far worse (e.g., 90+ Age + Education AUC=0.52 vs cingulate AUC=0.68 or whole-brain AUC=0.83). Therefore, it is clear that cortical thickness, while potentially correlated with these other factors, can be used to model TCP status irrespective of them.

Limitations

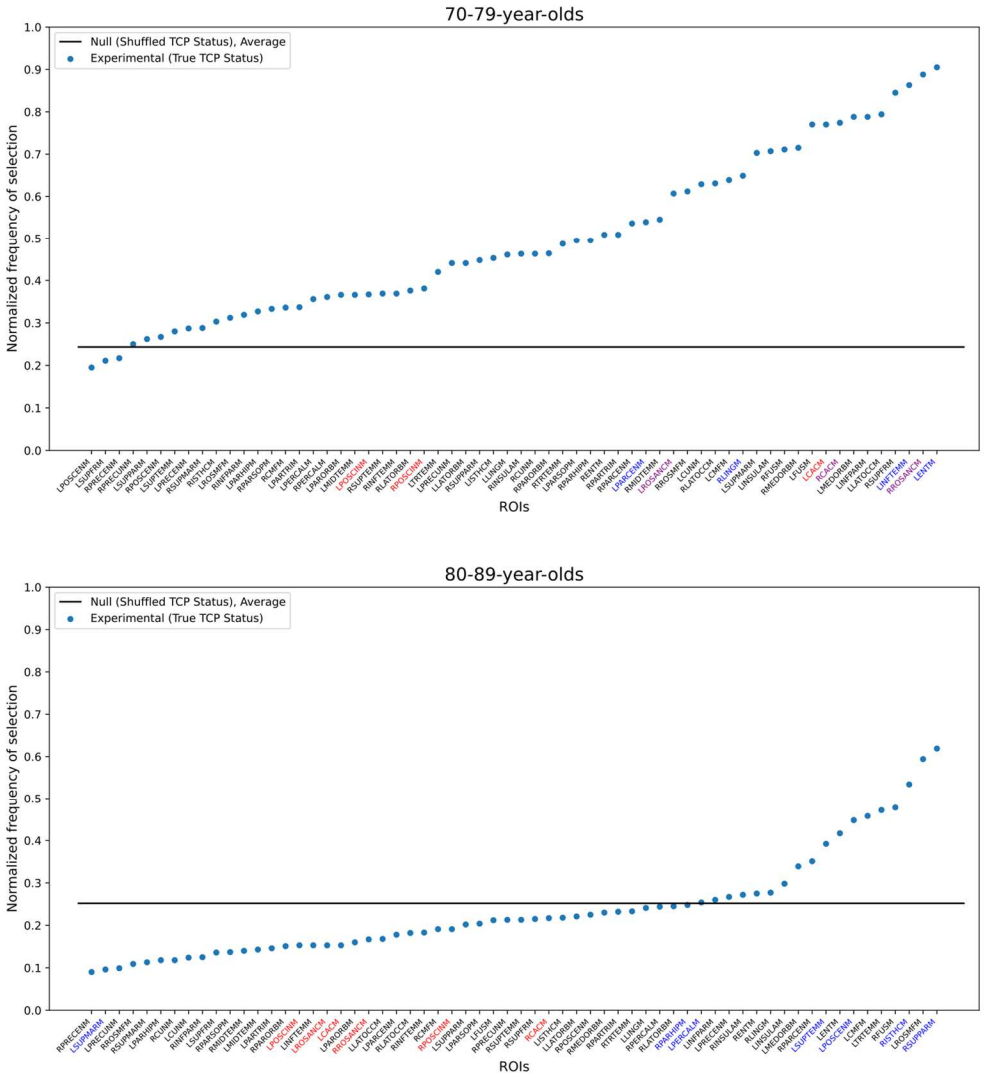
While participants were required to be diagnosed as cognitively normal, and thus determined to be free from MCI or dementia, it is possible that we are capturing some non-TCP individuals who are pre-clinical, defined here as asymptomatic participants with evidence of AD pathology or individuals who display cognitive symptoms that do not meet clinical criteria for mild cognitive impairment (MCI). AD-related lesions accumulate in the brain years before cognitive deficits, (Morris & Price, 2001a; C. C. Rowe et al., 2007a) with longitudinal studies showing amyloid deposition measured by PET 15 years before symptom onset (Bateman et al., 2012a). Thus, it is possible that the effects observed can be attributed to other aging biomarkers not captured on structural MRI, especially given the wide age range. Future studies examining such biomarkers will be informative for better understanding differences in the available data.

We should also point out that the behavioral measures chosen for these analyses were based on previous successful aging studies, which typically use a test of delayed recall (usually CVLT or Rey Auditory Verbal Learning Test (RAVLT)) and executive function (usually Trails B). The WMS-R IIA and CVLT were chosen as tests of delayed recall to mirror this standard as closely as possible, limited by what data is available in each dataset. There are some key differences between these tests of delay recall potentially influencing the differences found between cohorts. The WMS-R IIA requires participants to recall units of a provided story while the CVLT requires participants to recall words from a list. While a narrative will help memory and can be used in both cases, any such narrative must be constructed by the participant in the case of the CVLT, leading to potentially more contamination by executive function in a word list task like the CVLT (Tremont et al., 2000). While these tests are not identical in nature, both are measures

of verbal memory and tap into strategic organization of the information to help memory and we find it more likely that the differences observed between cohorts are better explained by additional complex changes the aging brain goes through that may change the importance of structural characteristics of certain brain regions throughout the lifespan, such as amyloid deposition or vascular changes. It is important to note that differences were also observed within NACC throughout age groups, thus making it less likely that differences are attributed test type.

In addition to the relatively modest sample sizes (particularly in the 80- and 90-year old subgroups), it is important to note the role of volunteer and selection biases these analyses common to many aging studies and potentially all neuroimaging studies. People who are able and willing to participate in imaging tend to be healthier and meet *a priori* selection criteria. One large study examining the nature of volunteer and selection biases found that those who were more likely to participate in studies were also more likely to be cognitively healthy, well-educated, and male compared to their counterparts who were not interested in participating (Ganguli et al., 2015). Inclusion criteria and recruitment, amongst other factors, have led to a more heterogenous population in NACC participants, which tend to be mostly Caucasian and of both high socioeconomic and education status. Given that participants from The 90+ Study are largely survivors of *Leisure World Cohort Study* and recruited from a retirement community in Laguna Woods, California, it is certainly possible that participants are not fully representative of the population. As reported by Melikyan et al., (2019b), compared with the oldest-old population in the United States (He & Muencharth., 2011), the cognitively normal sample in *The 90+ Study* has a higher proportion of Caucasians (98.5% vs. 88%) and a higher percentage of individuals with more than a high school education (78% vs. 28%). Previous research has shown that differences in sex and education may account for cognitive test performance (Hall et al., 2007; Hooren et al., 2007), and cortical thickness (Habeck et al., 2020; Seo et al., 2011; Steffener, 2021). As reported in Tables 2.1 & 2.2, the overall TCP NACC sample was 61% female with had an average of 15 years of education, while The 90+ Study sample was 64% female and 46% college educated and above. It is possible that higher education or

larger female distributions may be influencing external validity by: (1) introducing a moderation relationship between key demographics, test performance, and cortical thickness that we would not otherwise see in the general public or (2) significantly influencing the distribution of TCP (approximately 32% and 30% for current NACC and The 90+ Study analyses, respectively) that is not representative of all elderly individuals. It is also important to note that, given these potential biases and the fact that percentiles for TCP group inclusion were determined based on a very select subset of each of these cohorts (blue boxes reflected in Figure 2.1), inclusion in the top 50^{th} percentile for each of our cognitive domains may not reflect TCP in the general public. Finally, we should note that the present study cannot identify specific mechanisms that are associated with these differences in cortical thickness.



Supplemental Figure 1: A gradation of ROIs, ordered by predicative value for TCP status from bootstrapped forward selection, is seen for participants in their **(A-Top)** 70s and **(B-Bottom)** 80s. Frequency of selection was normalized by the number of iterations (n=1000), to scale from 0 to 1. ROI labels are color-coded by whether they are part of the cingulate (red), were in the original whole-brain model (blue), or both (purple). The horizontal line reflects the chance frequency of selection. ROI names are based on NACC labels. Highlighted Abbreviations (in order): (**A)** LPOSCINM: Left Posterior Cingulate; RPOSCINM: Right Posterior Cingulate; LPARCENM: Left Paracentral; LROSANCM: Left Rostral Anterior Cingulate; RLINGM: Right Lingual; LCACM: Left Caudal Anterior Cingulate; RCACM: Right Caudal Anterior Cingulate; LINFTEMM: Left Inferior Temporal; RROSANCM: Right Rostral Anterior Cingulate; LENTM: Left Entorhinal; (**B)** LSUPMARM: Left Supramarginal; LPOSCINM: Left Posterior Cingulate; LROSANCM: Left Rostral Anterior Cingulate; LCACM: Left Caudal Anterior Cingulate; RROSANCM: Right Rostral Anterior Cingulate; RPOSCINM: Right Posterior Cingulate; RCACM: Right Caudal Anterior Cingulate; RPARHIPM: Right Parahippocampal; LPERCALM: Left pericalcarine; LSUPTEMM: Left Superior temporal; LPOSCENM: Left Postcentral; RISTHCM: Right Isthmus Cingulate; RSUPPARM: Right Superior Parietal. For full list, please refer to NACC's Imaging Data Researcher's data dictionary: https://files.alz.washington.edu/documentation/rdd-imaging.pdf

Chapter 3

Other Structural Correlates of Top Cognitive Performance

What structural correlates other than cortical thickness can predict top performance? Chapter 2 established that (1) cortical thickness is a valuable predictor of successful aging, and (2) whole-brain, network-level regions can out-performed the localist cingulate models in predicting Top Cognitive Performance. While cortical thickness is a widely used biomarker of successful aging, there are additional structural properties of the brain that have well-established relationships with the full spectrum of aging such as greater performance in intelligence tests, poorer performance in cognitive domains such as executive function, and even predicting future onset of MCI. In this chapter, we will assess predictive power of regional cortical brain volume and total white matter hyperintensities volume, two structural measures easily derived from MRI. Additionally, here we assess various models of defining top performance with the addition of tests of language and attention to determine whether there is anything special about the domains we and others have used in past work. Given the large spread in successful aging definitions, highlighted in Table 1.1, we were interested in determining which model (example: single domain categorization (SDTP) versus combined domain categorization, Top 25th percentile versus Top 50th percentile) yielded more robust relationships with our measures. Results showed that regional cortical thickness and volume are similar in predicting TCP. When assessing the ability to predict Top 25th versus Top 50th percentile, we showed little evidence for drastic differences in SDTP models. We did observe a trend for regional cortical thickness in predicting memory SDTP in 80 year-olds, where the Top 25th percentile yielded a higher AUC. Unexpectedly, we saw no apparent differences across all combinations of TCP when using regional cortical thickness or white matter hyperintensity across both datasets.

3.1 Introduction

As highlighted above, differences in structural properties of the brain are known to make significant contributions to individual differences seen in cognition. For example, the size of our grey matter changes continuously throughout the lifespan and has proven relevant for understanding the cognitive problems, or lack thereof, that begin to accumulate as we age. Decreased thickness in the cortical signature of Alzheimer's disease (CSAD) successfully predicted future decline in cognitively unimpaired individuals (Knopman et al., 2018). When examining individuals with intact and superior cognitive abilities, many have shown preservation of grey matter both functionally and structurally, as well as a reduced risk of conversion to MCI and dementia (Dang, Harrington, et al., 2019b). As previously described, Harrison and colleagues found that 80 year old SuperAging individuals did not experience significant cortical atrophy and did not differ from middle age controls in whole brain cortical volume (Harrison et al., 2012). Thus, examining structural characteristics of grey matter, such as cortical thickness and volume, may be critical to characterize future decline or even maintenance of cognition.

Similarly, the location and extent of white matter hyperintensities are known to be associated with various types of cognition decline, age-related changes in the brain, and Alzheimer's Disease (DeCarli et al., 1995). Thought to be the result of cerebral small vessel disease, white matter hyperintensities are positively associated with age (de Leeuw et al., 2001) and may account for increased blood brain barrier permeability and demyelination seen in the aging brain (Haller et al., 2013; Prins & Scheltens, 2015; Tubi et al., 2020). Though there may be conflicting evidence due to differences in WMH rating, many studies have found that WMH are related to poorer executive function, processing speed, and episodic memory (Brickman et al., 2011; Kaskikallio et al., 2019; Maillard et al., 2012; Smith et al., 2007; Van Petten et al., 2004). Similar results are seen in The 90+ Study where higher baseline WMH volumes were associated with worse scores in global cognition, episodic memory, and executive functioning tasks (Legdeur et al., 2019). WMH has also been linked to poorer performance in domains

such as general intelligence (DeCarli et al., 1995), gait (Silbert et al., 2008), visuospatial memory and organization (Au et al., 2006), and attention (Puzo et al., 2019). To date, there are few studies examining the role of white matter hyperintensities in the antithesis of typical- and disease-related decline, successful aging. One study examined the post-mortem data of two cases of SuperAging elderly individuals and found that both displayed "mild" levels of WMH with prominent hyperintensities seen in periventricular regions of the brain, determined by visual ratings performed by a behavioral neurologist. Another study found that eighty year old SuperAgers displayed lower global white matter hyperintensities when compared to age-matched controls (Godoy et al., 2022)

All three measures have been used as prognostic and diagnostic measures in the research setting. In a study aiming to identify the best measure for assessing disease burden over a large age range, researchers compared measures of volume and cortical thickness in their ability to distinguish cognitively normal from Alzheimer's patients. By examining CSAD ROIs, they found that volume and cortical thickness were generally comparable in their ability to identify each group. Though not significant, they also found that cortical thickness yielded better correlations with pathology findings when compared to cortical thickness. They did, however, find that volume was more associated with total intercranial volume (TIV). This relationship makes using volume rely heavily on TIV correction, which can be imperfect, leading to the suggestion of cortical thickness measure when considering regions associated with Alzheimer's disease in cohorts with a large age range. (Schwarz et al., 2016). Similarly in our third measure, one study found that higher baseline and subsequent accumulation of white matter hyperintensities in the parietal lobe independently predicted progression to Alzheimer's in a group of 300 older adults (Brickman et al., 2011). Others have also been able to show that white matter hyperintensity burden is significantly associated with diagnosis (Yoshita et al., 2006) and the speed of future cognitive decline (Brickman et al., 2008).

Given their ability to predict disease status and future decline and the vast literature covering the importance of cortical thickness in successful aging, we aimed to assess their effectiveness in predicting

TCP across the full older adult life span. Loosely following the aims of Shwarz et al., this chapter examines the predictability of cortical thickness, volume, and white matter hyperintensities in distinguishing cognitively normal top performers versus non top performers in a combined measure of executive function and memory. Moreover, this chapter aims to identify whether the thresholds and domains used when selecting the "top" performers affects the relationship between top cognitive performance and our structural correlates of cognitive aging. As shown in Table 1.1, a standardized definition of successful aging has yet to be agreed up, and this in conjunction with the varying age groups and study population may account for the differences in results shown across studies. This last aim allows us to examine multiple possible models of successful aging within the same population across age groups (sixties, seventies, and eighty year old's). We also have the unique opportunity to see if these relationships persist in the oldest-old, using data from The 90+ Study.

3.2 Experimental Design And Methods

National Alzheimer's Coordinating Center

Participants

Six hundred and eighty two individuals were selected from the larger NACC cohort (Figure 3.1A). For this analysis, participants were required to be sixty years old and above (60-89 years old), have at least one T1 MRI scan available within 2 years of their initial UDS visit, and be cognitively normal at baseline visit.

Neuropsychological criteria for group inclusion

Chapter 1 describes neuropsychological criteria for TCP group inclusion. Here, we decided to test the robustness of this definition, chosen based on the structure of the SuperAging definition. First, we incorporated tests of key domains known to be associated with general cognitive decline: language (Boston Naming Task) and attention (Digits Span Backward). The Boston Naming task is a 60 item picture naming vocabulary test that assesses participants' ability to name common objects (Kaplan et al.,

1983). Like its name suggests, the Digit Span Backwards is a task that tests working memory capacity by asking participants to verbally recall a span of numbers backwards.

To test whether performance in the top 50th percentile was sufficient to dichotomize successfully aging individuals, we first compared performance in the top 25th versus performance in the top 50th percentile in all four of our singular domains, which we refer to here as single domain top performer (SDTP). To test whether our combination of domains (memory and executive function) from Chapter 1 was optimal for predicting TCP based off structural data, we modeled each possible combination of Top 50th performance in the 4 variables, which resulted in six classifications. Within each analysis, individuals who contained missing data in any individual criteria variables, described below, were excluded from the analyses. For example, if a participant was missing data in Trails-B but not Boston Naming task, they would be included in the Top 25th and Top 50th SDTP for attention, but not the combined top performance of executive function and attention. In other words, there are varying sample sizes depending on which neuropsychological variable is being included in the top versus non classification.

Image Data

As described in Chapter 2, pre-calculated regional cortical thickness, cortical volume, total white matter hyperintensities data for NACC MRIs were provided by the IDeA Lab at University of California, Davis. For the white matter hyperintensity (WMH) counts, two processing steps were added. As they were clearly not normally distributed, the provided counts were log transformed. To normalize predictor and account for confounding effects, we performed an initial step of regressing out age and education from WMH values (both were significantly associated with WMH initially) and analyses were performed on the residuals.

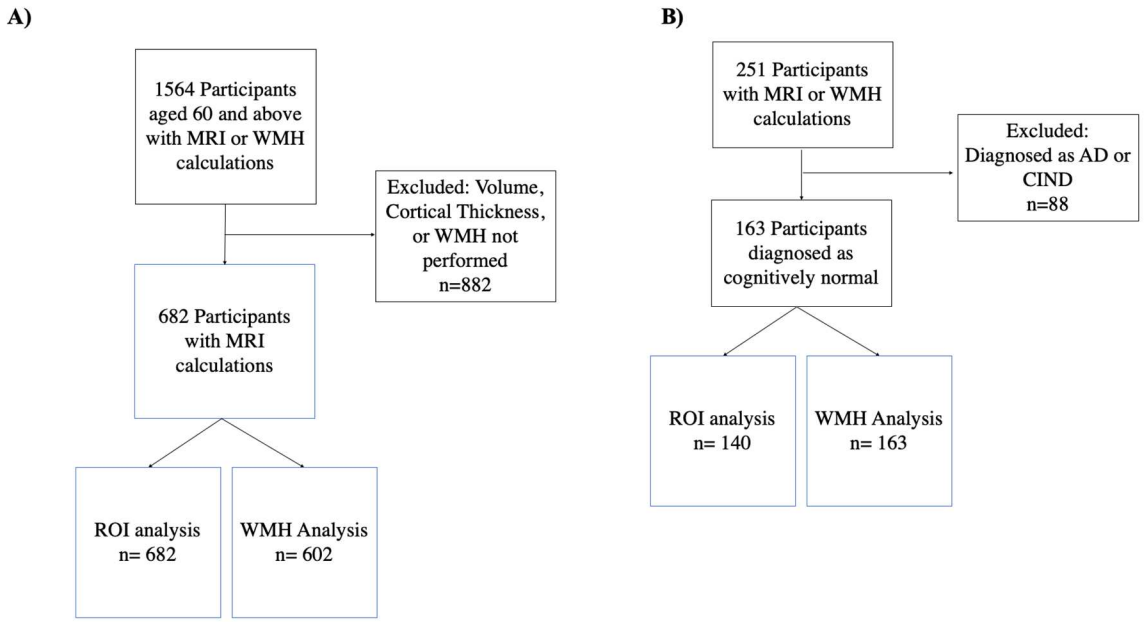


Figure 3.1: Inclusion flow chart for (A) NACC and (B) The 90+ Study Participants. Blue box reflects the participants included in the final analysis of top cognitive performers (TCP).

