Episodic memory and executive function in familial longevity

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Dissertation

EPISODIC MEMORY AND EXECUTIVE FUNCTION IN FAMILIAL LONGEVITY

by

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DEDICATION

I would like to dedicate this work to Dr. Edith Kaplan who inspired my love of investigating brain-behavior relationships and taught me that 10 after 11 is the best time of the day.
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EPISODIC MEMORY AND EXECUTIVE FUNCTION IN FAMILIAL LONGEVITY

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ABSTRACT

Successful aging, the ability to resist age-associated illnesses and functional disability, is of increasing importance as the population ages. Studies have shown that exceptionally long-lived individuals fit the successful aging paradigm by compressing disability toward the end of life. This study investigated whether there is evidence of successful cognitive aging in a familial longevity cohort, the Long Life Family Study (LLFS). Part 1 describes the feasibility of conducting a 2.5 hour neuropsychological battery emphasizing episodic memory and executive function, cognitive domains that elicit signs of cognitive dysfunction in relation to normal aging and dementia. The rationale for the selected tests is discussed within the context of minimizing effects from sensory impairments in an aged cohort and optimizing qualitative and quantitative data. In Part 2, the testing of 70 proband generation and 100 offspring generation LLFS participants and 140 generation-matched referent participants without familial longevity is described. Comparison of LLFS proband generation participants with their referent cohort revealed no significant differences in test scores. However, the referent cohort also had more years of
education (an important exposure which is discussed in Part 3). LLFS offspring generation participants had borderline significant better performance on a test of executive function (Clock Drawing Test) and attention (Digits Forward) compared with referents. These findings suggest that familial longevity is associated with better cognitive function even at relatively young ages. Continuing to follow these cohorts to older ages may reveal differences in rate of change in cognitive function. Part 3 examines the role of indicators of cognitive reserve. In the proband generation education and participation in mid- and late-life cognitively stimulating activities were found to be higher in the referent cohort. This suggests that people without familial longevity may be more reliant on higher cognitive reserve in order to achieve similar cognitive performance to those from long-lived families. Implications of preserved cognitive function in long-lived families and the effect of cognitive reserve in those without familial longevity are discussed in terms of compression of disability and successful cognitive aging.
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LIST OF ABBREVIATIONS

ADLs ......................................................................................... activities of daily living
AD ........................................................................................... Alzheimer’s disease
AFU .......................................................................................... annual follow-up
APOE ........................................................................................ apolipoprotein E
BNT ........................................................................................... Boston Naming Test
BQSS .......................................................... Boston Qualitative Scoring System
BRIEF-A .......... Behavior Rating Inventory of Executive Function – Adult Version
CA ........................................................................................... cognitive activity
CES-D ................................... Center for Epidemiologic Studies Depression Scale
CDT ......................................................................................... Clock Drawing Test
CMS ............................................................................... Centers for Medicare and Medicaid Services
COWA .......................................................... Controlled Oral Word Association
CVD ....................................................................................... cardiovascular disease
CVLT-II .......................................................... California Verbal Learning Test – Second Edition
D-KEFS .......................................................... Delis-Kaplan Executive Function System
DSB ....................................................................................... Backward Digit Span
DSF ....................................................................................... Forward Digit Span
DUREL ........................................................... Duke University Religion Index
FAQ .......................................................... Functional Activities Questionnaire
FHS ........................................................... Framingham Heart Study
FLoSS .......................................................... Family Longevity Selection Score
GEE .......................................................... generalized estimating equations
HDL ............................................................................................... high-density lipoprotein
IADL .................................................. instrumental activities of daily living
LDL .......................................................... low-density lipoproteins
LLFS .......................................................... Long Life Family Study
MCI .............................................................. mild cognitive impairment
MMSE .......................................................... Mini-Mental State Examination
NAART .......................................................... North American Adult Reading Test
NAB .......................................................... Neuropsychological Assessment Battery
NECS .......................................................... New England Centenarian Study
NPI .............................................................. Neuropsychiatric Inventory
PSQI .......................................................... Pittsburgh Sleep Quality Index
ROCF .......................................................... Rey-Osterrieth Complex Figure
TICS .......................................................... Telephone Interview for Cognitive Status
VCI .............................................................. vascular cognitive impairment
WGN .......................................................... Word Generation test
WMS-III .................................................. Wechsler Memory Scale – Third Edition
CHAPTER ONE: BACKGROUND AND LITERATURE REVIEW

The world’s population is aging. According to the 2000 census, in the USA, people age 85 and older comprise the fastest growing segment of the population among those age 65 and older (Hetzel & Smith, 2001). Chronic age-related diseases and disabilities, including cognitive impairment, create financial burden and decrease quality of life for this age group; 42% of people age 65 and older reported a long-lasting medical condition or disability (Gist & Hetzel, 2004). However, studies of long-lived populations have shown that increased lifespan is not necessarily associated with additional years of disability but rather an increased health span (Andersen, Sebastiani, Dworkis, Feldman, & Perls, 2012; Terry, Sebastiani, Andersen, & Perls, 2008). Investigating the ability to escape or delay the onset of disease, physical disability, and cognitive dysfunction amongst centenarians and other long-lived populations could contribute to the underlying mechanisms and pathways of aging better.