The 90+ Study

Participants

One hundred and sixty three individuals from the larger *The 90+ Study* cohort were included (Figure 3.2). Participants were selected based on the availability of total WMH calculations, at least one T1 MRI scan available, and a cognitively normal diagnosis at initial neuropsychological visit available. Like in NACC, individuals who contained missing data in any of the individual criteria variables were excluded from their respective analyses.

Neuropsychological criteria for group inclusion

Following the above mentioned criteria, The 90+ TCP individuals were required to perform at or above the top 50th percentile for their age group on the long-delay recognition portion of the California

Verbal Learning Test – short form (CVLT) and at or above the top 50th percentile on completion time for their age group in the Trails-B. All other individuals that did not fit these criteria were classified as non-Top Cognitive Performers (non-TCP). We additionally tested the top 25th and 50th of SDTPs in memory (CVLT), executive function (Trails-B), language (Boston Naming Task), and attention (Digit Span Backwards), as well as all possible combinations of the Top 50th SDTPs.

Image Data

As described in Chapter 2, estimation of cortical thickness from T1-weighted structural MRI were calculated using Advanced Normalization Tools. Total white matter hyperintensity volumes were calculated by The 90+ Study using four tissue segmentation following the methods described by the Alzheimer's Disease Neuroimaging Initiative (ADNI) (DeCarli et al., 2005) using a Linux container provided by the IDeA lab. To normalize these volumes, white matter hyperintensities were again log transformed. Unlike in NACC, age, sex, and education were not shown to be significantly associated with white matter hyperintensities and this regression was therefore not performed.

Statistical analysis

For both datasets, statistical analyses were performed using SAS and both the Statsmodels (https://www.statsmodels.org/) and skikit-learn (https://scikit-learn.org/) libraries in Python. We removed any analysis if it had fewer than 20 TCP/SDTP individuals and had a TCP rate of under 10% as these would be unlikely to yield reliable, meaningful results given the exceptionally low sample size. This resulted in the exclusion of two models in The 90+ Study: total white matter hyperintensity and cortical thickness in TCP (Boston Naming Task/Digit Span Backwards).

To simultaneously evaluate the utility of cortical thickness versus volume and Top 25th versus Top 50th in each decade, forward-selection logistic regression models (cutoff p-value for the F statistic, p=0.25) were used to model SDTP and all six combinations of TCP as a function of all 62 cortical ROIs.

This resulted in 14 models per age group: four models of Top 25th SDTP (memory, executive function, language, attention), four models of Top 50th SDTP, and six models of TCP combinations (e.g., TCP (Memory/Executive Function), TCP (Memory/Language), etc.). To assess the influence of age, sex, and education, these same models were run with these demographic variables included in the model. To understand the relationship between total white matter hyperintensities and our TCP classifications, logistic regressions were run for each age group in NACC and The 90+ Study with our classifications as the dependent binary variable and log transformed and age/education regressed total white matter hyperintensity volume as our predictor. For all models, Receiving Operating Characteristic (ROC) curves were created to assess the accuracy of TCP & SDTP status as a diagnostic marker.

It is possible that by allowing the forward selection model access to all ROIs and access to all participants that it has overfit the data, which would limit how well the data might generalize to other populations. To address this, we additionally performed a leave-out, cross-validation analysis for each of the individual and combined metric models. The cross-validation consisted of 100 random samples that split the data into a two-thirds training set and one-third left-out test set (stratified to retain the approximate ratios in the original population). Using the already-selected ROIs, we trained separate logistic regression models on each dataset and calculated the resulting AUC on the left-out participants and averaged the resulting 100 AUCs.

Table 3.1 NACC Demographics		
	Cortical Measures (n=682)	WMH Volume (n=602)
Mean Age (SD)	71.9 (7.2)	71.9 (7.2)
Number of Females (%)	426 (62.5%)	374 (62.1)
Education: Number of years (SD)	15.3 (3.5)	15.2 (3.4)
Mean WMS-R IIA Score (SD)	11.3 (4.2)	11.2 (4.1)
Mean Trails-B Score (SD)	92.9 (52.7)	93.6 (52.8)
Mean Boston Naming Task Score (SD)	27.0 (3.3)	27 (3.3)
Mean Digit Span Backward Score (SD)	6.4 (2.2)	6.3 (2.2)

Table 3.2 The 90+ Study Demographics		
	Cortical Measures (n=140)	WMH Volume (n=163)
Mean Age (SD)	92.5 (2.5)	92.5 (2.4)
Number of Females (%)	91 (65%)	109 (66.9%)
Education: High-school graduate or less (%) Some college to graduate (%) Some graduate school or higher (%)	 24 (17%) 60 (43%) 56 (40%)	 28 (17.2%) 67 (41.1%) 68 (41.7%)
Mean CVLT Score (SD)	6.6 (2.0)	6.7 (2.0)
Mean Trails-B Score (SD)	145.3 (69.1)	144.9 (71.7)
Mean Boston Naming Task Score (SD)	13.1 (1.8)	13.3 (1.7)
Mean Digit Span Backward Score (SD)	5.9 (1.7)	6.0 (1.8)

3.3 Results

Demographics

The 682 NACC participants had a mean age of 71.9, were majority female (62.5%), and highly educated (mean: 15.3 years). The 602 of these individuals who had total white matter hyperintensity

volumes available and were 71.9 years old on average, were mostly female (62.1%), and highly educated (mean: 15.2 years). The 140 The 90+ Study participants had a mean age of 92.5, had a high distribution of females (65%), and mostly attended college and beyond. Similarly, in those with white matter hyperintensity volume estimates, participants had a mean age of 92.5, were mostly female (66.9%), and were highly educated (82.8%).

Cortical Thickness versus Volume

Our first question was aimed at examining the performance of cortical thickness versus volume in predicting our original TCP definition (memory/executive function). As shown in Figure 3.2, we did not observe any major difference between the measures. For these comparisons, we used the methods described by Cumming & Finch (2005), using values below 50% overlap of confidence intervals as a rough estimate of statistical significance ($p < 0.05$). For AUC confidence interval comparison here, all percentage overlaps were well above the 50% cut off, suggesting no difference between the AUCs of cortical thickness versus volume. Also in Figure 3.2 are representations of each model with age, sex, and education included. As expected, adding measures correlated with cognition slightly increased AUCs. Given that volume and cortical thickness measures showed relatively no differences in the prediction ability, we continued to use cortical thickness for the rest of our analyses.

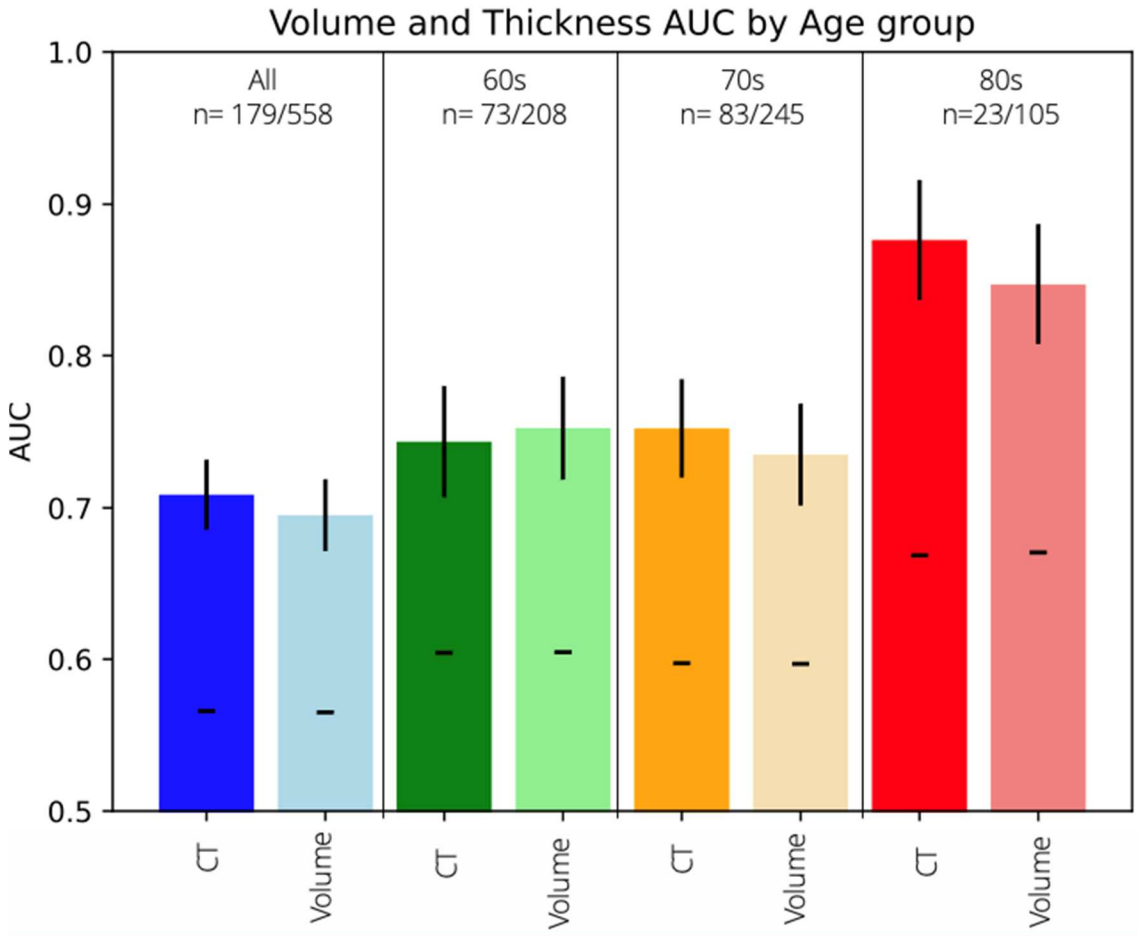


Figure 3.2: Cortical thickness and volume perform equally well in distinguishing original TCP: Bar plot of AUC values using either regional thickness or volume to predict TCP by age. Vertical bars represent 95% confidence intervals for each AUC. Horizontal bars represent the approximation of chance calculated from a permutation analysis. Abbreviations AUC: Area under the curve, CT: Cortical Thickness 60s: NACC 70 year old's, 70s: NACC 70 year old's, 80s: NACC 80 year old's,

Top 25th Versus Top 50th percentile: Cortical Thickness

Results comparing the AUCs of cortical thickness predicting the top 25th and top 50th percentiles of each SDTP showed highly consistent results across cognitive domains and across thresholds (Figure 3.3). Some evidence for differences in choice of threshold were found in modeling superior language in sixty year old's (Figure 3.3C), where Top 25th percentile yielded a higher AUC (AUC: 0.80, percent overlap 48.2) than the Top 50th percentile and in memory in the eighty year old's (Figure 3.3A), where once again, Top 25th percentile yielded a higher AUC (AUC: 0.86, percent overlap 51.6%). Together,

these suggest that the definition of a top-cognitive performer is relatively tolerant of the exact threshold used. It also shows, however, that the relationship between cognitive performance and cortical thickness can be found for any of these domains.

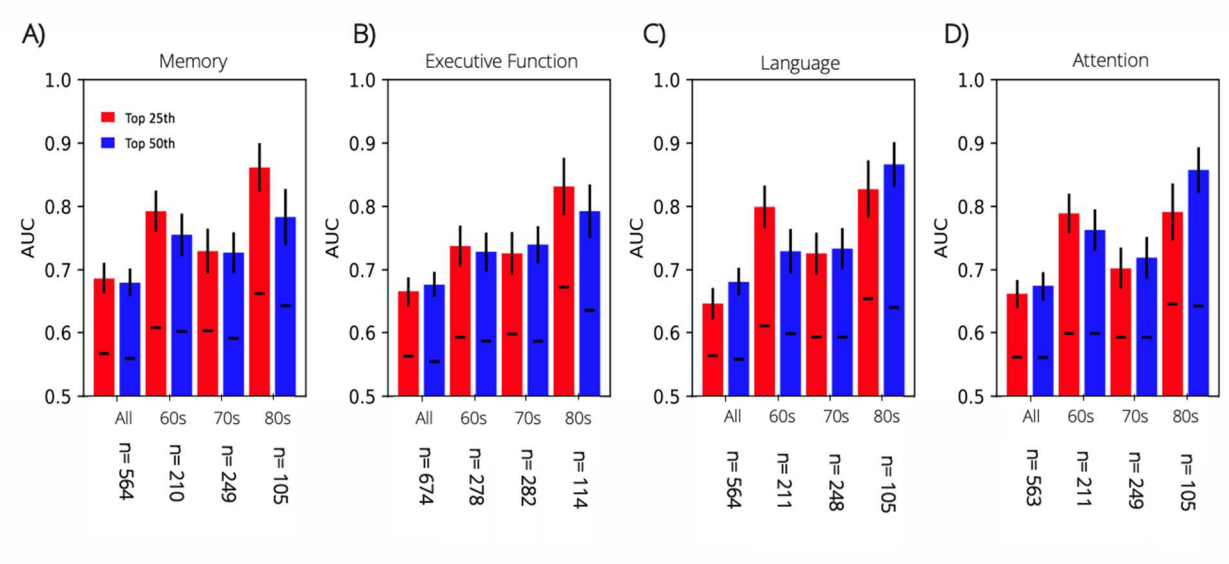


Figure 3.3: Little evidence for differences between Top 25th and Top 50th SDTP Percentile Bar plots of AUC values using regional thickness to predict SDTP by age in: A) Memory, B) Executive Function, C) Language, and D) Attention. Vertical bars represent 95% confidence intervals for each AUC. Horizontal bars represent the approximation of chance calculated from a permutation analysis. Abbreviations AUC: Area under the curve, CT: Cortical Thickness 60s: NACC 70 year old's, 70s: NACC 70 year old's, 80s: NACC 80 year old's

Combinations of TCP and Cortical Thickness

A similar pattern was found in our analysis of the various combinations of domains. Prior work in TCP has used a combination of memory and executive function as the basis for the definition of TCP. While there may be important aspects to this particular combination, as shown in Figure 3.4, when we consider cortical thickness' performance in predicting all 6 combinations, we observed very similar results across combinations. Each had a similar range of AUCS and pattern across age groups. Models that combined all participants performed worse overall and models were able to predict each potential TCP definition better as the participants aged. Interestingly, it appears that adding demographic variables such as age, sex, and education do not dramatically alter AUC estimations of each combination.

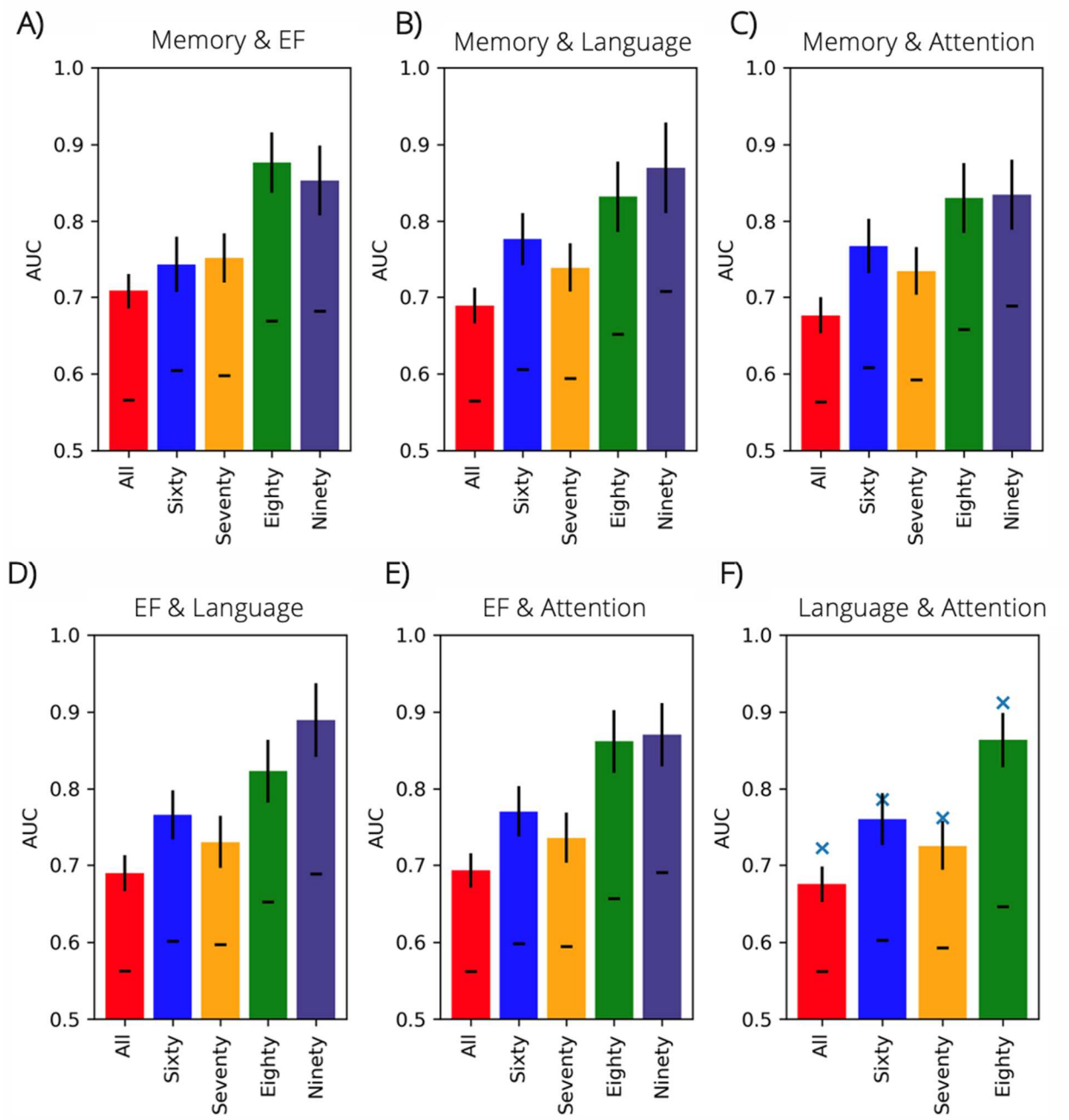


Figure 3.4: Cortical thickness Predicts Combinations of TCP Bar plots of AUC values using regional thickness to predict all 6 combinations of TCP by age in: A) Memory/Executive Functioning, B) Memory/Language, C) Memory/Attention, D) Executive Function/Language, E)Executive Function/Attention, and F) Language/Attention. Vertical bars represent 95% confidence intervals for each AUC. Horizontal bars represent the approximation of chance calculated from a permutation analysis. Abbreviations AUC: Area under the curve, EF: Executive Function

Top 25th Versus Top 50th percentile: Total White Matter Hyperintensity Volume

When examining how well WMH could predict SDTP (Figure 3.5), a notable feature is that overall model performance is far lower than observed with either cortical thickness or volume. Caution should be used here, as in these models, a single MRI value is being used rather than a selection of the best six values. Thus, chance in these models is far lower (0.5 vs. ~0.65). Results comparing the AUCs of white matter hyperintensities predicting the top 25th and top 50th percentiles of each SDTP showed similar performance between criteria for most models. Much like in cortical thickness, we see a possible trend in memory (Figure 3.5A) in the eighty year olds, where Top 25th percentile yielded a higher AUC (AUC: 0.65, percent overlap 50.1%), may reflect a small trend towards differences in percentile criteria. As expected, this model also showed an effect of total white matter hyperintensity volume in predicting TCP unlike in the top 50th criteria.