Successful Aging

There is significant disagreement over the definition of successful aging. A review of 28 studies found 29 definitions of this concept and a large variance in the prevalence of successful agers from 0.4% to 95% depending upon the age range investigated and the criteria for successful aging used in each study (Depp & Jeste, 2006). Disability or impairment in physical function as measured by performance on activities of daily living (ADLs) was included in almost all
definitions of successful aging. Cognitive function was a feature of 45% of definitions. A commonly used definition by Rowe and Kahn defines successful aging as a lack of diseases and their risk factors, preserved cognitive and physical function and the full utilization of those functions, and participation in social and productive activities (Rowe & Kahn, 1997). This definition has been contentious in the Gerontology community given findings suggesting that many people remain independently functioning with high quality of life despite the presence of age-related disease(s).

Numerous risk factors for age-associated diseases and disability are modifiable. Better health habits such as exercising and not smoking are associated with lower rates of disability (Vita, Terry, Hubert, & Fries, 1998). Cognitive and physical function can be preserved and even enhanced with continual participation in cognitively and physically demanding activities (Manini & Pahor, 2009; Y. Stern, 2009). Additionally, social support and a sense of value to society through productivity have been associated with better function and lower mortality (Gruenewald, Karlamangla, Greendale, Singer, & Seeman, 2007). Therefore, a reasonable definition of successful agers would seem to be those older adults with or without disease that minimize their risk factors, maintain and fully exploit their cognitive and functional abilities, remain connected with society, and participate in activities with societal value.

A study using measurable variables that fit the more constrained Rowe & Kahn definition of successful aging in participants age 51 and older found that
less than 12% of the participants could be classified as aging successfully (McLaughlin, Connell, Heeringa, Li, & Roberts, 2009). Approximately 40% of the population had a major disease which excluded them from this successful aging classification. A review of studies using various definitions of successful aging in populations aged 60 years and older found that an average of 35% of participants met at least one of the definitions for successful aging (Depp & Jeste, 2006). The most consistent predictors of successful aging across studies were younger age, absence of arthritis and hearing problems, preserved ADLs, and being a nonsmoker (Depp & Jeste, 2006).

The prevalence of successful aging appears to be particularly lower amongst people living beyond their eighties. A study of 85-year-olds using a definition of successful aging consisting of good physical, social, and cognitive functioning as well as feelings of well-being found that only 10% met all the criteria (von Faber et al., 2001). Interestingly, 45% of 85-year-olds reported high levels of well-being whereas only 13% met the criteria for overall functioning. This finding indicates that many with physical and cognitive deficits still report good quality of life, satisfaction with life, and absence of loneliness. The authors suggest that the ability to effectively adapt to changes that occur with age may be a better definition of successful aging (von Faber et al., 2001).

Successful aging has also been related to health outcomes. Healthier aging in a large group of nuns age 76 and older, as measured by higher scores on cognitive tests, ADLs and self-rated function was associated with a decreased
risk of mortality (Tyas, Snowdon, Desrosiers, Riley, & Markesbery, 2007). Furthermore, 86% of those classified at the excellent level of healthy aging had no infarcts, plaques, or tangles upon neuropathological study.

**Longevity and Non-Dementia Age-Related Diseases**

Centenarians are an intuitive choice for studying longevity and have become increasingly more prevalent. They occur in 1 out of approximately 5800 people in the United States (U.S. Census Bureau, 2012) and may represent a group of successful agers as they have been shown to delay, escape, or survive better with age-associated diseases such as heart disease, stroke, and diabetes (Andersen et al., 2012; Evert, Lawler, Bogan, & Perls, 2003).

Twenty-one percent of Danish centenarians were found to have no indication of cardiac disease (Andersen-Ranberg, Schroll, & Jeune, 2001). Similarly, a group of predominantly male centenarians had significantly fewer medical conditions and lower prevalence of hypertension, chronic low back pain, angina, myocardial infarction, and diabetes than younger persons age 85 to 99 (Selim et al., 2005). In addition to a decreased prevalence of cancer, centenarians experienced more than a 17 year delay in the onset of cancer compared to the general population (Andersen et al., 2005). Hypertension or the use of antihypertensive medications was found in only 19% of centenarians (Gareri et al., 1996). However, a study of Danish centenarians found a hypertension prevalence of 52% yet centenarians were taking an average of only
three prescribed medications (Andersen-Ranberg et al., 2001). Analyses of blood samples from centenarians found that 79% maintained blood count and chemistry values within normal ranges (The Italian Multicentric Study on Centenarians (IMSC), 1998). While plaque formation in carotid arterial walls was found to increase with age, centenarians had lower levels of plaques compared to nonagenarians and instead had similar levels to octogenarians (Homma, Hirose, Ishida, Ishii, & Araki, 2001). An autopsy study of centenarians comparing them to younger elderly subjects age 75 to 95 found that centenarians had a lower prevalence of cancer (16.4% vs. 38.5%) and myocardial infarction (5.9% vs. 20.5%) (Motta et al., 2009). Danish centenarians were shown to have fewer hospitalizations and shorter hospital stays at all time points than people of the same birth cohort who died at younger ages (Engberg, Oksuzyan, Jeune, Vaupel, & Christensen, 2009). In fact, the proportion of individuals who were hospitalized as well as the length of stay decreased with increasing age groups from age 71 to 100+. Additionally, 8% of centenarians had no hospitalizations from age 71 to 100. This suggests an increased resistance to illness in people capable of achieving or having achieved extreme old age.

Supercentenarians, people age 110 and older, represent the true extreme in human longevity. Supercentenarians are exceptionally rare, e.g., a continually updated list of validated worldwide claims of living supercentenarians generally remains under 100 individuals at any given time (Coles, Muir, & Young, 2014). Yet, two phenotypic studies have been performed on this population. A case
series of 32 supercentenarians found a low prevalence of myocardial infarction (6%), cardiac arrhythmia (3%), stroke (13%), adult-onset diabetes mellitus (3%) and no cases of angina or chronic obstructive pulmonary disease (Schoenhofen et al., 2006). A case series of 12 supercentenarians found that 83% delayed the onset of age-associated illnesses until age 105 or older (D. C. Willcox et al., 2008). In addition, they found no cases of cancer, diabetes mellitus, or hyperlipidemia.

However, not all of those who are exceptionally long-lived escape the diseases associated with aging. One study found that 38% of centenarians could be classified as survivors because they were able to reach extreme old age even though they were diagnosed with an age-associated illness before the age of 80. Additionally, 43% of centenarians were classified as delayers because they were diagnosed with an age-associated illness from age 80 to 99 and 19% were designated as escapers, or those who did not have a diagnosis of an age-associated disease before the age of 100 (Evert et al., 2003).

Gender plays an important role in determining morbidity profiles. Among centenarians, women were more than twice as likely as men to be survivors and men were more than twice as likely as women to be escapers (Evert et al., 2003). A study of Canadian community-dwelling nonagenarians found that men had higher self-rated health as well as a lower prevalence of arthritis, hypertension, and physical limitations compared to women (Wister & Wanless, 2007). This suggests that there are different sex-specific pathways to reaching
extreme old age involving mechanisms to prevent age-associated disease, postpone the onset of disease, or create increased resilience to disease.

**Compression of morbidity and disability**

Fries (2002) proposed that because human life span is fixed at around 100 years, those who live to approximately that age should compress the time in which they have age-related diseases towards the ends of their lives. Fries’ hypothesis regarding the compression of morbidity has been proven to be correct, though for individuals living to 100, but rather for those who live to even older and much rarer ages that truly approximate the limit of human lifespan (Andersen et al., 2012). Supercentenarians (ages 110+ years) are relatively close to the age of maximum human lifespan which is currently 122 years. In fact, on average and remarkably, they spend only the last 5 years of their lives with age-related diseases. Sixty-nine percent of supercentenarians are escapers (no age-related diseases at age 100 years) compared with 30% of centenarians who live to 100 to 104 years (Andersen et al., 2012).
Figure 1. Delayed age of onset of morbidity and compression of morbidity.


Left: the morbidity-free survival curves reveal the progressive delay in morbidity with increasing age of survival. Controls appear in black, nonagenarians in red, centenarians in green, semi-supercentenarians in blue, and supercentenarians in turquoise. Morbidity was defined as the presence of either cancer, cardiovascular disease, dementia, diabetes, or stroke.

Right: The boxplot displays the percentage of years spent with disease for each age group. Only deceased participants were included in this analysis.
Although compression of morbidity is not as ubiquitous among the nonagenarians and centenarians, other pathways of successful aging are evident. A study of centenarians who were diagnosed with an age-associated disease before age 85 still noted a marked delay in the age of onset of disability (Terry et al., 2008). Seventy-two percent of the centenarian males and 34% of the females had ADL scores in the independent range indicating maintained functional independence in the presence of chronic illness. Similarly, in another study, autonomous centenarians, those that were living in the community, cognitively intact, and functionally independent, had a similar number of comorbidities on average compared to those not fulfilling the criteria of autonomy (Andersen-Ranberg et al., 2001).

Some cross-sectional studies of centenarians, however, have noted high rates of disability. A study of 24 centenarians found that all had at least some impairment on instrumental activities of daily living (IADLs) or ADLs (Xie, Matthews, Jagger, Bond, & Brayne, 2008) and 92% of Italian centenarians were found to be dependent in IADLs with 73% having severe dependency (Motta et al., 2008). The discrepancy in disability rates between these studies could be explained in part by a healthy volunteer effect in some studies. This is clearly an issue for the New England Centenarian Study. Another cause for bias could be different assessment tools for functional status and different levels of sensitivity for disability. Still, one can conclude that a substantial subset of centenarians demonstrate that disability is not inevitable with increased life span. A study of
informant-rated ADLs among nonagenarians and centenarians found that 29% of those age 90 to 94 and 3% of centenarians had no difficulty in ADLs (Berlau, Corrada, & Kawas, 2009). Furthermore, when participants were assessed requiring help in performing six commonly assessed ADLs they found that 56% of those age 90 to 94 and 8% of centenarians did not require any help (Berlau, Corrada, & Kawas, 2009).