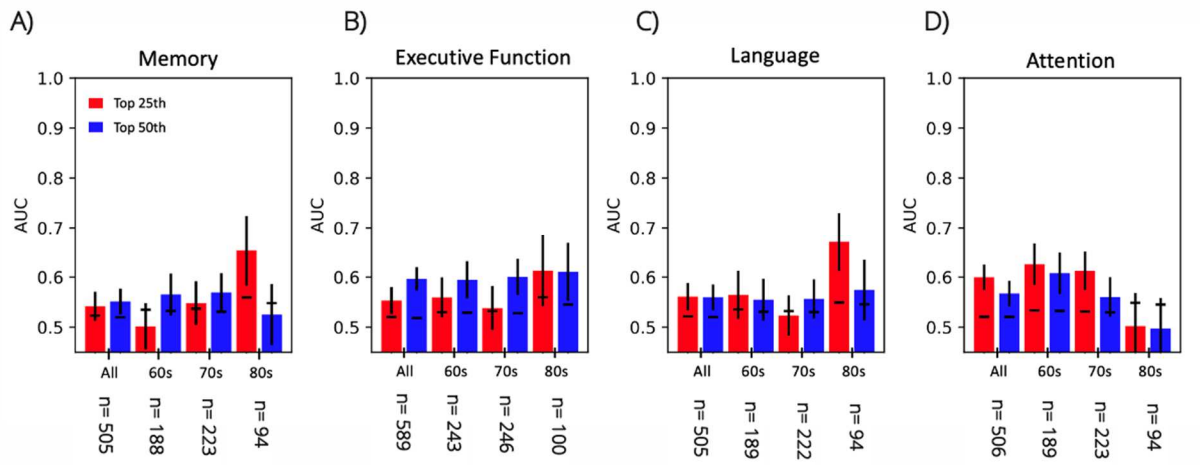


Figure 3.5: Total White Matter Hyperintensity Poor Predictor of Top 25th Percentile vs. Top 50th Percentile Bar plots of AUC values using regional thickness to predict SDTP by age in: A) Memory, B) Executive Function, C) Language, and D) Attention. Vertical bars represent 95% confidence intervals for each AUC. Horizontal bars represent the approximation of chance calculated from a permutation analysis. Abbreviations AUC: Area under the curve, CT: Cortical Thickness 60s: NACC 70 year old's, 70s: NACC 70 year old's, 80s: NACC 80 year old's

Combinations of TCP and White Matter Hyperintensity Volume

As seen in Figure 3.6, modeling of white matter hyperintensity volumes in predicting all six combinations of TCP generated relatively similar AUCs, as evidenced by overlapping confidence

intervals of each age comparison. It is possible that TCP (memory/attention) in the 90 year olds reflect a trend in comparison to all other combinations of SDTP categories, but further validation is necessary.

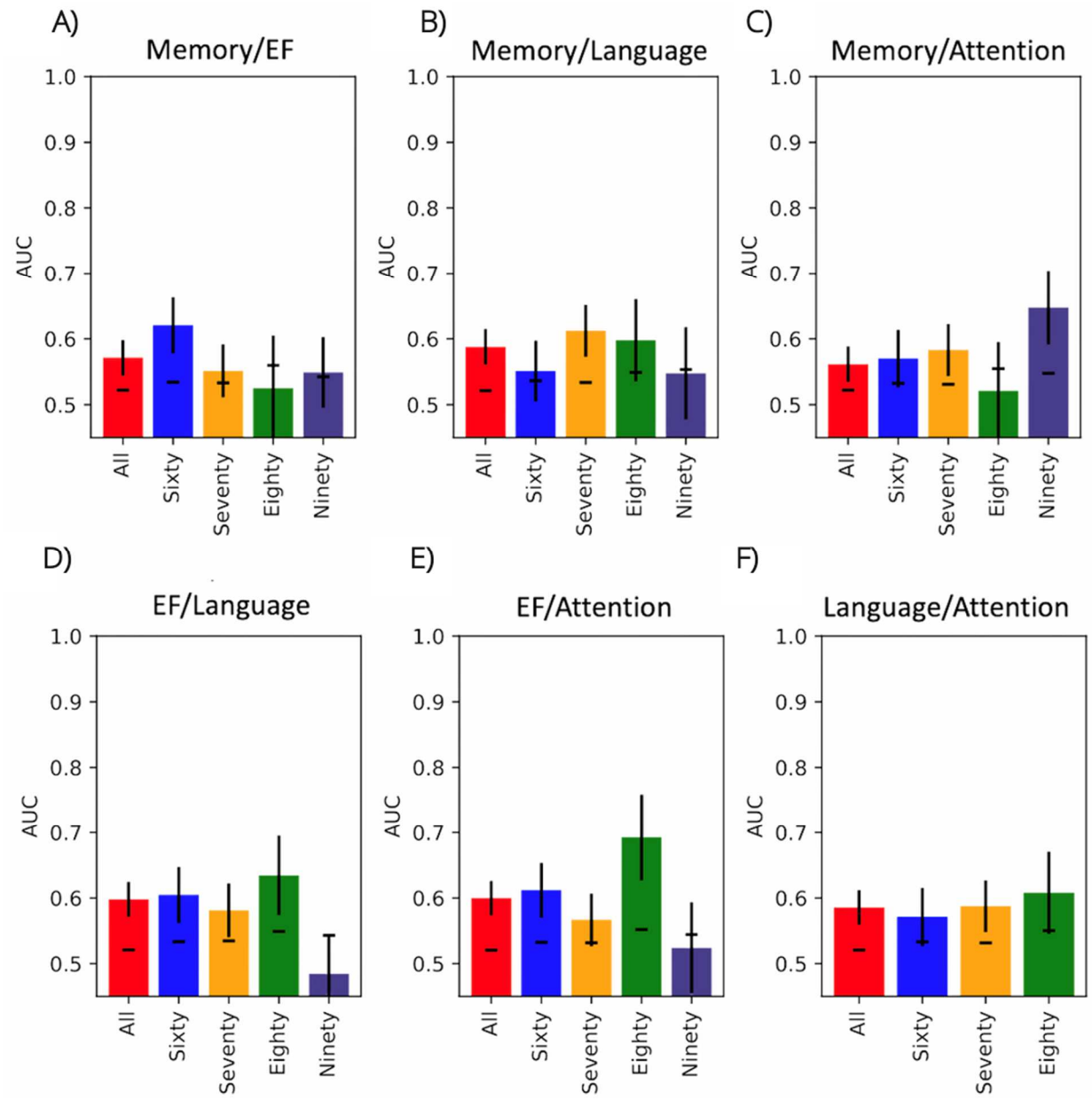


Figure 3.6: White Matter Hyperintensity Volume Poor Predictor of Combinations of TCP Bar plots of AUC values using regional thickness to predict all 6 combinations of TCP by age in: A) Memory/Executive Functioning, B) Memory/Language, C) Memory/Attention, D) Executive Function/Language, E)Executive Function/Attention, and F) Language/Attention. Vertical bars represent 95% confidence intervals for each AUC. Horizontal bars represent the approximation of chance calculated from a permutation analysis. Abbreviations AUC: Area under the curve, EF: Executive Function

Cross Validation of all Models

One hypothesis that would account for our observation that particular individual domains or combinations of domains has little effect on model performance is that our regression model is overfitting the data. To address this, we performed 100 sample, leave out (train on 2/3, test on 1/3) cross validation analyses for each of the initial cortical thickness models. The results, comparing our original AUCs to the validation AUCs are shown in Figure 3.7. As anticipated, the Validation AUCs were typically lower than the original full-model AUCs. In the validation, only two thirds of the data are used, and the AUC is generated on data not part of the model generation. Such transfer will almost certainly be lower. Yet, in each of these models, the validation AUCs were quite similar to the original ones and, importantly, they followed the same trends present in the original models. Where the original full model produced high AUCs, the validation produced high AUCs and where the original full model produced low AUCs, the validation produced low ones as well. Regardless of metric used, this consistent relationship was observed, indicating our original models did not suffer from severe overfitting and that they captured real, generalizable aspects of the data.

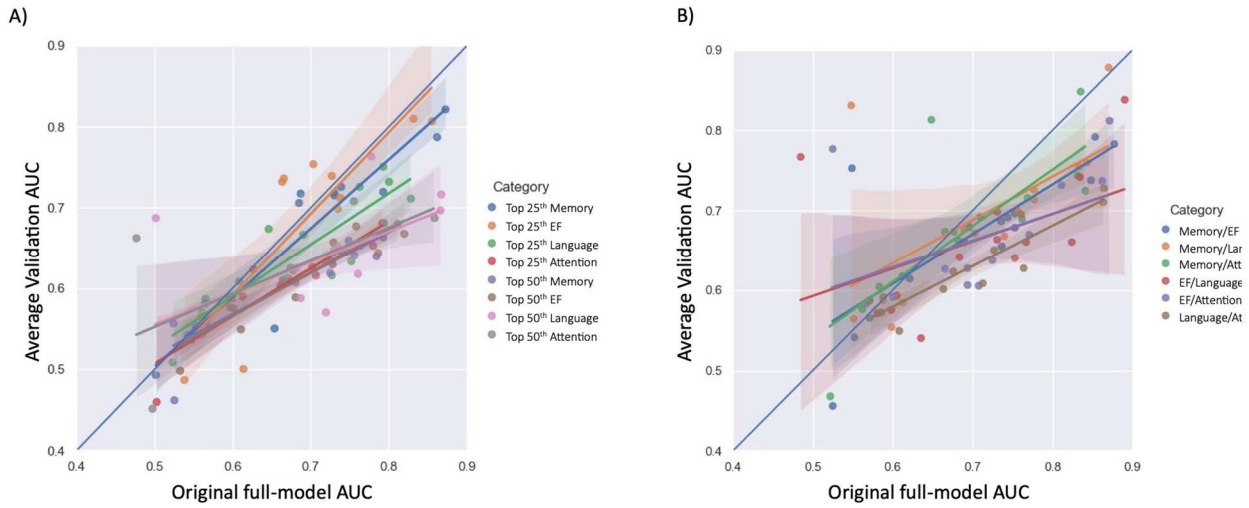


Figure 3.7: **Cross Validation Analysis: Models did not suffer from severe overfitting** Average validation AUC following leave-out cross-validation for each model plotted as a function of original, full-dataset AUC.

3.4 Discussion

This chapter aimed to assess the ability of three structural measures, cortical thickness, cortical volume, and total white matter hyperintensity volume, to predict the Top Cognitive Performance described in Chapter 1. These predictors were chosen based on their ability to distinguish cognitively declining individuals and those with Alzheimer's disease. Given the wide variety of successful aging definitions in the literature, we also aimed to examine which cut point and what cognitive measures might be best distinguished by said structural measures. We hypothesized that much like in relationships with cognitively normal/Alzheimer's identification described above, cortical thickness and volume would perform relatively the same. While structural measures such as cortical thickness and surface area of the brain are not linearly related, studies show that cortical volume is influenced by both (Panizzon et al., 2009; Winkler et al., 2010), possibly explaining their similarity in predictive power. Results here showed that cortical thickness and volume generally performed similarly when predicting our original TCP

(memory & executive function), with cortical thickness models generally producing slightly higher AUCs. This, in line with current successful aging literature, suggests the continued use of cortical thickness to distinguish high performing elderly individuals. As suggested by Shwarz et al., when examining large cohorts with possible effects of age and sex, cortical thickness is equally reliable and there is less need to tediously correct for confounding total intercranial volume effects.

When assessing the ability to predict Top 25th versus Top 50th percentile, we showed little evidence for drastic differences in SDTP models for both cortical thickness and white matter hyperintensity volume. This was a surprising finding given that, if we are to assume resistance to deleterious structural changes in high performing individuals given the literature, we would expect individuals in the top quarter of performance to exhibit sparing such changes. In further consideration of our inclusion criteria, it is important to note how our definition of TCP may limit our understanding of the spectrum of successful aging.

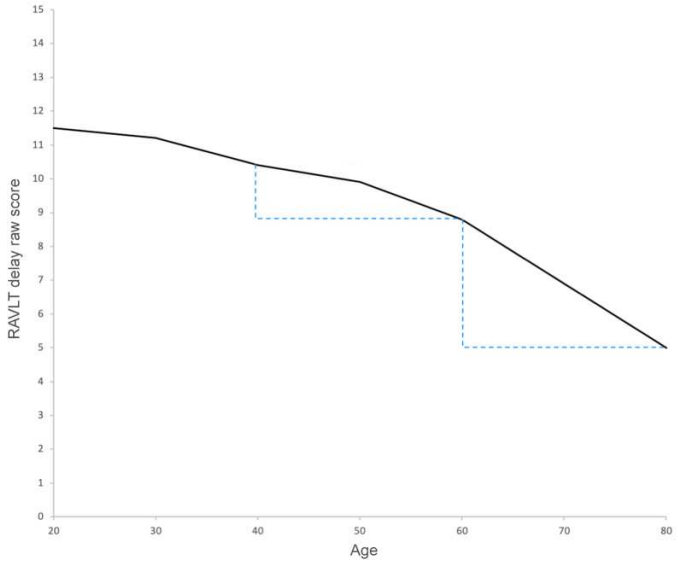


Figure 3.8: Longitudinal RAVLT Performance -Adapted from (Rogalski, 2019) Nonlinear decline in average episodic memory performance with age. Average episodic memory performance on the delayed recall portion of the RAVLT is provided by decade from age 20 to 80 using normative data. Dotted lines highlight differential magnitudes of decline over two 20-year periods showing steeper performance drops from age 60 to 80 than age 40 to 60.

The use of one cut point, either top 25th or 50th percentile, may blur effects that can be seen in individuals that straddle around this dichotomization. Like in many of the definitions highlighted in Table 1.1, study participants are either in the high performing group or not, ignoring the possibility of varying levels of successful aging. Thus, future directions include developing a model of TCP where we can assess multiple levels of cognitive maintenance and possibly better capture resistance. We did observe some evidence for regional cortical thickness in predicting memory SDTP in 80 year olds, where the Top 25th percentile yielded a higher AUC. The fact that this was seen in eighty year olds, but not sixty or seventy

year old's, may allude to the larger drop in memory seen in rising aging groups, as shown in Figure 3.8, and described in limitations below. It is possible that brain resistance is more meaningful in your eighties, though further testing is needed to assess the reliability of this finding. We also expected a difference.

Lack of differences in TCP combination models were also slightly surprising. Chapter one details the varying trajectories that are seen across age groups, and given these relationships, it was hypothesized that some combinations, particularly those including memory and executive given their strong negative relationship with age (5 out of the 6), would significantly differ from our other combination, TCP(language/attention). It is possible that given that these are all highly educated individuals, this lack of difference between structural characteristics is better explained by education level and not a function of age. Interestingly, changes in subcomponents of executive function, such as switching and flexibility, has been shown to be better explained by differences in education rather than age (H. Lin et al., 2007). Thus, future directions include stratifying analyses by education and assessing if there is a better separation of TCP versus non-TCP in each category.

Limitations

As with Chapter 1, results from these analyses are heavily subjected to selection and sample bias. As shown is Tables 3.1 and 3.2 this sample is highly educated and mostly female. Aside from the bias participation in imaging studies introduce, both of the larger cohorts are high skewed in their representation of key demographic variables. Though validation was attempted through test and train subsets, we still run the risk of overfitting the data given our slightly small sample sizes. Future directions include testing if similar relationships exist in similar datasets such as ADNI.

Additionally, to increase our sample size and gain a more robust understanding of the effect of age, 60 year olds were included in this analysis. In commentary by Rogalski, a pioneer in the SuperAging field, she suggested that the minimum cut off for SuperAging be set to 80 years old given that we see a

more precipitous and meaningful decline in older elderly adults compared to those aged 40-60 (Rogalski, 2019). She posits that concepts of resilience and resistance become more meaningful with rising age due to the vast differences in decline between middle age and older adults (Figure 3.7). It is important to note though that noticeable decreases in cognition happen nonetheless and studies of younger SuperAgers were still able to find detectable neurobiological differences.

In summary, we were able to show that while we saw group differences in total white matter hyperintensities, network style regional cortical thickness and cortical volume were both efficient in predicting Top Cognitive Performance. Additionally, our structural biomarkers were able to predict all TCP combinations of our SDTP variables measuring memory, executive function, language, and attention.

Chapter 4

4.1 Introduction

Do Top Cognitive Performers exhibit lower levels of Alzheimer's disease related pathology throughout the lifespan?

It is still yet to be determined if successful aging reflects *resilience* or *resistance*. Does their preserved cognition reflect a brain that is free of disease burden, or do they possess neurobiological characteristics that protect them from accumulation of neural injuries? While previous chapters and the literature establish that structural integrity is one of the keys in the maintenance of cognition, the contributions of AD-related burden to successful cognitive aging has not fully elucidated, especially in the oldest old. Here, we aimed to assess group differences in measures of amyloid and tau across the lifespan using data from the Alzheimer's Disease Neuroimaging Initiative (ADNI age: 60-89) and The 90+ Study (age: 90-101). Additionally, using the ADNI dataset, we performed exploratory ANOVAs of regional cingulate AV-45 SUVRs to assess if amyloid load in particular areas was associated with TCP. Consistent with the literature, results showed no group differences in amyloid SUVRs both regionally and in the whole cortex. We also observed no differences in Braak composite SUVRs. Interestingly, these relationships persisted in the oldest-old. This indicates that Top Cognitive Performance throughout the lifespan does not reflect resistance to amyloid and tau burden, and other mechanisms may be associated with protection against amyloid and tau related neurodegeneration.

Alzheimer's disease, one of the most common types of dementia, is a progressive disorder that is marked by a drop in various key cognitive faculties such as memory. According to the CDC, over five million Americans are currently living with this debilitating disease and vast efforts are being made to understand its mechanisms. Two well-known abnormal structures, amyloid plaques and neurofibrillary tangles, have been the subject of study in their contributions to conversion and cognitive decline in disease-related and normal aging. The presence of amyloid plaques has been linked to apoptosis, synaptic loss, altered calcium homeostasis, and disruptions in various cellular processes (Carrillo-Mora et al., 2014; Reiss et al., 2018). Similar toxic effects, such as synaptic dysfunction are seen in the presence of tau tangles and it was shown that eliminating tau through knockout mice protected against amyloid induced toxicity, alluding to its mediating effects (Bloom, 2014; Leroy et al., 2012). Though amyloid and tau are strongly linked to pathological processes associated with Alzheimer's, they also appear in successful aging and cognitively normal individuals, leading to the question of how they differentially contribute to any changes or preservation seen in cognition. Below, I will summarize the contributions of amyloid and tau to disease progression, decline in cognitively normal groups, and burden seen in successful aging cohorts.

Early post mortem studies of Alzheimer's disease showed that the accumulation of tau tangles was positively associated with the magnitude of cognitive decline seen in demented and cognitive normal individuals (Arriagada, Growdon, et al., 1992; Arriagada, Marzloff, et al., 1992). Furthermore, Braak and Braak developed a staging method that relied on the evidence that neurofibrillary tangles accumulate in a particularly characteristic fashion across the brain in stages (Braak & Braak, 1991) which was later used to see that staging was positively associated with memory impairment and conversion to dementia (Cho et al., 2016; Riley et al., 2002; Schöll et al., 2016). Early PET imaging studies shown that individuals with dementia displayed greater amounts of amyloid deposition when compared to cognitively normal participants (Klunk et al., 2004). AD-related lesions accumulate in the brain years before cognitive deficits (Morris & Price, 2001; Rowe et al., 2007), with longitudinal studies showing both concentrations

of amyloid-beta in the CSF and amyloid deposition measured by PET appearing 25 and 15 years before symptom onset, respectively (Bateman et al., 2012b). Amyloid burden is known to be associated with lower cognitive performance in elderly individuals (Hedden et al., 2013; Rentz et al., 2010). Earlier studies by *The 90+ Study* revealed that tau and amyloid continue to be significantly associated with Alzheimer's Disease in the oldest old (Robinson et al., 2011). For example, amyloid load in 13 participants was significantly correlated with global cognition and memory, and those deemed as amyloid positive exhibited steeper declines over a 1.5 year follow up (Kawas et al., 2013). Further, the rate of cognitive decline was found to be faster in amyloid positive individuals when compared to amyloid negative (Greenia et al., 2014), both suggesting that increased amyloid can be used as a surrogate marker for rapid cognitive decline in the oldest-old.