As noted earlier, among the centenarians enrolled in the New England Centenarian Study, duration of disability was compressed, along with morbidity with increasing age. Centenarians, regardless of their comorbidities, have been found to maintain their functional independence late in life with 89% scoring in the independent range on ADLs at a mean age of 92 (Hitt, Young-Xu, Silver, & Perls, 1999). A longitudinal study of Danish nonagenarians found that 30-40% of the cohort was independent from age 92 to 100 (Christensen, McGue, Petersen, Jeune, & Vaupel, 2008). In the Danish study, prevalence of independence modestly declined from 39% at age 92 to 33% at age 100. Those with greater disability had higher mortality rates, and therefore, there was a selection for subjects remaining alive who had higher levels of independence. A study of two nonagenarian cohorts in Denmark born 10 years apart from one another found that the later cohort born in 1915 had higher Mini-Mental State Examination (MMSE) scores and other cognitive tests scores even after adjustment for differences in education between the cohorts (Christensen et al., 2013). There were mixed results with regard to physical function measures. These findings
may suggest that cognitive function, as opposed to physical function, is a
stronger predictor of increased longevity in later cohorts.

Most supercentenarians also compress their disability towards the end of
their lives. Forty-one percent of supercentenarians were found to perform in the
independent or minimal assistance range of an ADLs questionnaire
(Schoenhofen et al., 2006). At age 100, 73% were living in the community with
family and 89% were independent in ADLs (D. C. Willcox et al., 2008). Male
supercentenarians showed the greatest delay in age of onset of physical function
impairment by maintaining on average, ADL scores in the independent range up
to almost 110 years of age (see Figure 2). They also delayed the onset of
moderate impairment on a general memory test until almost 108 years. Like the
age-related compression of morbidity, one also observed an age-related
compression of physical and cognitive disability.
Figure 2. Delayed age of physical function and cognitive impairment.


Figures 2a and 2b show the trajectories of physical (Barthel Activities of Daily Living Index) and cognitive (Blessed Information-Memory-Concentration Test) functional declines by age group.
Therefore, centenarians can be regarded as a model of successful aging based upon their compression of disability well into their nineties. Successful aging in terms of compression of morbidity appears to apply more to centenarians achieving older ages such as 105+ years. Because most supercentenarians compress both disability and morbidity towards the end of their lives, they are phenotypically, and likely genetically, more homogeneous which might also mean that this is a powerful sample of individuals for discovering factors that determine such extreme successful aging. Such discoveries may help the general population live a greater proportion of their lives independently and in good health.

Familial nature of longevity

The familial nature of longevity suggests a significant genetic component. The siblings of centenarians have a 50% reduction in mortality across their life spans compared to birth cohort-matched referent groups (Perls et al., 2002; B. J. Willcox, Willcox, He, Curb, & Suzuki, 2006). Female siblings of centenarians were found to live 6 years longer and male siblings 2.5 years longer than siblings of those who lived to average life expectancy in the United States (Perls, Bubrick, Wager, Vijg, & Kruglyak, 1998). This difference in lifespan was even greater for siblings of Okinawan centenarians as male and female siblings lived approximately 12 years longer on average than the general population (B. J. Willcox et al., 2006). Female siblings had a 2 to 3 times increased probability of
becoming a nonagenarian and male siblings had a 5 times increased probability (Perls et al., 1998; B. J. Willcox et al., 2006). As the survival advantage increases at extreme old ages, female siblings of centenarians had an 8 times greater probability and males a 17 times greater probability of reaching age 100 compared to a similar birth cohort (Perls et al., 2002).

Siblings of supercentenarians have also been shown to have an older mean age at death compared to their U.S. birth cohort with male siblings adding an extra 13.7 years to their lives and female siblings gaining 9.9 years (Perls et al., 2007). In addition, fathers of supercentenarians attained a mean age at death 4 years older and mothers 8.4 years older than their birth cohorts.

Offspring of centenarians have also been found to be predisposed to longevity (Atzmon et al., 2004). Longitudinal studies of these offspring allow for prospective examination of rates of change in clinical phenotypes associated with aging or longevity and the incidence of age-related diseases. Similar to centenarians, offspring of centenarians have demonstrated better cardiovascular health compared to their spouses or controls with evidence of reduced prevalence of myocardial infarction, hypertension, stroke, and diabetes mellitus (Atzmon et al., 2004; Terry, Wilcox, McCormick, & Perls, 2004; Westendorp et al., 2009). In addition to lower prevalence of age-related illnesses, there is also a delay in the onset of age-related diseases by 2 to more than 8 years (Terry et al., 2004). Over a mean follow-up period of 3.5 years, centenarian offspring were 86% less likely to have incident diabetes mellitus, 78% less likely to have a
myocardial infarction, 83% less likely to have a stroke, and showed a decreased risk of mortality compared with a referent cohort (Adams, Nolan, Andersen, Perls, & Terry, 2008). The centenarian offspring also have lipid profiles that are indicative of greater protection against atherosclerotic cardiovascular disease compared to their spouses and age-matched controls (Barzilai, Gabriely, Gabriely, Iankowitz, & Sorkin, 2001). Female offspring of centenarians had a 20% higher high-density lipoprotein (HDL) cholesterol level and male offspring of centenarians had a 35 to 50% lower plasma level of low-density lipoprotein (LDL) cholesterol.