Further, AD-related pathology has also been observed in the cingulate cortex via increased amyloid burden. Many studies have shown pronounced amyloid tracer uptake in the cingulate, which can be detected early in AD (Li et al., 2008). Chételat and colleagues (2012) even showed that elderly healthy individuals with increased amyloid burden displayed a greater rate of atrophy, particularly in the posterior cingulate cortex and temporal neocortex (Chetelat et al., 2012). These findings are particularly relevant given the contributing role of the cingulate in predicting superior cognitive performance.

Though evidence suggests that amyloid and tau are significant contributors to decline in most models of aging, less is known about whether highly successful cognitive aging is associated with either the absence of their accumulation (resistance) or with cognitive preservation despite the accumulation of disease-related insults (resilience). The current evidence, however, does suggest resilience is the more likely hypothesis. For example, despite a having a similar burden in amyloid to cognitive normal for age peers, SuperAgers exhibited a 69%–73% reduced risk to disease progression (Dang, Harrington, et al., 2019b). A majority of the literature, briefly described in Table 4.1, suggests that successfully aging individuals do not differ from other cognitively typical elderly controls in amyloid positivity or load, despite maintaining higher than typical levels of cognition. These data suggest that intact cognitive

performance does not reflect resistance to AD-related pathology, contrary to the notion that increased amyloid deposition drives cognitive decline. There is, however, sparse literature that may suggest the contrary, that SuperAgers don't accumulate these markers and are models of resistance. An early post-mortem study of a five SuperAger cases and five controls found that three of the five SuperAgers were determined to be Braak stage of 0, I, or II while only one control case exhibited a similar low pathology (Rogalski et al., 2013a). Similarly, the same research group examined the post mortem pathology of the entorhinal cortex and found that cognitively average normal controls (n=6) exhibited nearly 3 times more neurofibrillary tangles when compared with SuperAgers (n=7), despite there being no difference in amyloid plaques (Gefen et al., 2021). Though supernormals did not show normal control group differences in whole cortex amyloid, they did exhibit lower amyloid burn in the right isthmus cingulate following a brain wide ROI-analysis (Baran et al., 2018). Note however, that each of these studies is limited by their small sample sizes.

Given these conflicting relationships between amyloid and successful aging and the sparsity of in vivo tau/SuperAging research, this chapter aims to assess group differences in amyloid and tau in Top Cognitive Performers. Additionally, these relationships are understudied in the oldest-old, leaving us with questions of how these associations present in advanced aging. Thus, our aim is to assess group differences in amyloid and tau burden via PET, using datasets from the Alzheimer's Disease Neuroimaging Initiative (ADNI) and 90+ Study.

Table 4.1: Alzheimer's Related Pathology in Successful Aging
*Indicates noted caveat

Group	Subjects	Pathology measure	Outcome	Citation
Reduced Pathology in Successful Aging				
SuperAgers	SuperAgers (n=5, mean age=88.6) vs. Elderly Control (n=5, mean age= 87.8)	Histological amyloid and tau plaque count of the cingulate cortex	SuperAger displayed lower amyloid and tau plaque counts in the caudal anterior cingulate cortex when compared to elderly controls	(Gefen et al., 2015)

Supernormals*	Supernormals (n=122, mean age: 73.9) vs. AD (n=27 mean, age= 73.18) vs. MCI (n=69, mean age=71.3) vs. Normal Cognition (n=172, mean 74.6)	- PET (18F-AV-45) "A standardized uptake value ratio (SUVR) was calculated for each PET voxel, with the reference region set to the whole cerebellum. SUVRs were extracted from 68 cortical ROIs."	*SNs displayed lower whole cortex amyloid than MCI and AD, but not normal controls. However, regional analysis revealed that amyloid burden in the right isthmus cingulate cortex differed in SN when compared to all other groups.	(Baran et al., 2018) See also: Lin, 2017
SuperAgers*	SuperAgers (n=25, mean age=85.2), vs. Normal agers (n=25, mean age= 84.5) vs. MCI (n=25, mean age= 84.8) vs. Young controls (n=25, mean age=63.6)	- PET (18F-AV-45 & 18F-AV-1451) "The voxel-wise ROI approach included 5 meta-ROIs (entorhinal cortex, inferior temporal, middle occipital, precuneus, and orbitofrontal gyrus)"	SuperAgers exhibited lower tau burden in the inferior temporal lobe and precuneus when compared to normal agers, but exhibited no differences in amyloid burden*	(Hoenig et al., 2020)
SuperAgers*	SuperAgers (n=7, mean age=89.9) vs. Elderly Control (n=6, mean age= 86.6)	Histological amyloid and tau plaque count of the entorhinal cortex	SuperAgers exhibited greater neurofibrillary tau when compared to Elderly controls but not amyloid plaques. *	(Gefen et al., 2021)
No Difference in Pathology in Successful Aging				
Optimal Perfor mers (OP) and maintainers	OP (n=25 mean age= 77.5) vs. Typical performer (TP) (n=100, mean age= 78.9)	- PET (PiB) "PiB data were analyzed using the distribution volume ratio (DVR) created using the Logan graphical analysis method with cerebellar cortex as reference tissue"	No differences in amyloid burden between OP and TP. However, maintainers exhibited lower amyloid burden at baseline when compared with non-maintainers.	(Dekhtyar et al., 2017)
Successful Agers	Successful Agers (n=26 mean age= 74.9) vs. Typical older adult (n=103 mean age= 75.9)	- PET (PiB) "A global PiB DVR threshold of 1.065 was used."	While amyloid burden did not differ between groups, successful agers showed a significant negative relationship between amyloid and age, such that older successful agers were less likely to have high brain β-amyloid.	(Harrison et al., 2018)

SuperAgers	SuperAgers (n=179, mean age=68.43) vs Cognitively Normal for Age (CNFA) (n=179, mean age=68.53)	- One of the following tracers were used: Florbetapir, PIB, or Flutemetamol "SUVR/BeCKeT threshold of 1.40 was used."	No group differences were observed in prevalence of amyloid positivity.	(Dang, Harrington, et al., 2019a)
SuperAgers	SuperAgers (n=10, mean age=83.3) vs Healthy age-matched controls (n=10, mean age=83.5) vs Healthy middle age controls (n=10, mean age=58.7)	- PiB-PET "an adaptation of the AD-signature ROI composite (Jack et al., 2017) was accomplished using the average of the mean uptake in the prefrontal, orbitofrontal, parietal, temporal, anterior and posterior cingulate, and precuneus ROIs."	No group differences between SuperAgers and healthy age-matched controls in amyloid deposition.	(Borelli et al., 2019a)
SuperAgers	SuperAgers (n=10, mean age=82.1) vs Healthy age-matched controls (n=10, mean age=84.2) vs Healthy middle age controls (n=10, mean age=58.5)	- PiB-PET "SUVR was transformed to CTX (Global Cortical Target region) using the whole cerebellum (WC) as reference."	No group differences between SuperAgers, healthy controls, or middle age controls in amyloid SUVR	(de Souza et al., 2021)

4.2 Experimental Design And Methods

Alzheimer's Disease Neuroimaging Initiative (ADNI)

Participants

The data used here were obtained from the ADNI database (adni.loni.usc.edu), downloaded on June 19, 2022. ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and

neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimer's disease (AD). For up-to-date information, see www.adni-info.org.

Using ADNIMERGE, which includes 2,415 participants, we restricted this analysis to baseline visits. Individuals were required to be sixty years old and above (60-89 years old) and having at least one 18F-AV1451 or [18F]-AV45 PET scan. Additionally, participants were required to have a diagnosis indicating cognitively normal, as determined by absence of depression, mild cognitive impairment, or dementia. Individuals who were missing data in any of the criteria variables, described below, were excluded from the analyses. As a result, three hundred and eighteen individuals were selected as a subset of the larger ADNI cohort (inclusion criteria found in Figure 4.1A).

Neuropsychological criteria for group inclusion

Previous studies of successfully aging cohorts have used neuropsychological tests with specific criteria based either on performance being consistent with a younger population or with performance being atypically high for their age group. Following the latter, TCPs were required to be in the top 50th percentile for both the Wechsler Memory Scale-revised Logical Memory IIA-Delayed Recall (WMS-R IIA) and Trails Making Test- Part B (Trails-B). The WMS-R IIA tests verbal and visual modalities and asks participants to recall units of a story after a 15 minute delay (Wechsler, 1987). Trails-B engages executive function and processing speed by asking the participant to draw a line that connects an ordered progression of alternating letters and numbers (e.g. 1 – A – 2 – B – 3 – C…) as quickly as possible (Tombaugh, 2004). All individuals that did not fit these criteria were classified as non-Top Cognitive Performers (non-TCP).

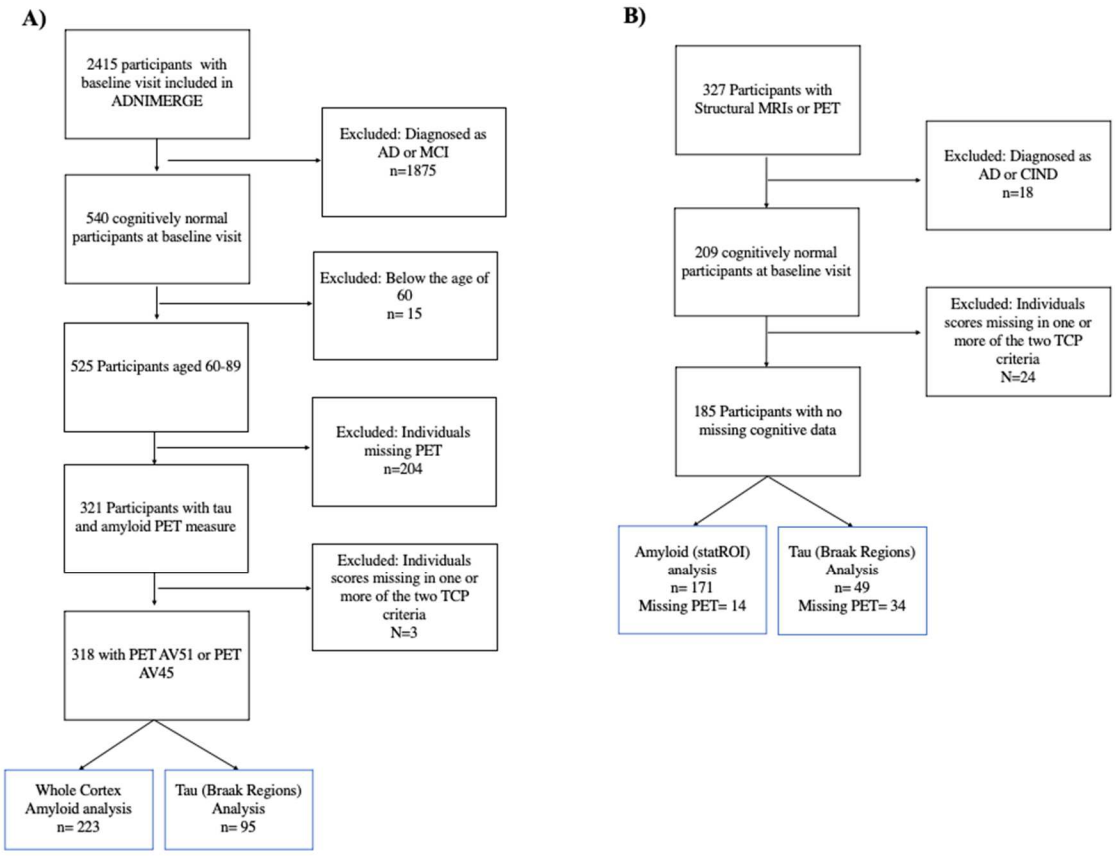


Figure 4.1: Inclusion flow chart for (A) ADNI and (B) The 90+ Study Participants. Blue box reflects the participants included in the final analysis of top cognitive performers (TCP).

Image Data

In the ADNI cohort, all imaging data were drawn from ADNI-supplied summary metrics. Details on ADNI's collection and processing methods are described elsewhere (Landau et al., 2021; Landau & Jagust, 2015). For the present study, only minor processing was done. For the AV45 (Florbetapir) data, the provided SUVRs from all 68 cortical ROIs were used to calculate a weighted average of whole cortex amyloid burden to account for the varying sizes of each ROI. For the AV1451 (flortaucipir) data, we used the inferior cerebellum as a reference region for all Braak composite SUVRs provided by ADNI. Examples of regions included in each composite score are as follows: Braak 1 (entorhinal cortex), Braak 3 (parahippocampal, fusiform, lingual, and amygdala), Braak 4 (middle temporal, caudal anterior

cingulate, rostral anterior cingulate, posterior cingulate, isthmus cingulate, insula, inferior temporal, temporal pole), Braak 5 (superior frontal, lateral orbitofrontal, caudal middle frontal, rostral middle frontal, etc.) and Braak 6 (pericalcarine postcentral, cuneus, precentral, and paracentral) (see full list in Landau et al., 2021). Braak 2 SUVR data was not included in this analysis as ADNI states this region was contaminated by off-target binding in the choroid plexus.

The 90+ Study

Participants

One hundred and eighty five individuals from the larger *The 90+ Study* cohort were included (Figure 4.1B)**.** The 90+ Study, established in 2003, is an ongoing longitudinal investigation of aging and dementia in individuals aged 90 and above, consisting of the survivors of the Leisure World Cohort Study (Kawas, 2008). Participants were selected based on the availability of PET measures of amyloid (StatROI) and tau (BakerBraak1_2, BakerBraak3_4, BakerBraak5_6) and a cognitively normal diagnosis at baseline visit. Cognitively normal was determined by *The 90+ Study* and refers to a primary diagnosis, determined by neurological examiners, where an individual is deemed as normal, absent of impairment in any cognitive domains, and able to complete Instrumental activities of daily living (IADL). Individuals who contained missing data in any of the criteria variables were excluded from the analyses.

Neuropsychological criteria for group inclusion

Following NACC & ADNI TCP criteria, The 90+ TCP individuals were required to perform at or above the top 50th percentile for their age group on the long-delay recognition portion of the California Verbal Learning Test – short form (CVLT) and at or above the top 50th percentile on completion time for their age group in the Trails-B. All other individuals that did not fit these criteria were classified as non-Top Cognitive Performers (non-TCP).

Image Data

As with the ADNI dataset, amyloid estimates were generated using AV45 (Florbetapir) and fully processed summary data were provided by the 90+ Study. Details on their processing are available elsewhere (Lau et al., 2021). Note that amyloid burden in The 90+ Study (StatROI) is quantified slightly differently than in ADNI, here as standard uptake SUVR of posterior cingulate and precuneus regions relative to an eroded cerebral white matter mask as a reference region. These regions were chosen by The 90+ because their mean SUVR distributions were able to distinguish cognitively normal individuals from the impaired (Lau et al., 2021).

Statistical analysis of PET study participants and SUVR

For both datasets, statistical analyses were performed using SAS and the Statsmodels (https://www.statsmodels.org/) library in Python. ANCOVAs were used to evaluate group differences in StatROI (amyloid), whole cortex amyloid, and Braak composites scores (tau). Additionally, unpaired t-tests were used to evaluate differences in continuous variables (age, education-ADNI, and neuropsychological performance) and Fisher's exact test to evaluate gender distribution, across the two subject groups.

4. 3 Results

Table 4.2 ADNI Demographics						
	Amyloid PET (n=223)			Tau PET (n=95)		
	TCP (n=58)	non-TCP (n=165)	T-Test/ Chi-Square	TCP (n=26)	Non (n=69)	T-Test/ Chi-Square
Mean Age (SD)	72.5 (6.0)	73.0 (6.2)	0.54	70.5 (4.5)	69.4 (5.1)	0.32
Number of Females (%)	34 (58.6%)	88 (53.3%)	0.54	18 (69.2%)	41 (59.4%)	0.48
Education: Number of years (SD)	17.3 (2.4)	16.3 (2.5)	0.007*	18.0 (1.5)	16.5 (2.3)	0.001*
Mean WMS-R IIA Score (SD)	16.6 (1.8)	12.4 (2.6)	<.0001*	17.0 (1.7)	12.4 (3.1)	<.0001*
Mean Trails B Score (SD)	55.2 (12.2)	87.2 (41.2)	<.0001*	50 (8.5)	78.6 (37.2)	.0002*

Table 4.3 The 90+ Study Demographics						
	Amyloid PET (n=171)			Tau PET (n=49)		
	TCP (n= 41)	non-TCP (n=130)	T-Test/ Chi-Square	TCP (n=13)	non-TCP (n=36)	T-Test/ Chi-Square
Mean Age (SD)	91.9 (1.5)	92.3 (2.2)	0.20	91.8 (1.4)	91.5 (1.3)	0.53
Number of Females (%)	24 (58.5)	80 (61.5)	0.85	9 (69.2%)	17 (47.2%)	0.21
Education: High-school graduate or less (%) Some college to graduate (%) Some graduate school or higher (%)	 6 (14.6%) 18 (43.9%) 17 (41.5%)	 21 (16.2%) 58 (44/6%) 51 (39.2%)	0.90	 4 (30.8%) 4(30.8%) 5 (38.4%)	 6 (16.7%) 13 (36.1%) 17 (47.2%)	n/a
Mean CVLT Score (SD)	8.5 (0.5)	6.2 (2.0)	<.0001*	8.5 (0.5)	5.6 (2.0)	<0.0001*
Mean Trails B Score (SD)	93.2 (18.4)	156.1 (71.7)	<.0001*	95.9 (16.2)	158.8 (80.4)	0.008

Demographics And Neuropsychological Performance At Baseline

As shown in Table 4.2, there were 223 and 95 ADNI individuals who fit our inclusion criteria for our amyloid and tau analyses, respectively. For both sets of participants, unpaired t-tests revealed TCP vs. non-TCP differences in education (amyloid: $t(221)= 2.72$, $p= 0.007$ & tau: $t(93)= 3.33$, $p= 0.001$), mean performance in memory (amyloid: $t(221)= 11.3$, $p < 0.0001$ & tau: $t(93)= 7.2$, $p < 0.0001$), and mean performance in executive function (amyloid: $t(221)= 5.8$, $p < 0.0001$ & tau: $t(93)= 3.9$, $p= 0.0002$). The latter two are, of course, to be expected given the criteria for TCP group inclusion. There were no differences in age (amyloid: $t(221)=0.6$, $p= .55$ & tau: $t(93)=1.0$, $p= 0.32$) or sex distribution (amyloid: Fisher's exact $p=0.5$ & Fisher's exact $p=0.5$).

As seen in Table 4.3, there were 171 and 49 individuals in The 90+ Study who fit our inclusion criteria for our amyloid and tau analyses, respectively. In contrast to the ADNI cohort, The 90+ exhibited no group differences in any demographics (note, the low sample size precluded testing for differences in education for those with tau scans), but did, of course, show the by-definition differences in mean performance in memory (amyloid: $t(169)=7.5$, $p < 0.0001$ & tau: $t(47)=5.3$, $p < 0.0001$) and executive function (amyloid: $t(169)= 5.6$, $p < 0.0001$ & tau: $t(47)=2.8$, $p= 0.007$).

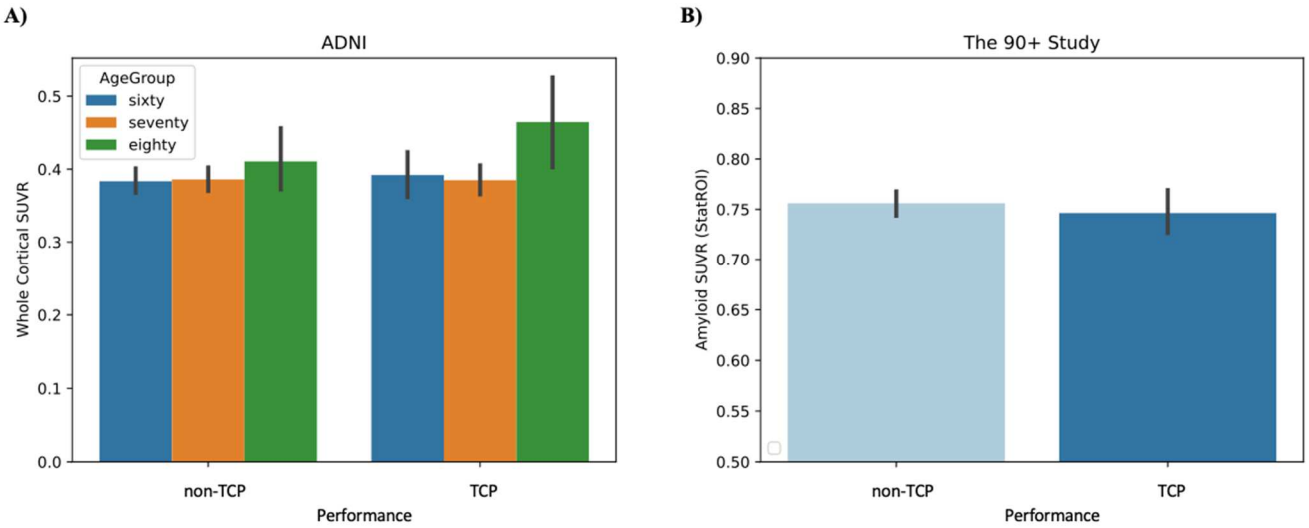


Figure 4.2: **No group differences in amyloid burden** Bar plots show no group differences in amyloid burden across the lifespan. A) Whole cortex amyloid SUVR measures of TCP versus non-TCP in sixty, seventy, and eighty year olds from the ADNI dataset. B) StatROI SUVR measures of TCP versus non-TCP in ninety year old's from The 90+ Study.
* Error bars represent 95% confidence intervals. Each Respective SUVR calculation further described in the methods section.

We used an ANCOVA with factors for TCP status, age group (sixty, seventy, eighty), sex, and education to examine whole cortex amyloid SUVR levels in the ADNI dataset (Figure 4.2A). After adjusting for age group, sex, and education (Type III sum of squares), the ANCOVA revealed no group differences in whole cortex amyloid SUVR ($F(1,222)=2.55$, $p= 0.11$; the unadjusted effect was not reliable as well). As one might anticipate, after adjusting for the other factors, however, there was an effect of age group on SUVR ($F(2,222)=4.48$, $p=0.01$) with greater amyloid present in older individuals. However, adjusting for sex and education, results showed no interaction between age group and TCP ($F(2,222)=1.30$, $p= 0.28$; the unadjusted effect was not reliable as well). Additionally, an exploratory analysis was conducted to determine if there were regional differences in amyloid by age group. Separate ordinary least squares regressions were run using TCP status, age group, sex, and education for each of the 68 regions, setting an uncorrected alpha threshold of 0.01 to only mildly correct for multiple

comparisons. Despite this, none of the regions showed any effect of TCP group status on regional SUVR levels. Similarly, as shown in Figure 4.2B, data from The 90+ study did not reveal any differences between TCP and non-TCP in StatROI SUVRs ($F(1,170)=1.04$, $p= 0.43$).

Tau Burden and Top Cognitive Performance Across the Elderly Lifespan

The same approach was used in the analysis of the tau data, here analyzing the tau load in each Braak region set separately. ANCOVA's in the ADNI dataset did not reveal group difference in the Braak ROI 1 SUVR ($F(1,94)=0.02$, $p= 0.89$), Braak 3 & 4 composite SUVR ($F(1,94)=0.43$, $p= 0.51$), or Braak 5 & 6 composite SUVR ($F(1,94)=0.84$, $p= 0.36$) after accounting for age, sex, and education, as shown in Figure 4.3. Unlike in measures of amyloid, there was no effect of age group on any of the Braak ROI

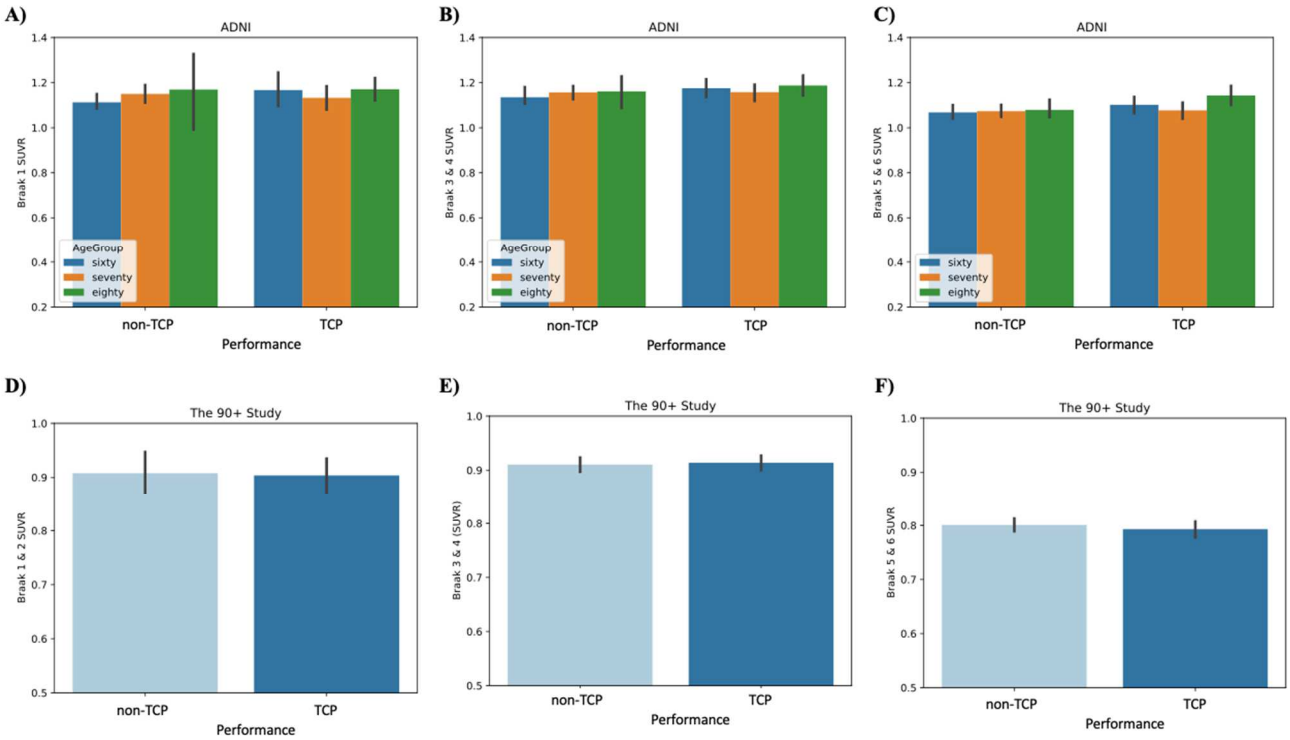


Figure 4.3: **No group differences in amyloid burden** Bar plots show no group differences in Braak region tau burden across the lifespan. TOP: Bar plots representing SUVR measures of TCP versus non-TCP in sixty, seventy, and eighty year olds from the ADNI dataset in the A) Braak 1 ROI, B) Braak 3 and 4 composite ROI, and C) Braak 5 and 6 composite ROI. BOTTOME: Bar plots representing SUVR measures of TCP versus non-TCP in ninety year old's from The 90+ Study dataset in the A) Braak 1 and 2 composite ROI, B) Braak 3 and 4 composite ROI, and C) Braak 5 and 6 composite ROI.
* Error bars represent 95% confidence intervals. Each Respective SUVR calculation further described in the methods section.

SUVRs (all p's > 0.1). Additionally, there were no interactions of age group by TCP in each SUVR (all p's >0.2). Similarly, data from The 90+ Study showed no differences in Braak ROI 1 & 2 composite SUVR ($F(1,48)=0.01$, $p= 0.98$), Braak 3&4 composite SUVR ($F(1,48)=0.05$, $p= 0.82$), or Braak 3&4 composite SUVR ($F(1,48)=0.42$, $p= 0.52$).

4. 4 Discussion

The goal of this chapter was to assess whether TCPs, a cohort of successful aging individuals, exhibited group differences in Alzheimer's related pathology when compared to their peers. Given the literature, it was hypothesized Top Cognitive Performers would reflect resilience and show similar pathology to their non-TCP peers rather than showing less pathology (in the form of amyloid or tau loads). It was possible, however, that being a TCP, or having a combined increased performance in two key cognitive domains, was a function of there being little to no pathology. Gefen and colleagues, for example, found that SuperAgers exhibited lower neurofibrillary tau and amyloid plaque counts in the pregenual anterior cingulate anterior midcingulate cortex when compared to elderly controls in a small subset of participants (Gefen et al., 2015). While 'amyloid deposition and neurodegeneration has been documented in about 50–60% of cognitively healthy elderly individuals (aged 60 years or older)', some individuals in their 70s can be absent of both (Burnham et al., 2016; Jack et al., 2012). The Mayo Clinic Study of Aging (MCSA) showed that 43% of their 450 participants were classified as stage 0, defined as cognitively normal subjects who did not present any evidence of AD biomarkers (Jack et al., 2012). Similarly, Burnham and colleagues (2016) found that 54% of cognitively normal individuals did not display AD pathology or neurodegeneration, measured by Aβ deposition and hippocampal volume respectively. These individuals exhibited slower cognitive decline and slower hippocampal atrophy when compared to those who showed positive signs of AD pathology and neurodegeneration.

In line with the majority current literature highlighted in Table 4.1, results from this chapter confirm that TCP individuals do not exhibit group differences in measures of amyloid, and these

relationships persist in the oldest-old. Despite conflicting reports, most studies have shown that successfully aging individuals did not differ from other cognitively normal elderly controls in amyloid burden (Borelli et al., 2019b; Dang, Harrington, et al., 2019a; de Souza et al., 2021; Harrison et al., 2018), despite maintaining high levels of cognition. These data suggest that intact cognitive performance does not reflect resistance to AD-related pathology, contrary to the notion that increased amyloid deposition is correlated to cognitive decline. Given individual differences in pathology at large and the above-mentioned competing theories, it is possible that structural characteristics, such as cortical thickness, act as a compensatory mechanism that aid in coping with typical age-related insults. The accumulation of amyloid has been repeatedly associated with abnormalities in functional and structural imaging. fMRI studies have shown a difference in functional connectivity between amyloid positive and negative groups in key regions such as the precuneus, hippocampus, and anterior cingulate cortex, similar to comparisons with individuals diagnosed with AD (Sheline et al., 2010). Structural studies have shown reduced grey matter volume (Oh et al., 2011) and cortical thinning with increased amyloid deposition (Becker et al., 2011). These findings show that amyloid deposition is associated with poorer cognition, faster cognitive decline, and vast brain abnormalities, even in asymptomatic individuals.

We also found that TCP did not exhibit any group differences in measures of tau throughout the full elderly lifespan. To our knowledge, only one study has examined in-vivo tau in relation to SuperAging. While there is also a difference in our samples, Hoenig & colleagues employed a voxel wise analysis of four specific meta ROIs (inferior temporal, precuneus, entorhinal cortex, middle occipital, and orbitofrontal). It is possible they identified a network of individual regions that reflect resistance to pathology that might explain their preserved cognition. For reasons of comparison with The 90+ Study, we utilized composite SUVR values of Braak ROIs. Though their significant regions (inferior temporal lobe and precuneus) are encompassed within our tau SUVRs, they are included amongst other key ROIs in a composite measure, listed in the methods section. Thus, future directions include conducting a regional analysis of tau SUVR to possibly capture specific areas that may be associated with TCP.

Lastly, an exploratory analysis was conducted to assess if there were regional differences in amyloid. Baran and colleagues (Baran et al., 2018) were able to show that though their Supernormals did not exhibit any differences in whole cortical amyloid, there was a difference in the isthmus cingulate following a 68 ROI analysis across the cortex. They noted, though, that since the isthmus cingulate is a small ROI and their FreeSurfer segmentations were done manually, their analysis was 'vulnerable to subjectivity in the correction of topological defects' (Baran et al., 2018). Our analysis revealed no differences in any of the age groups in amyloid burden, suggesting that even regionally, amyloid is not associated with TCP.

Limitations

We acknowledge the limitations on the generalizability of the results of this chapter. As described in Chapter 2 and 3, inclusion criteria and recruitment, amongst other factors, have led to a more heterogenous population in ADNI and The 90+ Study participants, which tend to be mostly Caucasian and of both high socioeconomic and education status. We also acknowledge that the lack of a standard successful aging definition, as highlighted in Table 1.1, makes comparisons between studies difficult. Given the nature of data availability in ADNI and The 90+ Study, even we had to use different measures of delayed memory. As previously mentioned, the WMS-R IIA and CVLT were chosen as tests of delayed recall to mirror SuperAging standard as closely as possible, limited by what data is available in each dataset.

Like the results in this chapter, it is important to note that some of the studies highlighted in Table 4.1 are cross-sectional and only represent a snapshot of an individual's cognition and pathological profile. One successful aging study that did include longitudinal data found that while amyloid burden did not differ between Harvard Aging Brain Study's optimal and typical performers, those who maintained their cognition over 3 years (e.g., maintainers) displayed lower amyloid burden at baseline when compared to those that did not. Dekhtyar and colleagues suggested that individuals who did not maintain their optimal

performance may be representative of a preclinical trajectory (Dekhtyar et al., 2017). Preclinical Alzheimer's disease, first described as cognitively normal individuals that exhibit pathology at autopsy, is the stage before diagnosis and noticeable symptoms appear (Dubois et al., 2016; Hubbard et al., 1990). Longitudinal studies show amyloid deposition measured by PET 15 years before symptom onset (Bateman et al., 2012a). Similar to Dekhtyar and colleagues' theory, it is possible that since we are studying baseline visits, we are capturing individuals on the preclinical trajectory to Alzheimer's disease. Though participants were required to have a diagnosis of cognitively normal, we don't yet fully understand which of these individuals are set to convert. Thus, future directions include incorporating the diagnosis of subsequent visits to assess if the lack of group differences between our cohorts are really a reflection of the preclinical trajectory.

Chapter 5

5.1 Conclusions

As described in Chapter 1, many cognitive domains are subject to age-related decline and these changes in performance are often correlated with changes seen in the brain. There are some individuals, though, that are able to avoid the deleterious effects of rising aging and exhibit superior or maintained cognition, uncharacteristic of peers similar in age. This dissertation aimed to capture this phenomenon and further examine which structural and pathological measures, established as biomarkers of normal and disease related declines, are related to this preserved cognition. Using data from ADNI, NACC, and The 90+ Study, we were able to test the utility of cortical thickness, cortical volume, white matter hyperintensity volume, amyloid, and tau in modeling Top Cognitive Performance, defined here by performance in the Top 50th percentile of both memory and executive function, two hallmark domains of cognition that are effected by dementia. spread of data available allowed us to test these relationships in the young- and oldest-old, thus informing us on which biomarkers are useful across the older adult lifespan. A summary of this dissertation is as follows:

Chapter 2: Is cortical thickness of the cingulate cortex key in predicting successful aging?

Many have found that cortical thickness in the cingulate cortex, a region involved in information processing, memory, and attention, distinguish those with exceptional cognitive abilities when compared to their cognitively more typical elderly peers (Fjell et al., 2006; Gefen et al., 2015; Harrison et al., 2018; Sun et al., 2016b). Though the cingulate has proven to be important in successful aging, the structural integrity of other regions and networks have also been identified in preserved cognitions. This chapter assessed if cortical thickness of the cingulate as a localized a priori network sufficiently predicted successful aging versus a more data driven selection of regions. We were able to show that whole brain network level models outperformed the popular cingulate model in predicting TCP, suggesting the need for a more network style approach.

Chapter 3: What factors other than cortical thickness can predict Top Cognitive Performance?

Expanding on Chapter 2, this section aimed to assess structural features that have some diagnostic ability in predicting future decline and distinguishing cognitively normal individuals from those that have Alzheimer's disease (Brickman et al., 2008, 2015; Schwarz et al., 2016). This chapter additionally examined the robustness of our TCP definition, testing other cognitive domains (memory, executive function, language, and attention) and cut points for group inclusion (performance with in the Top 25th versus Top 50th percentile). Results showed that cortical thickness and cortical volume performed relatively similar in predicting TCP, with cortical thickness yielding a slightly higher AUC in some models. This in combination with past literature showing its lacking relationship with TIV (Schwarz et al., 2016) suggests the continued use of cortical thickness as a reliable measure of TCP, especially in large populations where effects of age and sex may be of interest. We also observed some evidence for regional cortical thickness in predicting memory SDTP in 80 year olds, where the Top 25th percentile yielded a higher AUC. Though the reliability of this result needs to be further assessed, it is possible that this is capturing the relevance of age and how brain maintenance becomes more meaningful in cognitive preservation later in life. Lastly, though we saw some group differences in total white matter hyperintensity volume, it did not perform well in predicting TCP across all criteria and age groups. Given this relationship, it is possible that regional white matter hyperintensity volume may be key rather than total burden as lesions in specific areas such as periventricular white matter have been shown to be independently related to dementia. In summary, we were able to show that structural neuroimaging biomarker measures, such as cortical thickness and volume, are related to Top Cognitive Performance in a network-like regional manner that is sufficient in predicting these successfully aging individuals.

Chapter 4: Do Top Cognitive Performers exhibit lower levels of Alzheimer's disease related pathology throughout the lifespan?

In line with current literature, results from Chapter 2 & 3 highlight the importance of structural measures in predicting successful aging. In addition to structure, one study showed that SuperAgers have a 69%–73% reduced risk to disease progression in comparison to their cognitively normal age matched peers (Dang, Harrington, et al., 2019a; Dang, Yassi, et al., 2019). Despite this, there are conflicting reports on whether successful aging individuals also exhibit lower disease-related pathology, with the majority of research leaning to lack of group differences. Thus, this chapter aimed to examine group differences in amyloid and tau, two hallmark markers of Alzheimer's disease. In line with most of the literature, results showed no reliable differences in whole cortical amyloid or tau, indicated by the SUVR of Braak composite regions, across all age groups. Given that TCP did not display differential levels of Alzheimer's disease related burden, this further confirms that successful aging individual may reflect resilience rather than resistance, given their maintained cognition in the face of such brain insults.

5.2 Future Directions

In addition to structural and neuropathological measures that are related to both disease-related decline and successful aging, it is also possible that other health and lifestyle factors are significant contributors and/or predictors of TCP. For example, one study that loosely mirrors our definition for TCP found that SuperAgers were less likely to have a history of cardiac problems, which they suggest might be a proxy of lower vascular risk (Villar et al., 2021). Early SuperAging studies in a small set of individuals (n=10) found that SuperAgers found had a lower likelihood of having APOE4 (Rogalski et al., 2013b). Interestingly, one study suggested that a cohort of individuals with high performance in Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) tended to live a work-filled socially isolated lifestyle. Thus, I aim to characterize the individuals included in these analyses to assess if there are any contributing group differences in factors such as APOE4 status and exercise.

As described in some of the conclusions above, each one of these datasets are cross-sectional and can only represent a snapshot of cognition. Examples of issues this introduces are: (1) individuals

included in these analyses developed cognitive symptoms shortly after their initial visit, (2) the cognitive scores they received do indeed represent a drop from an untested period of time, or (3) some individuals included in these analyses were just born with larger brains, blurring comparisons of cortical thinning. Thus, a future direction of this dissertation is to incorporate longitudinal data to either calculate the degree of TCP maintenance over several visits and assess if baseline measures such as cortical thickness can predict it early on, or, assess changes in the brain over time using multiple scans and see its relationship to maintaining top performance. Gefen and colleagues showed that SuperAgers did not show any significant differences in tests of memory, attention, language, or executive function following a 1.5 year follow up (Gefen et al., 2014). Though this aim introduces new limitations such as the influence of practice effects, both questions assess a more robust measure of successful aging as it captures maintenance where there should be an increase in decline as a function of age.