Following evidence for a strong genetic component to familial longevity and potentially to successful aging, cohorts of familial longevity are now being evaluated. The National Institute on Aging-funded Long Life Family Study (LLFS) is a cohort of families with unusual clustering for exceptional longevity with the aim to evaluate genetic and environmental contributions to exceptional survival (Newman et al., 2011). Individuals from long-lived families tended to have lower pulmonary disease, diabetes, and peripheral arterial disease compared to similarly aged cohorts not selected for familial longevity. They also have more favorable lipid profiles and pulse pressures. Results have been mixed for other age-associated diseases depending on the comparison cohorts. A comparison of the proband generation of LLFS to a control group without familial longevity found a sex-specific increase in disease-free survival from age-associated diseases of 2 to over 20 years depending on the specific disease,
with diabetes, hypertension and cancer showing the greatest gains (Sebastiani et al., 2013).

**Cognition in Exceptional Longevity**

Until recently, the conventional wisdom was that the risk of dementia increases with age and markedly so at extreme age, such that all people, by the time they reach 100 years of age, should have some form of dementia (Kliegel, Moor, & Rott, 2004). Instead, evidence that centenarians delay and in some cases, even escape dementia indicates that they may be a model of resistance to neurodegenerative disease (Perls, 2004). Cognitive impairment is associated with increased mortality in older adults as a whole (Langa et al., 2008) and in those over age 95 (Borjesson-Hanson, Gustafson, & Skoog, 2007). However, among centenarians, the picture is less clear. Kliegel et al. (2004) found a small but statistically significant decline in cognition in centenarians 6 months prior to death. The authors suggest that this indicates a reduction in the terminal decline effect (Wilson, Beckett, Bienias, Evans, & Bennett, 2003) of cognitive function in older age groups. Perhaps cognitive impairment is not as strong an indicator of mortality in centenarians as in younger age groups because centenarians are able to survive better with cognitive dysfunction, or have preserved cognitive function even with significant amounts of underlying pathology.
Prevalence of dementia amongst centenarians

Dementia prevalence rates show high variability ranging from 50 to 100 percent in centenarians because of differences in sample selection and methods of determining dementia diagnoses (Calvert, Hollander-Rodriguez, Kaye, & Leahy, 2006). However, a meta-analysis of studies investigating dementia prevalence found a leveling off in prevalence rates at age 95 with 40% of nonagenarians having dementia (Ritchie & Kildea, 1995). Similarly, a study of people age 90 and older selected from a community in California using various indicators of dementia found that 45% of women and 28% of men had dementia (Corrada, Brookmeyer, Berlau, Paganini-Hill, & Kawas, 2008). Important gender differences exist, with men at these ages having better cognitive function and a lower prevalence of dementia than women (note, however, that there are far fewer men as well) (Franceschi et al., 2000).

Global cognition

Brief tests of global cognition are the most commonly used means of assessing cognitive impairment in the oldest old. Seventy-nine percent of centenarians tested with a brief, global cognitive measure were found to have some cognitive impairment (Evert et al., 2003). Similarly a study using the Mini-Mental State Examination (MMSE, Folstein, Folstein, & McHugh, 1975) found that 74% of nonagenarians and 87% of centenarians had some cognitive impairment (a score of less than 26) (Xie et al., 2008). Other centenarian studies
have shown a more positive assessment. Mild or no impairment on the MMSE was found in 54% of a group of Italian centenarians (Motta et al., 2008) and in 41% of German centenarians (Kliegel et al., 2004). However, MMSE studies of cognition in centenarians have shown considerable heterogeneity with scores ranging from zero to perfect performance (Kliegel et al., 2004). This heterogeneity is also observed for change in cognition over time. Twenty-five percent of centenarians were found to experience a decline in MMSE score over 1.5 years, 14% improved, and 61% remained stable, although 33% of those who remained stable had scores of zero at both time points (Kliegel et al., 2004).

Neuropsychological studies

Neuropsychological studies beyond the scope of mental status tests are rare in centenarians due to inherent difficulties in testing this population (e.g., hearing, vision, and motor impairments, and fatigue) (Silver, Jilinskaia, & Perls, 2001). However, a neuropsychological battery was administered to a population-based sample 74 centenarians living in the Boston area and 24% did not have dementia (CDR=0 or 0.5) (Silver, Newell, Brady, Hedley-White, & Perls, 2002). Rates of dementia in other studies have been lower. A study of the oldest old in England and Wales used the MMSE and a diagnostic interview for neuropsychiatric symptoms and found that 30% of nonagenarians and 44% of centenarians had dementia (Xie et al., 2008). A study assessing cognitive function of people age 90 and older using neuropsychological tests administered
in-person found that only 18% of men and 39% of women had dementia (Corrada et al., 2008). However, it must be noted that prevalence assumptions based on in-person assessments may be biased because those with more impairment are unable to participate.