Cortical measures were used as our first predictor of interest given it popularity in the literature, but a few studies also assessed the relationship of subcortical volumes such as hippocampus with successful aging. On one side, hippocampal atrophy has been shown to predict future memory decline in the elderly (Gorbach et al., 2017) and conversion to MCI and dementia (Csernansky et al., 2005; Eckerström et al., 2008; Jack et al., 1999). On the other side, researchers found that SuperAgers have greater hippocampal volumes when compared to normal peers (Dekhtyar et al., 2017; Harrison et al., 2018; Sun et al., 2016b). A small trending result was also found in the amygdala of SuperAgers when compared to younger adults (Sun et al., 2016b). Given these findings on both sides of the aging spectrum, future directions include examining the relationship of subcortical structures, such as those included in the limbic system, in predicting Top Cognitive Performance

Lastly, data from NACC and ADNI present a possible mode of replication for Chapters 1 and 2. Given our modest sample sizes in both datasets, it is important to assess the generalizability of our results and see if similar relationships persist. Thus, we aim to repeat these analyses in the data available.

5.3 Closing Remarks

In summary, we were able to show that structural neuroimaging biomarker measures, such as cortical thickness, are related to Top Cognitive Performance in a network-like regional manner that is sufficient in predicting these successfully aging individuals. Contrary to this pathologically, we were able to show that, unlike clear difference seen in structural characteristics of the brain, our cohort of TCP were similarly vulnerable to Alzheimer's disease related burden, despite their maintained cognition. Determining the exact structural and pathological properties that protect against aging-related cognitive decline will enable us to develop therapies that target these protective features. These results take us one step closer to identifying biomarkers that may aid in uncovering the path to avoiding the onset of cognitive decline.

References

Allain, P., Nicoleau, S., Pinon, K., Etcharry-Bouyx, F., Barré, J., Berrut, G., Dubas, F., & Le Gall, D. (2005). Executive functioning in normal aging: A study of action planning using the Zoo Map Test. *Brain and Cognition*, *57*(1), 4–7.

Anatomical Mapping of White Matter Hyperintensities (WMH) | Stroke. (n.d.). Retrieved July 20, 2022, from https://www.ahajournals.org/doi/full/10.1161/01.STR.0000150668.58689.f2

Andrés, P., & Van der Linden, M. (2000). Age-related differences in supervisory attentional system functions. *The Journals of Gerontology Series B: Psychological Sciences and Social Sciences*, *55*(6), P373–P380.

Anstey, K. J., & Low, L. F. (2004). Normal cognitive changes in aging. *Australian Family Physician*, *33*(10), 783.

Arriagada, P. V., Growdon, J. H., Hedley-Whyte, E. T., & Hyman, B. T. (1992). Neurofibrillary tangles but not senile plaques parallel duration and severity of Alzheimer's disease. *Neurology*, *42*(3), 631–631. https://doi.org/10.1212/WNL.42.3.631

Arriagada, P. V., Marzloff, K., & Hyman, B. T. (1992). Distribution of Alzheimer□type pathologic changes in nondemented elderly individuals matches the pattern in Alzheimer's disease. *Neurology*, *42*(9), 1681–1681. https://doi.org/10.1212/WNL.42.9.1681

Au, R., Massaro, J. M., Wolf, P. A., Young, M. E., Beiser, A., Seshadri, S., D'Agostino, R. B., & DeCarli, C. (2006). Association of White Matter Hyperintensity Volume With Decreased

Cognitive Functioning: The Framingham Heart Study. *Archives of Neurology*, *63*(2), 246–250. https://doi.org/10.1001/archneur.63.2.246

Baran, T. M., Lin, F. V., & Initiative, A. D. N. (2018). Amyloid and FDG PET of Successful Cognitive Aging: Global and Cingulate-Specific Differences. *Journal of Alzheimer's Disease*, *66*(1), 307–318. https://doi.org/10.3233/JAD-180360

Bateman, R. J., Xiong, C., Benzinger, T. L. S., Fagan, A. M., Goate, A., Fox, N. C., Marcus, D. S., Cairns, N. J., Xie, X., Blazey, T. M., Holtzman, D. M., Santacruz, A., Buckles, V., Oliver, A., Moulder, K., Aisen, P. S., Ghetti, B., Klunk, W. E., McDade, E., … Morris, J. C. (2012a). Clinical and Biomarker Changes in Dominantly Inherited Alzheimer's Disease. *New England Journal of Medicine*, *367*(9), 795–804. https://doi.org/10.1056/NEJMoa1202753

Bateman, R. J., Xiong, C., Benzinger, T. L. S., Fagan, A. M., Goate, A., Fox, N. C., Marcus, D. S., Cairns, N. J., Xie, X., Blazey, T. M., Holtzman, D. M., Santacruz, A., Buckles, V., Oliver, A., Moulder, K., Aisen, P. S., Ghetti, B., Klunk, W. E., McDade, E., … Morris, J. C. (2012b). Clinical and Biomarker Changes in Dominantly Inherited Alzheimer's Disease. *New England Journal of Medicine*, *367*(9), 795–804. https://doi.org/10.1056/NEJMoa1202753

Becker, J. A., Hedden, T., Carmasin, J., Maye, J., Rentz, D. M., Putcha, D., Fischl, B., Greve, D. N., Marshall, G. A., Salloway, S., Marks, D., Buckner, R. L., Sperling, R. A., & Johnson, K. A. (2011). Amyloid-β associated cortical thinning in clinically normal elderly. *Annals of Neurology*, *69*(6), 1032–1042. https://doi.org/10.1002/ana.22333

Beekly, D. L., Ramos, E. M., van Belle, G., Deitrich, W., Clark, A. D., Jacka, M. E., Kukull, W. A., & Centers, the N.-A. D. (2004). The National Alzheimer's Coordinating Center (NACC) Database: An Alzheimer Disease Database. *Alzheimer Disease & Associated Disorders*, *18*(4), 270–277.

Berlau, D. J., Corrada, M. M., & Kawas, C. (2009). The prevalence of disability in the oldest-old is high and continues to increase with age: Findings from The 90+ Study. *International Journal of Geriatric Psychiatry*, *24*(11), 1217–1225. https://doi.org/10.1002/gps.2248

Bloom, G. S. (2014). Amyloid-β and Tau: The Trigger and Bullet in Alzheimer Disease Pathogenesis. *JAMA Neurology*, *71*(4), 505–508. https://doi.org/10.1001/jamaneurol.2013.5847

Borelli, W. V., Leal-Conceição, E., Andrade, M. A., Esper, N. B., Feltes, P. K., Soder, R. B., Matushita, C. S., Hartmann, L. M., Radaelli, G., Schilling, L. P., Moriguchi-Jeckel, C., da Silva, A. M. M., Portuguez, M. W., Franco, A. R., & da Costa, J. C. (2019a). *Neural correlates of exceptional memory ability in SuperAgers: A multimodal approach using FDG-PET, PIB-PET, and MRI* [Preprint]. Neuroscience. https://doi.org/10.1101/666438

Borelli, W. V., Leal-Conceição, E., Andrade, M. A., Esper, N. B., Feltes, P. K., Soder, R. B., Matushita, C. S., Hartmann, L. M., Radaelli, G., Schilling, L. P., Moriguchi-Jeckel, C., da Silva, A. M. M., Portuguez, M. W., Franco, A. R., & da Costa, J. C. (2019b). *Neural correlates of exceptional memory ability in SuperAgers: A multimodal approach using FDG-PET, PIB-PET, and MRI* [Preprint]. Neuroscience. https://doi.org/10.1101/666438

Braak, H., & Braak, E. (1991). Neuropathological stageing of Alzheimer-related changes. *Acta Neuropathologica*, *82*(4), 239–259. https://doi.org/10.1007/BF00308809

Brickman, A. M., Honig, L. S., Scarmeas, N., Tatarina, O., Sanders, L., Albert, M. S., Brandt, J., Blacker, D., & Stern, Y. (2008). Measuring Cerebral Atrophy and White Matter Hyperintensity Burden to Predict the Rate of Cognitive Decline in Alzheimer Disease. *Archives of Neurology*, *65*(9), 1202–1208. https://doi.org/10.1001/archneur.65.9.1202

Brickman, A. M., Siedlecki, K. L., Muraskin, J., Manly, J. J., Luchsinger, J. A., Yeung, L.-K., Brown, T. R., DeCarli, C., & Stern, Y. (2011). White matter hyperintensities and cognition: Testing the reserve hypothesis. *Neurobiology of Aging*, *32*(9), 1588–1598. https://doi.org/10.1016/j.neurobiolaging.2009.10.013

Brickman, A. M., Zahodne, L. B., Guzman, V. A., Narkhede, A., Meier, I. B., Griffith, E. Y., Provenzano, F. A., Schupf, N., Manly, J. J., Stern, Y., Luchsinger, J. A., & Mayeux, R. (2015). Reconsidering harbingers of dementia: Progression of parietal lobe white matter hyperintensities predicts Alzheimer's disease incidence. *Neurobiology of Aging*, *36*(1), 27–32. https://doi.org/10.1016/j.neurobiolaging.2014.07.019

Burnham, S. C., Bourgeat, P., Doré, V., Savage, G., Brown, B., Laws, S., Maruff, P., Salvado, O., Ames, D., Martins, R. N., Masters, C. L., Rowe, C. C., & Villemagne, V. L. (2016). Clinical and cognitive trajectories in cognitively healthy elderly individuals with suspected non-Alzheimer's disease pathophysiology (SNAP) or Alzheimer's disease pathology: A longitudinal study. *The Lancet Neurology*, *15*(10), 1044–1053. https://doi.org/10.1016/S1474-4422(16)30125-9

Cahn-Weiner, D. A., Boyle, P. A., & Malloy, P. F. (2002). Tests of Executive Function Predict Instrumental Activities of Daily Living in Community-Dwelling Older Individuals. *Applied Neuropsychology*, *9*(3), 187–191. https://doi.org/10.1207/S15324826AN0903_8

Carrillo-Mora, P., Luna, R., & Colín-Barenque, L. (2014). Amyloid Beta: Multiple Mechanisms of Toxicity and Only Some Protective Effects? *Oxidative Medicine and Cellular Longevity*, *2014*, 795375. https://doi.org/10.1155/2014/795375

Chetelat, G., Villemagne, V. L., Villain, N., Jones, G., Ellis, K. A., Ames, D., Martins, R. N., Masters, C. L., & Rowe, C. C. (2012). Accelerated cortical atrophy in cognitively normal elderly with high β-amyloid deposition. *Neurology*, *78*(7), 477–484.

Cho, H., Choi, J. Y., Hwang, M. S., Kim, Y. J., Lee, H. M., Lee, H. S., Lee, J. H., Ryu, Y. H., Lee, M. S., & Lyoo, C. H. (2016). In vivo cortical spreading pattern of tau and amyloid in the Alzheimer disease spectrum. *Annals of Neurology*, *80*(2), 247–258. https://doi.org/10.1002/ana.24711

Christensen, H. (2001). What Cognitive Changes can be Expected with Normal Ageing? *Australian & New Zealand Journal of Psychiatry*, *35*(6), 768–775. https://doi.org/10.1046/j.1440-1614.2001.00966.x

Churchill, J. D., Stanis, J. J., Press, C., Kushelev, M., & Greenough, W. T. (2003). Is procedural memory relatively spared from age effects? *Neurobiology of Aging*, *24*(6), 883–892. https://doi.org/10.1016/S0197-4580(02)00194-X

Cohen-Mansfield, J., Shmotkin, D., Blumstein, Z., Shorek, A., Eyal, N., & Hazan, H. (2013). The Old, Old-Old, and the Oldest Old: Continuation or Distinct Categories? An Examination of the Relationship between Age and Changes in Health, Function, and Wellbeing. *The International Journal of Aging and Human Development*, *77*(1), 37–57. https://doi.org/10.2190/AG.77.1.c

Commodari, E., & Guarnera, M. (2008). Attention and aging. *Aging Clinical and Experimental Research*, *20*(6), 578–584. https://doi.org/10.1007/BF03324887

Cook, A. H., Sridhar, J., Ohm, D., Rademaker, A., Mesulam, M.-M., Weintraub, S., & Rogalski, E. (2017). Rates of Cortical Atrophy in Adults 80 Years and Older With Superior vs Average Episodic Memory. *JAMA*, *317*(13), 1373–1375. https://doi.org/10.1001/jama.2017.0627

Corrada, M. M., Brookmeyer, R., Berlau, D., Paganini-Hill, A., & Kawas, C. H. (2008). Prevalence of dementia after age 90: Results from The 90+ Study. *Neurology*, *71*(5), 337–343. https://doi.org/10.1212/01.wnl.0000310773.65918.cd

Corrada, M. M., Brookmeyer, R., Paganini-Hill, A., Berlau, D., & Kawas, C. H. (2010). Dementia incidence continues to increase with age in the oldest old: The 90+ study. *Annals of Neurology*, *67*(1), 114–121. https://doi.org/10.1002/ana.21915

Craik, F. I. (1990). Changes in memory with normal aging: A functional view. *Adv Neurol*, *51*, 201–205.

Cumming, G., & Finch, S. (2005). Inference by Eye: Confidence Intervals and How to Read Pictures of Data. *American Psychologist*, *60*(2), 170–180. https://doi.org/10.1037/0003-066X.60.2.170

Dang, C., Harrington, K. D., Lim, Y. Y., Ames, D., Hassenstab, J., Laws, S. M., Yassi, N., Hickey, M., Rainey-Smith, S. R., Robertson, J., Rowe, C. C., Sohrabi, H. R., Salvado, O., Weinborn, M., Villemagne, V. L., Masters, C. L., & Maruff, P. (2019a). Superior Memory Reduces 8-year Risk of Mild Cognitive Impairment and Dementia But Not Amyloid β-Associated Cognitive Decline in Older Adults. *Archives of Clinical Neuropsychology*, *34*(5), 585–598. https://doi.org/10.1093/arclin/acy078

Dang, C., Harrington, K. D., Lim, Y. Y., Ames, D., Hassenstab, J., Laws, S. M., Yassi, N., Hickey, M., Rainey-Smith, S. R., Robertson, J., Rowe, C. C., Sohrabi, H. R., Salvado, O., Weinborn, M., Villemagne, V. L., Masters, C. L., & Maruff, P. (2019b). Superior Memory Reduces 8-year Risk of Mild Cognitive Impairment and Dementia But Not Amyloid β-Associated Cognitive Decline in Older Adults. *Archives of Clinical Neuropsychology*, *34*(5), 585–598. https://doi.org/10.1093/arclin/acy078

Dang, C., Yassi, N., Harrington, K. D., Xia, Y., Lim, Y. Y., Ames, D., Laws, S. M., Hickey, M., Rainey-Smith, S., Sohrabi, H. R., Doecke, J. D., Fripp, J., Salvado, O., Snyder, P. J., Weinborn, M., Villemagne, V. L., Rowe, C. C., Masters, C. L., Maruff, P., … Woodward, M. (2019). Rates of age- and amyloid β-associated cortical atrophy in older adults with superior memory performance. *Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring*, *11*(1), 566–575. https://doi.org/10.1016/j.dadm.2019.05.005

Das, S. R., Avants, B. B., Grossman, M., & Gee, J. C. (2009). Registration based cortical thickness measurement. *NeuroImage*, *45*(3), 867–879. https://doi.org/10.1016/j.neuroimage.2008.12.016

Daselaar, S., Dennis, N. A., & Cabeza, R. (2007). Ageing: Age-related changes in episodic and working memory. *Clinical Applications of Functional Brain MRI*, 115–148.

de Souza, G. S., Andrade, M. A., Borelli, W. V., de Araújo, A. S., De Almeida Mantovani, D. B., Schilling, L. P., Matushita, C. S., da Costa, J. C., Portuguez, M. W., & da Silva, A. M. M. (2021). Centiloid scale evaluation for β-amyloid PET of cognitively normal elderly and SuperAgers. *Alzheimer's & Dementia*, *17*(S4), e052699. https://doi.org/10.1002/alz.052699

Deary, I. J., Corley, J., Gow, A. J., Harris, S. E., Houlihan, L. M., Marioni, R. E., Penke, L., Rafnsson, S. B., & Starr, J. M. (2009). Age-associated cognitive decline. *British Medical Bulletin*, *92*(1), 135–152. https://doi.org/10.1093/bmb/ldp033

DeCarli, C., Murphy, D. G. M., Tranh, M., Grady, C. L., Haxby, J. V., Gillette, J. A., Salerno, J. A., Gonzales-Aviles, A., Honvitz, B., Rapoport, S. I., & Schapiro, M. B. (1995). The effect of white matter hyperintensity volume on brain structure, cognitive performance, and cerebral metabolism of glucose in 51 healthy adults. *Neurology*, *45*(11), 2077–2084. https://doi.org/10.1212/WNL.45.11.2077

Dekhtyar, M., Papp, K. V., Buckley, R., Jacobs, H. I. L., Schultz, A. P., Johnson, K. A., Sperling, R. A., & Rentz, D. M. (2017). Neuroimaging markers associated with maintenance of optimal memory performance in late-life. *Neuropsychologia*, *100*, 164–170. https://doi.org/10.1016/j.neuropsychologia.2017.04.037

Desikan, R. S., Ségonne, F., Fischl, B., Quinn, B. T., Dickerson, B. C., Blacker, D., Buckner, R. L., Dale, A. M., Maguire, R. P., Hyman, B. T., Albert, M. S., & Killiany, R. J. (2006). An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *NeuroImage*, *31*(3), 968–980. https://doi.org/10.1016/j.neuroimage.2006.01.021

Dominguez, E. N., Stark, S. M., Ren, Y., Corrada, M. M., Kawas, C. H., & Stark, C. E. L. (2021). Regional Cortical Thickness Predicts Top Cognitive Performance in the Elderly. *Frontiers in Aging Neuroscience*, *13*. https://www.frontiersin.org/article/10.3389/fnagi.2021.751375

Dubois, B., Hampel, H., Feldman, H. H., Scheltens, P., Aisen, P., Andrieu, S., Bakardjian, H., Benali, H., Bertram, L., Blennow, K., Broich, K., Cavedo, E., Crutch, S., Dartigues, J.-F., Duyckaerts, C., Epelbaum, S., Frisoni, G. B., Gauthier, S., Genthon, R., … Jack, C. R. (2016). Preclinical Alzheimer's disease: Definition, natural history, and diagnostic criteria. *Alzheimer's & Dementia : The Journal of the Alzheimer's Association*, *12*(3), 292–323. https://doi.org/10.1016/j.jalz.2016.02.002

Ebaid, D., Crewther, S. G., MacCalman, K., Brown, A., & Crewther, D. P. (2017). Cognitive Processing Speed across the Lifespan: Beyond the Influence of Motor Speed. *Frontiers in Aging Neuroscience*, *9*. https://doi.org/10.3389/fnagi.2017.00062

Edwards, J. D., Bart, E., O'Connor, M. L., & Cissell, G. (2010). Ten Years Down the Road: Predictors of Driving Cessation. *The Gerontologist*, *50*(3), 393–399. https://doi.org/10.1093/geront/gnp127

Etkin, A., Egner, T., & Kalisch, R. (2011). Emotional processing in anterior cingulate and medial prefrontal cortex. *Trends in Cognitive Sciences*, *15*(2), 85–93. https://doi.org/10.1016/j.tics.2010.11.004

Etkin, A., Egner, T., Peraza, D. M., Kandel, E. R., & Hirsch, J. (2006). Resolving Emotional Conflict: A Role for the Rostral Anterior Cingulate Cortex in Modulating Activity in the Amygdala. *Neuron*, *51*(6), 871–882. https://doi.org/10.1016/j.neuron.2006.07.029

Finkel, D., Reynolds, C. A., McArdle, J. J., & Pedersen, N. L. (2007). Age changes in processing speed as a leading indicator of cognitive aging. *Psychology and Aging*, *22*(3), 558–568. https://doi.org/10.1037/0882-7974.22.3.558