The Georgia Centenarian Study clustered centenarian test performance results from their sample and found that the best fit was a two class model in which the low cognitive performance group had neuropsychological test scores of 1 standard deviation below the mean and the high performing group had test scores at about 0.5 standard deviations above the mean across tests (Davey et al., 2013). In another study comparing performance on individual cognitive processes, researchers found that centenarians without cognitive impairment performed worse on tests of fluency and abstraction and were much slower to complete tasks compared to a referent group with a mean age of 65 (Luczywek et al., 2007). The differences between the two groups were not significant for tests of visual memory, judgment, and problem solving. This implies, in contrast with the Georgia Centenarian Study, that there is not a decline in all aspects of cognitive function but rather some specific processes may be well preserved at very old ages. The differences in cognitive function abilities indicate the importance of testing various cognitive domains and processes in the oldest old.
Neuropathological studies

Neuropathological studies of centenarians have confirmed that Alzheimer’s disease (AD) is not a necessary consequence of achieving old age (Imhof et al., 2007). A neuropathological study of 14 centenarians found that only six of the fourteen had significant AD pathology, one had Pick’s disease, and one had hippocampal sclerosis (Silver et al., 2002). Ding and colleagues (2006) also found that 6 out of 32 centenarian brains had no indication of a significant neuropathological process. Furthermore, it was found that the neuropathology did not always correlate with the clinical diagnosis. Two out of six people with neuropathological indications of AD had no dementia upon clinical testing within one year of their deaths, suggesting the presence of cognitive reserve which allowed these centenarians to maintain their function in spite of neuropathological insults (Silver et al., 2002). Additionally, the opposite pattern was found in four patients that had dementia upon clinical testing but showed very limited signs of the neuropathological hallmarks of AD. One patient had Pick’s disease, one had hippocampal sclerosis, and two had depression that was suspected to result in clinical dementia. These findings suggest that rarer forms of neurodegenerative processes as well as depression and medical illness may be important contributors to or causes of cognitive impairment in centenarians. Another study examining the correlation of neuritic plaques and tangles to clinical dementia severity ratings found a significant but much lower degree of correlation between neuropathology and neuropsychological
examination in people age 90 to 107 years of age compared to those 60 to 80 years old (average r=0.26 and r=0.67 respectively) (Haroutunian et al., 2008). Similarly, Savva and colleagues (2009) found that although hippocampal and neocortical volumes decreased with age in those with or without clinical dementia, neuritic plaques and neurofibrillary tangles increased with age only in those without clinical dementia prior to death. In those with clinical dementia, the density of neuritic plaques and neurofibrillary tangles remained the same or decreased with increasing age indicating a decreased association of AD pathology with clinical dementia at older ages compared to younger ages. Although senile plaques are common in the neocortex of centenarians, they do not correlate with clinical severity as closely as in younger age groups (Giannakopoulos et al., 1995). Gold and colleagues (2000) found that Braak and Braak staging of neurofibrillary tangle involvement correlated with clinical dementia severity overall, however, neurofibrillary tangle levels causing clinical dementia in younger age groups did not predict cognitive impairment in some nonagenarians and centenarians. A study of non-demented nonagenarians and centenarians found that plaque and tangle staging did not predict performance on a general cognitive measure and a word list delayed recall task or change in cognitive performance over time (Balasubramanian, Kawas, Peltz, Brookmeyer, & Corrada, 2012). While microscopic infarcts were common in centenarians (92%) cerebral amyloid angiopathy was only found in only 54% and was milder than younger AD cases (Itoh, Yamada, Suematsu, Matsushita, & Otomo, 1998).
These studies indicate that the exceptionally old may have a different clinical-neuropathological relationship than younger people. Moreover, there may be other psychological processes such as depression, acute illness, or environmental factors that may account for their dementia-like symptoms.

Alternatively, different neuropathological processes may be occurring in this age group that are very rare in younger age groups or perhaps that have not yet been discovered. For instance, in a group of older individuals with a mean age of 90, greater mean capillary diameter was found to be associated with lower clinical dementia severity scores even after adjusting for neurofibrillary tangles, whereas amyloid volume, a typical pathological hallmark of AD, was not associated with dementia severity (Bouras et al., 2006).

**Cognition in Familial Longevity**

Findings of better cognitive function in association with familial longevity have begun to emerge from the LLFS. Subjects in the proband generation have a significantly lower risk of severe dementia and a later age of onset compared with controls not selected for longevity (Sebastiani et al., 2013). The offspring of probands had a lower risk of cognitive impairment compared with spouse controls (Cosentino et al., 2013) Analysis of neuropsychological test performance in the LLFS found higher MMSE scores in the proband generation compared with similarly aged cohorts (Newman et al., 2011). Both the proband and offspring generations showed better scores on the Digit-Symbol Substitution, a test of processing speed and sustained attention. In addition, the offspring generation
performed significantly better on tests of attention, working memory, and verbal fluency compared with their spouses (Barral et al., 2012). Another study of familial longevity found better performance on a picture learning test and a task requiring inhibition among offspring of families with nonagenarian siblings compared with the spouses of the offspring (Stijntjes et al., 2013). The Framingham Heart Study (FHS) analyzed cognitive performance of offspring of participants in the study and found that those with at least one parent who lived to age 85 years or older had better attention scores but no differences were found in other domains (Murabito et al., 2013). In addition, offspring with parental longevity showed slower decline in attention, executive function, and visual memory over time.

Factors Associated With Resistance to Dementia

Health habits

Lack of exercise has been associated with poorer cognitive function. Low levels of physical activity at an average age of 61 were associated with greater impairment on tests of executive function and immediate episodic memory (Sabia et al., 2009). Additionally, low physical activity five years earlier was associated with lower executive function scores. However, level of physical activity at a mean time point of 17 years earlier was not significantly associated with cognitive function. A longitudinal study found that although levels of physical activity were not predictive of cognitive decline, a higher level of physical activity at any given
time point was associated with better test scores at that same time point (Bielak, Cherbuin, Bunce, & Anstey, 2014). Exercise may also have a protective effect. In men with low strength and functional ability, higher levels of physical activity were shown to be associated with a 50% decreased risk of dementia (Taaffe et al., 2008). Similarly, in comparing those with higher levels of physical activity to those with low levels, a meta-analysis found a 28% reduced risk of unspecified dementia and a 45% reduced risk of AD (Hamer & Chida, 2009). A separate study found a reduced risk of vascular dementia even after adjusting for cardiovascular risk factors (Ravaglia et al., 2008). Studies of cognitive change in older people found that those who participated in moderate exercise at least once per week, or who had activity levels of walking or more vigorous activities at least three times per week, were more likely to show no change or some improvement over time rather than a decline on a brief test of global cognition (Middleton, Mitnitski, Fallah, Kirkland, & Rockwood, 2008; Yaffe et al., 2009). Even in the oldest old, increased physical activity is also associated with delayed physical disability and lower mortality (Stessman, Hammerman-Rozenberg, Cohen, Ein-Mor, & Jacobs, 2009). Furthermore, high physical activity is associated with approximately a 20% decrease in the risk for developing cardiovascular disease (CVD) as well as a delay in the onset of CVD of more than three years (Nusselder, Franco, Peeters, & Mackenbach, 2009).

Lack of sleep and the presence of sleep disorders can also affect neuropsychological test performance. A higher risk of cognitive impairment on a
general cognitive measure and a mental tracking task was associated with several indicators of greater sleep disturbance (Blackwell et al., 2006). On the other hand, total sleep time of more than 8 hours compared with 7 to 8 hours of sleep was associated with lower cognitive function scores (Blackwell et al., 2011). Assessment of quality of sleep prior to the onset of cognitive impairment revealed a greater likelihood of cognitive impairment for those with sleep-disordered breathing at baseline (Yaffe et al., 2011). Poorer sleep quality was also associated with a higher risk of Alzheimer’s disease (Lim et al., 2013). Furthermore, better sleep quality was shown to lower the risk of Alzheimer’s disease associated with apolipoprotein E (APOE) genotype and the risk of baseline cognitive impairment and cognitive decline in relation to APOE genotype. Good quality sleep may also play a role in longevity as centenarians have been found to be night sleepers who sleep an average of 7.5 hours at night, 1.5 hours during the day, and fall asleep quickly, traits that were consistent throughout life (Spadafora et al., 1996). However, 43% of centenarians experienced sleep disorders (Tafaro et al., 2007). Furthermore, in those who tended to be awake at night and slept throughout the daytime, MMSE scores were significantly lower compared to those with less severe or no sleep disturbances.
Social networks and connectedness

Social networks have been shown to be related to better cognitive performance. Greater participation in activities with a social component and perception of availability of social support were found to be associated with a composite measure of neuropsychological test performance, however, size of social network was not associated (Krueger et al., 2009). Another study of participation in activities with a social component in an aged cohort found better cognitive performance in those with higher participation as well as reduced cognitive decline over time (James, Wilson, Barnes, & Bennett, 2011). Number of social network ties has also been associated with decreased probability of cognitive decline over time (Bassuk, Glass, & Berkman, 1999) as well as decreased risk of dementia (Crooks, Lubben, Petitti, Little, & Chiu, 2008). Another study found that although size of social networks was not associated with neuropsychological test scores, it did have a mediating effect on the association between neurofibrillary tangles and cognition, particularly for test performance in the domains of episodic memory, semantic memory, working memory, and perceptual speed (Bennett, Schneider, Tang, Arnold, & Wilson, 2006).