Fjell, A. M., McEvoy, L., Holland, D., Dale, A. M., & Walhovd, K. B. (2014). What is normal in normal aging? Effects of aging, amyloid and Alzheimer's disease on the cerebral cortex and the hippocampus. *Progress in Neurobiology*, *117*, 20–40. https://doi.org/10.1016/j.pneurobio.2014.02.004

Fjell, A. M., Walhovd, K. B., Reinvang, I., Lundervold, A., Salat, D., Quinn, B. T., Fischl, B., & Dale, A. M. (2006). Selective increase of cortical thickness in high-performing elderly—Structural indices of optimal cognitive aging. *NeuroImage*, *29*(3), 984–994. https://doi.org/10.1016/j.neuroimage.2005.08.007

Fletcher, E., Singh, B., Harvey, D., Carmichael, O., & DeCarli, C. (2012). Adaptive image segmentation for robust measurement of longitudinal brain tissue change. *2012 Annual International Conference of the IEEE Engineering in Medicine and Biology Society*, 5319–5322. https://doi.org/10.1109/EMBC.2012.6347195

Ganguli, M., Lee, C.-W., Hughes, T., Snitz, B. E., Jakubcak, J., Duara, R., & Chang, C.-C. H. (2015). WHO WANTS A FREE BRAIN SCAN? ASSESSING AND CORRECTING FOR RECRUITMENT BIASES IN A POPULATION-BASED sMRI PILOT STUDY. *Brain Imaging and Behavior*, *9*(2), 204–212. https://doi.org/10.1007/s11682-014-9297-9

Gefen, T., Kawles, A., Makowski-Woidan, B., Engelmeyer, J., Ayala, I., Abbassian, P., Zhang, H., Weintraub, S., Flanagan, M. E., Mao, Q., Bigio, E. H., Rogalski, E., Mesulam, M. M., & Geula, C. (2021). Paucity of Entorhinal Cortex Pathology of the Alzheimer's Type in SuperAgers with Superior Memory Performance. *Cerebral Cortex*, *31*(7), 3177–3183. https://doi.org/10.1093/cercor/bhaa409

Gefen, T., Peterson, M., Papastefan, S. T., Martersteck, A., Whitney, K., Rademaker, A., Bigio, E. H., Weintraub, S., Rogalski, E., Mesulam, M.-M., & Geula, C. (2015). Morphometric and Histologic Substrates of Cingulate Integrity in Elders with Exceptional Memory Capacity. *Journal of Neuroscience*, *35*(4), 1781–1791. https://doi.org/10.1523/JNEUROSCI.2998-14.2015

Gefen, T., Shaw, E., Whitney, K., Martersteck, A., Stratton, J., Rademaker, A., Weintraub, S., Mesulam, M.-M., & Rogalski, E. (2014). Longitudinal Neuropsychological Performance of Cognitive SuperAgers. *Journal of the American Geriatrics Society*, *62*(8), 1598–1600. https://doi.org/10.1111/jgs.12967

Godoy, L. de, Studart-Neto, A., Nitrini, R., Jager, R., Bisdas, S., & Leite, C. da C. (2022). Brain Health Signature in Superagers: A Multimodal Brain MRI Study. *Biological Psychiatry*, *91*(9), S40. https://doi.org/10.1016/j.biopsych.2022.02.118

Good, C. D., Johnsrude, I. S., Ashburner, J., Henson, R. N., Friston, K. J., & Frackowiak, R. S. (2001). A voxel-based morphometric study of ageing in 465 normal adult human brains. *Neuroimage*, *14*(1), 21–36.

Grady, C. (2012). The cognitive neuroscience of ageing. *Nature Reviews Neuroscience*, *13*(7), 491–505. https://doi.org/10.1038/nrn3256

Greenia, D., Kawas, C., Caunca, M., Bullain, S., & Corrada, M. (2014). *PET Amyloid Imaging with Florbetapir Predicts Cognitive Decline in the Oldest-Old (P4. 011)*. AAN Enterprises.

Habeck, C., Gazes, Y., Razlighi, Q., & Stern, Y. (2020). Cortical thickness and its associations with age, total cognition and education across the adult lifespan. *PLOS ONE*, *15*(3), e0230298. https://doi.org/10.1371/journal.pone.0230298

Hall, C. B., Derby, C., LeValley, A., Katz, M. J., Verghese, J., & Lipton, R. B. (2007). Education delays accelerated decline on a memory test in persons who develop dementia. *Neurology*, *69*(17), 1657–1664. https://doi.org/10.1212/01.wnl.0000278163.82636.30

Haller, S., Kövari, E., Herrmann, F. R., Cuvinciuc, V., Tomm, A.-M., Zulian, G. B., Lovblad, K.-O., Giannakopoulos, P., & Bouras, C. (2013). Do brain T2/FLAIR white matter hyperintensities correspond to myelin loss in normal aging? A radiologic-neuropathologic correlation study. *Acta Neuropathologica Communications*, *1*, 14. https://doi.org/10.1186/2051-5960-1-14

Harrison, T. M., Maass, A., Baker, S. L., & Jagust, W. J. (2018). Brain morphology, cognition, and β-amyloid in older adults with superior memory performance. *Neurobiology of Aging*, *67*, 162–170. https://doi.org/10.1016/j.neurobiolaging.2018.03.024

Harrison, T. M., Weintraub, S., Mesulam, M.-M., & Rogalski, E. (2012). Superior Memory and Higher Cortical Volumes in Unusually Successful Cognitive Aging. *Journal of the International Neuropsychological Society*, *18*(6), 1081–1085. https://doi.org/10.1017/S1355617712000847

Harvey, P. D. (2019). Domains of cognition and their assessment. *Dialogues in Clinical Neuroscience*, *21*(3), 227–237. https://doi.org/10.31887/DCNS.2019.21.3/pharvey

He, W., Muenchrath, M. N., Muenchrath, M. N., Glei, D. A., Humes, K., Lee, M. A., & S, A. (2011). *Economics and Statistics Administration U.S. CENSUS BUREAUAcknowledgments*.

Hedden, T., & Gabrieli, J. D. E. (2004). Insights into the ageing mind: A view from cognitive neuroscience. *Nature Reviews Neuroscience*, *5*(2), 87–96. https://doi.org/10.1038/nrn1323

Hedden, T., Oh, H., Younger, A. P., & Patel, T. A. (2013). Meta-analysis of amyloid-cognition relations in cognitively normal older adults. *Neurology*, *80*(14), 1341–1348. https://doi.org/10.1212/WNL.0b013e31828ab35d

Hoenig, M. C., Willscheid, N., Bischof, G. N., van Eimeren, T., Drzezga, A., & Alzheimer's Disease Neuroimaging Initiative. (2020). Assessment of Tau Tangles and Amyloid-β Plaques Among Super Agers Using PET Imaging. *JAMA Network Open*, *3*(12), e2028337. https://doi.org/10.1001/jamanetworkopen.2020.28337

Hooren, S. A. H. van, Valentijn, A. M., Bosma, H., Ponds, R. W. H. M., Boxtel, M. P. J. van, & Jolles, J. (2007). Cognitive Functioning in Healthy Older Adults Aged 64–81: A Cohort Study into the Effects of Age, Sex, and Education. *Aging, Neuropsychology, and Cognition*, *14*(1), 40–54. https://doi.org/10.1080/138255890969483

Hubbard, B. M., Fentonm, G. W., & Anderson, J. M. (1990). A quantitative histological study of early clinical and preclinical Alzheimer's disease. *Neuropathology and Applied Neurobiology*, *16*(2), 111–121. https://doi.org/10.1111/j.1365-2990.1990.tb00940.x

Hultsch, D. F., Hertzog, C., Small, B. J., McDonald-Miszczak, L., & Dixon, R. A. (1992). Short-term longitudinal change in cognitive performance in later life. *Psychology and Aging*, *7*(4), 571–584. https://doi.org/10.1037/0882-7974.7.4.571

Hurtz, S., Woo, E., Kebets, V., Green, A. E., Zoumalan, C., Wang, B., Ringman, J. M., Thompson, P. M., & Apostolova, L. G. (2014). Age Effects on Cortical Thickness in Cognitively Normal Elderly Individuals. *Dementia and Geriatric Cognitive Disorders Extra*, *4*(2), 221–227. https://doi.org/10.1159/000362872

Jack, C. R., Knopman, D. S., Weigand, S. D., Wiste, H. J., Vemuri, P., Lowe, V., Kantarci, K., Gunter, J. L., Senjem, M. L., Ivnik, R. J., Roberts, R. O., Rocca, W. A., Boeve, B. F., & Petersen, R. C. (2012). An operational approach to National Institute on Aging–Alzheimer's Association criteria for preclinical Alzheimer disease. *Annals of Neurology*, *71*(6), 765–775. https://doi.org/10.1002/ana.22628

Jernigan, T. L., Archibald, S. L., Fennema-Notestine, C., Gamst, A. C., Stout, J. C., Bonner, J., & Hesselink, J. R. (2001). Effects of age on tissues and regions of the cerebrum and cerebellum. *Neurobiology of Aging*, *22*(4), 581–594. https://doi.org/10.1016/S0197-4580(01)00217-2

Johnson, J. K., Lui, L.-Y., & Yaffe, K. (2007). Executive Function, More Than Global Cognition, Predicts Functional Decline and Mortality in Elderly Women. *The Journals of Gerontology: Series A*, *62*(10), 1134–1141. https://doi.org/10.1093/gerona/62.10.1134

Kaplan, E., Goodglass, H., Weintraub, S., & Goodglass, H. (1983). *Boston naming test*. Lea & Febiger.

Kaskikallio, A., Karrasch, M., Koikkalainen, J., Lötjönen, J., Rinne, J. O., Tuokkola, T., Parkkola, R., & Grönholm-Nyman, P. (2019). White Matter Hyperintensities and Cognitive Impairment in Healthy and Pathological Aging: A Quantified Brain MRI Study. *Dementia and Geriatric Cognitive Disorders*, *48*(5–6), 297–307. https://doi.org/10.1159/000506124

Kawas, C. H. (2008). The oldest old and the 90+ Study. *Alzheimer's & Dementia*, *4*(1, Supplement 1), S56–S59. https://doi.org/10.1016/j.jalz.2007.11.007

Kawas, C. H., Greenia, D. E., Bullain, S. S., Clark, C. M., Pontecorvo, M. J., Joshi, A. D., & Corrada, M. M. (2013). Amyloid imaging and cognitive decline in nondemented oldest-old: The 90+ Study. *Alzheimer's & Dementia*, *9*(2), 199–203. https://doi.org/10.1016/j.jalz.2012.06.005

Klein, A., Ghosh, S. S., Bao, F. S., Giard, J., Häme, Y., Stavsky, E., Lee, N., Rossa, B., Reuter, M., Chaibub Neto, E., & Keshavan, A. (2017). Mindboggling morphometry of human brains. *PLOS Computational Biology*, *13*(2), e1005350. https://doi.org/10.1371/journal.pcbi.1005350

Klunk, W. E., Engler, H., Nordberg, A., Wang, Y., Blomqvist, G., Holt, D. P., Bergström, M., Savitcheva, I., Huang, G.-F., Estrada, S., Ausén, B., Debnath, M. L., Barletta, J., Price, J. C., Sandell, J., Lopresti, B. J., Wall, A., Koivisto, P., Antoni, G., … Långström, B. (2004). Imaging brain amyloid in Alzheimer's disease with Pittsburgh Compound-B. *Annals of Neurology*, *55*(3), 306–319. https://doi.org/10.1002/ana.20009

Knopman, D. S., Lundt, E. S., Therneau, T. M., Vemuri, P., Lowe, V. J., Kantarci, K., Gunter, J. L., Senjem, M. L., Mielke, M. M., Machulda, M. M., Roberts, R. O., Boeve, B. F., Jones, D. T., Petersen, R. C., & Jack, C. R. (2018). Joint associations of β-amyloidosis and cortical thickness with cognition. *Neurobiology of Aging*, *65*, 121–131. https://doi.org/10.1016/j.neurobiolaging.2018.01.017

Landau, S., & Jagust, W. (2015). *Florbetapir processing methods*. 6.

Landau, S., Murphy, A. E., Lee, J. Q., Ward, T. J., & Jagust, W. (2021). *Flortaucipir (AV-1451) processing methods*. 8.

Lau, W. L., Fisher, M., Fletcher, E., DeCarli, C., Troutt, H., Corrada, M. M., Kawas, C., & Paganini-Hill, A. (2021). Kidney Function Is Not Related to Brain Amyloid Burden on PET Imaging in The 90+ Study Cohort. *Frontiers in Medicine*, *8*, 671945. https://doi.org/10.3389/fmed.2021.671945

Leech, R., & Sharp, D. J. (2014). The role of the posterior cingulate cortex in cognition and disease. *Brain*, *137*(1), 12–32. https://doi.org/10.1093/brain/awt162

Leeuw, F.-E. de, Groot, J. C. de, Achten, E., Oudkerk, M., Ramos, L. M. P., Heijboer, R., Hofman, A., Jolles, J., Gijn, J. van, & Breteler, M. M. B. (2001). Prevalence of cerebral white matter lesions in elderly people: A population based magnetic resonance imaging study. The Rotterdam Scan Study. *Journal of Neurology, Neurosurgery & Psychiatry*, *70*(1), 9–14. https://doi.org/10.1136/jnnp.70.1.9

Legdeur, N., Visser, P. J., Woodworth, D. C., Muller, M., Fletcher, E., Maillard, P., Scheltens, P., DeCarli, C., Kawas, C. H., & Corrada, M. M. (2019). White Matter Hyperintensities and Hippocampal Atrophy in Relation to Cognition: The 90+ Study. *Journal of the American Geriatrics Society*, *67*(9), 1827–1834. https://doi.org/10.1111/jgs.15990

Lemaitre, H., Goldman, A. L., Sambataro, F., Verchinski, B. A., Meyer-Lindenberg, A., Weinberger, D. R., & Mattay, V. S. (2012). Normal age-related brain morphometric changes: Nonuniformity across cortical thickness, surface area and gray matter volume? *Neurobiology of Aging*, *33*(3), 617.e1-617.e9. https://doi.org/10.1016/j.neurobiolaging.2010.07.013

Leroy, K., Ando, K., Laporte, V., Dedecker, R., Suain, V., Authelet, M., Héraud, C., Pierrot, N., Yilmaz, Z., Octave, J.-N., & Brion, J.-P. (2012). Lack of Tau Proteins Rescues Neuronal Cell Death and Decreases Amyloidogenic Processing of APP in APP/PS1 Mice. *The American Journal of Pathology*, *181*(6), 1928–1940. https://doi.org/10.1016/j.ajpath.2012.08.012

Li, Y., Rinne, J. O., Mosconi, L., Pirraglia, E., Rusinek, H., DeSanti, S., Kemppainen, N., Någren, K., Kim, B.-C., Tsui, W., & de Leon, M. J. (2008). Regional analysis of FDG and PIB-PET images in normal aging, mild cognitive impairment, and Alzheimer's disease. *European Journal of Nuclear Medicine and Molecular Imaging*, *35*(12), 2169–2181. https://doi.org/10.1007/s00259-008-0833-y

Lin, F., Ren, P., Mapstone, M., Meyers, S. P., Porsteinsson, A., & Baran, T. M. (2017). The Cingulate Cortex of Older Adults with Excellent Memory Capacity. *Cortex; a Journal Devoted to the Study of the Nervous System and Behavior*, *86*, 83–92. https://doi.org/10.1016/j.cortex.2016.11.009

Lin, H., Chan, R. C. K., Zheng, L., Yang, T., & Wang, Y. (2007). Executive functioning in healthy elderly Chinese people. *Archives of Clinical Neuropsychology*, *22*(4), 501–511. https://doi.org/10.1016/j.acn.2007.01.028

Maccora, J., Peters, R., & Anstey, K. J. (2021). Gender Differences in Superior-memory SuperAgers and Associated Factors in an Australian Cohort. *Journal of Applied Gerontology*, *40*(4), 433–442. https://doi.org/10.1177/0733464820902943

Madden, D. J. (2007). Aging and Visual Attention. *Current Directions in Psychological Science*, *16*(2), 70–74. https://doi.org/10.1111/j.1467-8721.2007.00478.x

Maddock, R. J., Garrett, A. S., & Buonocore, M. H. (2001). Remembering familiar people: The posterior cingulate cortex and autobiographical memory retrieval. *Neuroscience*, *104*(3), 667–676. https://doi.org/10.1016/S0306-4522(01)00108-7

Maddock, R. J., Garrett, A. S., & Buonocore, M. H. (2003). Posterior cingulate cortex activation by emotional words: FMRI evidence from a valence decision task. *Human Brain Mapping*, *18*(1), 30–41. https://doi.org/10.1002/hbm.10075

Maillard, P., Carmichael, O., Fletcher, E., Reed, B., Mungas, D., & DeCarli, C. (2012). Coevolution of white matter hyperintensities and cognition in the elderly. *Neurology*, *79*(5), 442–448. https://doi.org/10.1212/WNL.0b013e3182617136

Mann, S. L., Hazlett, E. A., Byne, W., Hof, P. R., Buchsbaum, M. S., Cohen, B. H., Goldstein, K. E., Haznedar, M. M., Mitsis, E. M., Siever, L. J., & Chu, K.-W. (2011). Anterior and posterior cingulate cortex volume in healthy adults: Effects of aging and gender differences. *Brain Research*, *1401*, 18–29. https://doi.org/10.1016/j.brainres.2011.05.050

Margulies, D. S., Kelly, A. M. C., Uddin, L. Q., Biswal, B. B., Castellanos, F. X., & Milham, M. P. (2007). Mapping the functional connectivity of anterior cingulate cortex. *NeuroImage*, *37*(2), 579–588. https://doi.org/10.1016/j.neuroimage.2007.05.019

Melikyan, Z. A., Corrada, M. M., Dick, M. B., Whittle, C., Paganini-Hill, A., & Kawas, C. H. (2019a). Neuropsychological Test Norms in Cognitively Intact Oldest-Old. *Journal of the International Neuropsychological Society*, *25*(5), 530–545. https://doi.org/10.1017/S1355617719000122

Melikyan, Z. A., Corrada, M. M., Dick, M. B., Whittle, C., Paganini-Hill, A., & Kawas, C. H. (2019b). Neuropsychological Test Norms in Cognitively Intact Oldest-Old. *Journal of the International Neuropsychological Society*, *25*(05), 530–545. https://doi.org/10.1017/S1355617719000122

Mitchell, D. B., Brown, A. S., & Murphy, D. R. (1990). Dissociations between procedural and episodic memory: Effects of time and aging. *Psychology and Aging*, *5*(2), 264–276. https://doi.org/10.1037/0882-7974.5.2.264

Montine, T. J., Cholerton, B. A., Corrada, M. M., Edland, S. D., Flanagan, M. E., Hemmy, L. S., Kawas, C. H., & White, L. R. (2019). Concepts for brain aging: Resistance, resilience, reserve, and compensation. *Alzheimer's Research & Therapy*, *11*(1), 22. https://doi.org/10.1186/s13195-019-0479-y

Morris, J. C., & Price, J. L. (2001a). Pathologic correlates of nondemented aging, mild cognitive impairment, and early-stage Alzheimer's disease. *Journal of Molecular Neuroscience*, *17*(2), 101.

Morris, J. C., & Price, J. L. (2001b). Pathologic correlates of nondemented aging, mild cognitive impairment, and early-stage Alzheimer's disease. *Journal of Molecular Neuroscience*, *17*(2), 101.

Nilsson, L.-G. (2003). Memory function in normal aging. *Acta Neurologica Scandinavica*, *107*, 7–13.
Oh, H., Mormino, E. C., Madison, C., Hayenga, A., Smiljic, A., & Jagust, W. J. (2011). β-Amyloid affects frontal and posterior brain networks in normal aging. *NeuroImage*, *54*(3), 1887–1895. https://doi.org/10.1016/j.neuroimage.2010.10.027
Palomero-Gallagher, N., Hoffstaedter, F., Mohlberg, H., Eickhoff, S. B., Amunts, K., & Zilles, K. (2019). Human Pregenual Anterior Cingulate Cortex: Structural, Functional, and Connectional Heterogeneity. *Cerebral Cortex*, *29*(6), 2552–2574. https://doi.org/10.1093/cercor/bhy124
Panizzon, M. S., Fennema-Notestine, C., Eyler, L. T., Jernigan, T. L., Prom-Wormley, E., Neale, M., Jacobson, K., Lyons, M. J., Grant, M. D., Franz, C. E., Xian, H., Tsuang, M., Fischl, B., Seidman, L., Dale, A., & Kremen, W. S. (2009). Distinct Genetic Influences on Cortical Surface Area and Cortical Thickness. *Cerebral Cortex*, *19*(11), 2728–2735. https://doi.org/10.1093/cercor/bhp026
Pardo, J. V., Lee, J. T., Sheikh, S. A., Surerus-Johnson, C., Shah, H., Munch, K. R., Carlis, J. V., Lewis, S. M., Kuskowski, M. A., & Dysken, M. W. (2007). Where the brain grows old: Decline in anterior cingulate and medial prefrontal function with normal aging. *NeuroImage*, *35*(3), 1231–1237. https://doi.org/10.1016/j.neuroimage.2006.12.044
Pearson, J. M., Heilbronner, S. R., Barack, D. L., Hayden, B. Y., & Platt, M. L. (2011a). Posterior cingulate cortex: Adapting behavior to a changing world. *Trends in Cognitive Sciences*, *15*(4), 143–151. https://doi.org/10.1016/j.tics.2011.02.002
Pearson, J. M., Heilbronner, S. R., Barack, D. L., Hayden, B. Y., & Platt, M. L. (2011b). Posterior cingulate cortex: Adapting behavior to a changing world. *Trends in Cognitive Sciences*, *15*(4), 143–151. https://doi.org/10.1016/j.tics.2011.02.002
Perbal, S., Droit-Volet, S., Isingrini, M., & Pouthas, V. (2002). Relationships Between Age-Related Changes in Time Estimation and Age-Related Changes in Processing Speed, Attention, and Memory. *Aging, Neuropsychology, and Cognition*, *9*(3), 201–216. https://doi.org/10.1076/anec.9.3.201.9609
Prins, N. D., & Scheltens, P. (2015). White matter hyperintensities, cognitive impairment and dementia: An update. *Nature Reviews Neurology*, *11*(3), 157–165. https://doi.org/10.1038/nrneurol.2015.10
Pudas, S., Persson, J., Josefsson, M., Luna, X. de, Nilsson, L.-G., & Nyberg, L. (2013). Brain Characteristics of Individuals Resisting Age-Related Cognitive Decline over Two Decades. *Journal of Neuroscience*, *33*(20), 8668–8677. https://doi.org/10.1523/JNEUROSCI.2900-12.2013
Puzo, C., Labriola, C., Sugarman, M. A., Tripodis, Y., Martin, B., Palmisano, J. N., Steinberg, E. G., Stein, T. D., Kowall, N. W., McKee, A. C., Mez, J., Killiany, R. J., Stern, R. A., & Alosco, M. L. (2019). Independent effects of white matter hyperintensities on cognitive, neuropsychiatric, and functional decline: A longitudinal investigation using the National Alzheimer's Coordinating Center Uniform Data Set. *Alzheimer's Research & Therapy*, *11*(1), 64. https://doi.org/10.1186/s13195-019-0521-0
Raz, N., Ghisletta, P., Rodrigue, K. M., Kennedy, K. M., & Lindenberger, U. (2010). Trajectories of brain aging in middle-aged and older adults: Regional and individual differences. *NeuroImage*, *51*(2), 501–511. https://doi.org/10.1016/j.neuroimage.2010.03.020
Reiss, A. B., Arain, H. A., Stecker, M. M., Siegart, N. M., & Kasselman, L. J. (2018). Amyloid toxicity in Alzheimer's disease. *Reviews in the Neurosciences*, *29*(6), 613–627. https://doi.org/10.1515/revneuro-2017-0063

Rentz, D. M., Locascio, J. J., Becker, J. A., Moran, E. K., Eng, E., Buckner, R. L., Sperling, R. A., & Johnson, K. A. (2010). Cognition, reserve, and amyloid deposition in normal aging. *Annals of Neurology*, *67*(3), 353–364.

Resnick, S. M., Pham, D. L., Kraut, M. A., Zonderman, A. B., & Davatzikos, C. (2003). Longitudinal Magnetic Resonance Imaging Studies of Older Adults: A Shrinking Brain. *Journal of Neuroscience*, *23*(8), 3295–3301. https://doi.org/10.1523/JNEUROSCI.23-08-03295.2003

Riley, K. P., Snowdon, D. A., & Markesbery, W. R. (2002). Alzheimer's neurofibrillary pathology and the spectrum of cognitive function: Findings from the Nun Study. *Annals of Neurology*, *51*(5), 567–577. https://doi.org/10.1002/ana.10161

Robinson, J. L., Geser, F., Corrada, M. M., Berlau, D. J., Arnold, S. E., Lee, V. M.-Y., Kawas, C. H., & Trojanowski, J. Q. (2011). Neocortical and hippocampal amyloid-β and tau measures associate with dementia in the oldest-old. *Brain*, *134*(12), 3708–3715. https://doi.org/10.1093/brain/awr308

Rogalski, E. J. (2019). Don't forget—Age is a relevant variable in defining SuperAgers. *Alzheimer's & Dementia : Diagnosis, Assessment & Disease Monitoring*, *11*, 560–561. https://doi.org/10.1016/j.dadm.2019.05.008

Rogalski, E. J., Gefen, T., Shi, J., Samimi, M., Bigio, E., Weintraub, S., Geula, C., & Mesulam, M.-M. (2013a). Youthful Memory Capacity in Old Brains: Anatomic and Genetic Clues from the Northwestern SuperAging Project. *Journal of Cognitive Neuroscience*, *25*(1), 29–36. https://doi.org/10.1162/jocn_a_00300

Rogalski, E. J., Gefen, T., Shi, J., Samimi, M., Bigio, E., Weintraub, S., Geula, C., & Mesulam, M.-M. (2013b). Youthful Memory Capacity in Old Brains: Anatomic and Genetic Clues from the Northwestern SuperAging Project. *Journal of Cognitive Neuroscience*, *25*(1), 29–36. https://doi.org/10.1162/jocn_a_00300

Rosano, C., Aizenstein, H. J., Newman, A. B., Venkatraman, V., Harris, T., Ding, J., Satterfield, S., & Yaffe, K. (2012). Neuroimaging differences between older adults with maintained versus declining cognition over a 10-year period. *NeuroImage*, *62*(1), 307–313. https://doi.org/10.1016/j.neuroimage.2012.04.033

Rowe, C. C., Ng, S., Ackermann, U., Gong, S. J., Pike, K., Savage, G., Cowie, T. F., Dickinson, K. L., Maruff, P., & Darby, D. (2007a). Imaging β-amyloid burden in aging and dementia. *Neurology*, *68*(20), 1718–1725.

Rowe, C. C., Ng, S., Ackermann, U., Gong, S. J., Pike, K., Savage, G., Cowie, T. F., Dickinson, K. L., Maruff, P., & Darby, D. (2007b). Imaging β-amyloid burden in aging and dementia. *Neurology*, *68*(20), 1718–1725.

Rowe, J. W., & Kahn, R. L. (1997). Successful Aging. *The Gerontologist*, *37*(4), 433–440. https://doi.org/10.1093/geront/37.4.433

Salat, D. H., Buckner, R. L., Snyder, A. Z., Greve, D. N., Desikan, R. S., Busa, E., Morris, J. C., Dale, A. M., & Fischl, B. (2004). Thinning of the cerebral cortex in aging. *Cerebral Cortex*, *14*(7), 721–730.

Salthouse, T. A. (1996). The Processing-Speed Theory of Adult Age Differences in Cognition. *Psychological Review*, *103*(3), 403–428. Scopus. https://doi.org/10.1037/0033-295X.103.3.403

Schöll, M., Lockhart, S. N., Schonhaut, D. R., O'Neil, J. P., Janabi, M., Ossenkoppele, R., Baker, S. L., Vogel, J. W., Faria, J., Schwimmer, H. D., Rabinovici, G. D., & Jagust, W. J. (2016). PET Imaging of Tau Deposition in the Aging Human Brain. *Neuron*, *89*(5), 971–982. https://doi.org/10.1016/j.neuron.2016.01.028

Schretlen, D., Pearlson, G. D., Anthony, J. C., Aylward, E. H., Augustine, A. M., Davis, A., & Barta, P. (2000). Elucidating the contributions of processing speed, executive ability, and frontal lobe volume to normal age-related differences in fluid intelligence. *Journal of the International Neuropsychological Society*, *6*(1), 52–61. https://doi.org/10.1017/S1355617700611062

Schwarz, C. G., Gunter, J. L., Wiste, H. J., Przybelski, S. A., Weigand, S. D., Ward, C. P., Senjem, M. L., Vemuri, P., Murray, M. E., Dickson, D. W., Parisi, J. E., Kantarci, K., Weiner, M. W., Petersen, R. C., & Jack, C. R. (2016). A large-scale comparison of cortical thickness and volume methods for measuring Alzheimer's disease severity. *NeuroImage: Clinical*, *11*, 802–812. https://doi.org/10.1016/j.nicl.2016.05.017

Seo, S. W., Im, K., Lee, J.-M., Kim, S. T., Ahn, H. J., Go, S. M., Kim, S.-H., & Na, D. L. (2011). Effects of demographic factors on cortical thickness in Alzheimer's disease. *Neurobiology of Aging*, *32*(2), 200–209. https://doi.org/10.1016/j.neurobiolaging.2009.02.004

Sheline, Y. I., Raichle, M. E., Snyder, A. Z., Morris, J. C., Head, D., Wang, S., & Mintun, M. A. (2010). Amyloid Plaques Disrupt Resting State Default Mode Network Connectivity in Cognitively Normal Elderly. *Biological Psychiatry*, *67*(6), 584–587. https://doi.org/10.1016/j.biopsych.2009.08.024

Silbert, L. C., Nelson, C., Howieson, D. B., Moore, M. M., & Kaye, J. A. (2008). Impact of white matter hyperintensity volume progression on rate of cognitive and motor decline. *Neurology*, *71*(2), 108–113. https://doi.org/10.1212/01.wnl.0000316799.86917.37

Singer, T., Verhaeghen, P., Ghisletta, P., Lindenberger, U., & Baltes, P. B. (2003). The fate of cognition in very old age: Six-year longitudinal findings in the Berlin Aging Study (BASE). *Psychology and Aging*, *18*(2), 318–331. https://doi.org/10.1037/0882-7974.18.2.318

Smith, C. D., Chebrolu, H., Wekstein, D. R., Schmitt, F. A., & Markesbery, W. R. (2007). Age and gender effects on human brain anatomy: A voxel-based morphometric study in healthy elderly. *Neurobiology of Aging*, *28*(7), 1075–1087. https://doi.org/10.1016/j.neurobiolaging.2006.05.018

Stanislav, K., Alexander, V., Maria, P., Evgenia, N., & Boris, V. (2013a). Anatomical characteristics of cingulate cortex and neuropsychological memory tests performance. *Procedia-Social and Behavioral Sciences*, *86*, 128–133.

Stanislav, K., Alexander, V., Maria, P., Evgenia, N., & Boris, V. (2013b). Anatomical characteristics of cingulate cortex and neuropsychological memory tests performance. *Procedia-Social and Behavioral Sciences*, *86*, 128–133.

Steffener, J. (2021). Education and age-related differences in cortical thickness and volume across the lifespan. *Neurobiology of Aging*, *102*, 102–110. https://doi.org/10.1016/j.neurobiolaging.2020.10.034

Sun, F. W., Stepanovic, M. R., Andreano, J., Barrett, L. F., Touroutoglou, A., & Dickerson, B. C. (2016a). Youthful Brains in Older Adults: Preserved Neuroanatomy in the Default Mode and Salience Networks Contributes to Youthful Memory in Superaging. *Journal of Neuroscience*, *36*(37), 9659–9668. https://doi.org/10.1523/JNEUROSCI.1492-16.2016

Sun, F. W., Stepanovic, M. R., Andreano, J., Barrett, L. F., Touroutoglou, A., & Dickerson, B. C. (2016b). Youthful Brains in Older Adults: Preserved Neuroanatomy in the Default Mode and Salience Networks Contributes to Youthful Memory in Superaging. *Journal of Neuroscience*, *36*(37), 9659–9668. https://doi.org/10.1523/JNEUROSCI.1492-16.2016

Thambisetty, M., Wan, J., Carass, A., An, Y., Prince, J. L., & Resnick, S. M. (2010). Longitudinal changes in cortical thickness associated with normal aging. *NeuroImage*, *52*(4), 1215–1223. https://doi.org/10.1016/j.neuroimage.2010.04.258

Tisserand, D. J., Pruessner, J. C., Arigita, E. J. S., van Boxtel, M. P., Evans, A. C., Jolles, J., & Uylings, H. B. (2002). Regional frontal cortical volumes decrease differentially in aging: An MRI study to compare volumetric approaches and voxel-based morphometry. *Neuroimage*, *17*(2), 657–669.

Tombaugh, T. N. (2004). Trail Making Test A and B: Normative data stratified by age and education. *Archives of Clinical Neuropsychology: The Official Journal of the National Academy of Neuropsychologists*, *19*(2), 203–214. https://doi.org/10.1016/S0887-6177(03)00039-8

Torta, D. M., & Cauda, F. (2011). Different functions in the cingulate cortex, a meta-analytic connectivity modeling study. *NeuroImage*, *56*(4), 2157–2172. https://doi.org/10.1016/j.neuroimage.2011.03.066

Treitz, F. H., Heyder, K., & Daum, I. (2007). Differential course of executive control changes during normal aging. *Aging, Neuropsychology, and Cognition*, *14*(4), 370–393.

Tremont, G., Halpert, S., Javorsky, D. J., & Stern, R. A. (2000). Differential Impact of Executive Dysfunction on Verbal List Learning and Story Recall. *The Clinical Neuropsychologist*, *14*(3), 295–302. https://doi.org/10.1076/1385-4046(200008)14:3;1-P;FT295

Tubi, M. A., Feingold, F. W., Kothapalli, D., Hare, E. T., King, K. S., Thompson, P. M., & Braskie, M. N. (2020). White matter hyperintensities and their relationship to cognition: Effects of segmentation algorithm. *NeuroImage*, *206*, 116327. https://doi.org/10.1016/j.neuroimage.2019.116327

Vaidya, J. G., Paradiso, S., Ponto, L. L. B., McCormick, L. M., & Robinson, R. G. (2007a). Aging, grey matter, and blood flow in the anterior cingulate cortex. *Neuroimage*, *37*(4), 1346–1353.

Vaidya, J. G., Paradiso, S., Ponto, L. L. B., McCormick, L. M., & Robinson, R. G. (2007b). Aging, grey matter, and blood flow in the anterior cingulate cortex. *Neuroimage*, *37*(4), 1346–1353.

Van Petten, C., Plante, E., Davidson, P. S. R., Kuo, T. Y., Bajuscak, L., & Glisky, E. L. (2004). Memory and executive function in older adults: Relationships with temporal and prefrontal gray matter volumes and white matter hyperintensities. *Neuropsychologia*, *42*(10), 1313–1335. https://doi.org/10.1016/j.neuropsychologia.2004.02.009

Verhaeghen, P., & Salthouse, T. (1997). Meta-analyses of age-cognition relations in adulthood: Estimates of linear and nonlinear age effects and structural models. *Psychological Bulletin*, *122*, 231–249. https://doi.org/10.1037//0033-2909.122.3.231

Villar, D., Milman, S., Gao, T., Barzilai, N., & Weiss, E. F. (2021). A-17 Examining Cognitive Trajectories in SuperAgers within the LonGenity Study. *Archives of Clinical Neuropsychology*, *36*(6), 1058. https://doi.org/10.1093/arclin/acab062.35

Wang, X., Ren, P., Baran, T. M., Raizada, R. D. S., Mapstone, M., & Lin, F. (2019). Longitudinal Functional Brain Mapping in Supernormals. *Cerebral Cortex*, *29*(1), 242–252. https://doi.org/10.1093/cercor/bhx322

Wechsler, D. (1987). *WMS-R: Wechsler Memory Scale–Revised: Manual*. Psychological Corporation. https://books.google.com/books?id=Q2RIPwAACAAJ

Whittle, C., Corrada, M. M., Dick, M., Ziegler, R., Kahle-Wrobleski, K., Paganini-Hill, A., & Kawas, C. (2007). Neuropsychological data in nondemented oldest old: The 90+ Study. *Journal of Clinical and Experimental Neuropsychology*, *29*(3), 290–299. https://doi.org/10.1080/13803390600678038

Wilson, R. S., Beckett, L. A., Barnes, L. L., Schneider, J. A., Bach, J., Evans, D. A., & Bennett, D. A. (2002). Individual differences in rates of change in cognitive abilities of older persons. *Psychology and Aging*, *17*(2), 179–193. https://doi.org/10.1037/0882-7974.17.2.179

Winkler, A. M., Kochunov, P., Blangero, J., Almasy, L., Zilles, K., Fox, P. T., Duggirala, R., & Glahn, D. C. (2010). Cortical thickness or grey matter volume? The importance of selecting the phenotype for imaging genetics studies. *NeuroImage*, *53*(3), 1135–1146. https://doi.org/10.1016/j.neuroimage.2009.12.028

Wu, W., & Jia, F. (2013). A New Procedure to Test Mediation With Missing Data Through Nonparametric Bootstrapping and Multiple Imputation. *Multivariate Behavioral Research*, *48*(5), 663–691. https://doi.org/10.1080/00273171.2013.816235

Yaffe, K., Fiocco, A. J., Lindquist, K., Vittinghoff, E., Simonsick, E. M., Newman, A. B., Satterfield, S., Rosano, C., Rubin, S. M., Ayonayon, H. N., & Harris, T. B. (2009). Predictors of maintaining cognitive function in older adults: The Health ABC Study. *Neurology*, *72*(23), 2029–2035. https://doi.org/10.1212/WNL.0b013e3181a92c36

Yang, Z., Wen, W., Jiang, J., Crawford, J. D., Reppermund, S., Levitan, C., Slavin, M. J., Kochan, N. A., Richmond, R. L., Brodaty, H., Trollor, J. N., & Sachdev, P. S. (2016). Age-associated differences on structural brain MRI in nondemented individuals from 71 to 103 years. *Neurobiology of Aging*, *40*, 86–97. https://doi.org/10.1016/j.neurobiolaging.2016.01.006

Yao, Z., Hu, B., Liang, C., Zhao, L., & Jackson, M. (2012). A Longitudinal Study of Atrophy in Amnestic Mild Cognitive Impairment and Normal Aging Revealed by Cortical Thickness. *PLoS ONE*, *7*(11), Article 11. https://doi.org/10.1371/journal.pone.0048973

Yonelinas, A. P., Otten, L. J., Shaw, K. N., & Rugg, M. D. (2005). Separating the Brain Regions Involved in Recollection and Familiarity in Recognition Memory. *Journal of Neuroscience*, *25*(11), 3002–3008. https://doi.org/10.1523/JNEUROSCI.5295-04.2005

Yoshita, M., Fletcher, E., Harvey, D., Ortega, M., Martinez, O., Mungas, D. M., Reed, B. R., & DeCarli, C. S. (2006). Extent and distribution of white matter hyperintensities in normal aging, MCI, and AD. *Neurology*, *67*(12), 2192–2198. https://doi.org/10.1212/01.wnl.0000249119.95747.1f

Zhang, J., Andreano, J. M., Dickerson, B. C., Touroutoglou, A., & Barrett, L. F. (2020). Stronger Functional Connectivity in the Default Mode and Salience Networks Is Associated With Youthful Memory in Superaging. *Cerebral Cortex*, *30*(1), 72–84. https://doi.org/10.1093/cercor/bhz071