Size of social network and frequency of contact among centenarians was found to be significantly lower in those living in nursing homes compared with those living in private homes or assisted-living facilities (Randall et al., 2010). Whether placement in a nursing home is a result of a smaller social network or a
smaller social network is associated with functional declines that necessitate a move to a nursing home remains to be determined. Nonetheless, size of social network may have important implications in maintaining health and independence in longevity.

Religiosity and spirituality are types of social networks and are associated with feelings of connectedness. Those with higher levels of religiosity have been shown to have personality characteristics, health habits, and social networks that lend themselves to greater longevity (McCullough, Friedman, Enders, & Martin, 2009). A study of patients with Alzheimer’s disease found that those with high religiosity at baseline showed no cognitive decline on a test of general cognition, whereas those with low religiosity significantly declined over one year (Coin et al., 2010). Similarly, a slower rate of decline over follow-up was found for AD patients with higher spirituality and greater participation in private religious activities (Kaufman, Anaki, Binns, & Freedman, 2007).

The creation of social networks and religious and spiritual ties may provide a healthy support system that helps one reach old age. Social interactions engage the mind and give a sense of purpose. Larger social networks also provide an emotional support system. Alternatively, people who are more socially active, religious, and spiritual may have personality characteristics that also lead to better health and social habits.
Cognitive reserve

Resistance to AD in long-lived populations has been speculated to result in part from the building of cognitive reserve. The hypothesis of cognitive reserve suggests that some people have more resilient cognitive networks and/or the ability to invoke the use of alternate cognitive networks and processes following damage to existing networks allowing for the preservation of overall cognitive function (Y. Stern, 2009). It is suggested that cognitive reserve results from some innate abilities such as native intellect but is also gained from experiences over the entire lifetime such as education, occupation, and leisure activities (Y. Stern, 2009).

Other concepts regarding ability to maintain cognitive function in spite of neuronal insult have also emerged. Brain reserve refers to differences in the ability to withstand damage to the brain based on a measurable index such as brain volume or neuronal count (Satz, 1993; Satz, Cole, Hardy, & Rassovsky, 2011). Greater brain reserve results in a greater threshold of brain insult that must be achieved to result in functional impairment, whereas less brain reserve lowers the threshold for functional impairment with the same amount of damage. Recently, the distinction has been made that brain reserve is in itself a changing variable as the brain is able to adapt at the neuronal level to damage (Satz et al., 2011). The cognitive reserve theory attempts to explain the lack of association between functional impairment and neuropathology (Barulli & Stern, 2013). It suggests that the ability to more efficiently use existing networks, or recruit
additional networks, underlies the lack of association between functional
impairment and neuropathology, such that individuals with the same brain size
and degree of neuropathology may have different levels of cognitive reserve and
therefore, different functional outcomes (Y. Stern, 2002). This theory focuses on
neural activity rather than neuronal or brain structure and is more affected by life
experiences than the brain reserve model (Barulli & Stern, 2013). However, it is
likely that brain reserve and cognitive reserve are intertwined concepts since
exposures that increase cognitive reserve (e.g., participation in cognitively
stimulating activities) are known to also result in changes at the structural level of
the brain.

The cognitive reserve theory has been expanded to include proposed
origins which are divided into two processes (Y. Stern, 2006). Neural reserve is
described as the efficiency of using neural networks, the capacity of the networks
to process demanding tasks, and flexibility of neural network selection. Neural
reserve is based on both predetermined abilities and modification by
environmental exposure. The second process is neural compensation in which
those with higher cognitive reserve are able to recruit additional networks in
instances of brain pathology or cognitively demanding tasks.

The scaffolding theory of cognitive aging is a concept similar to neural
compensation in that it suggests that alternate neural networks that are
complimentary but less efficient than primary networks are recruited in the
presence of neuronal insult or disruption (Park & Reuter-Lorenz, 2009) However,
this theory builds on the neural compensation concept by suggesting that these alternate neural networks can be created but also diminished with cognitive training.

Another concept related to successful cognitive aging is brain maintenance. Instead of explaining individual differences in the association of functional impairment and neuropathology, brain maintenance focuses on the innate or experiential differences that are protective against damage to brain structures and function (Nyberg, Lovden, Riklund, Lindenberger, & Backman, 2012). However, a recent study found that higher education and intellectual ability were related to cognitive performance when decline in gray matter was held constant, suggesting that cognitive reserve rather than brain maintenance is more highly associated with preserved cognitive function (Steffener et al., 2014). It must be noted that the average age of older adults in this study was a relatively young 65 years. Therefore, this does not preclude the role of brain maintenance in successful cognitive aging but suggests that cognitive reserve may be a more prevalent phenomenon in the general population.

As the concepts of brain reserve and brain maintenance are tied to neuronal integrity and function, they require analysis by neuropathological or neuroradiological studies. Therefore, analysis of cognitive reserve is better suited to the present study. Studies of cognitive reserve have shown that low premorbid IQ (Schmand, Smit, Geerlings, & Lindeboom, 1997), lower educational attainment (Caamano-Isorna, Corral, Montes-Martinez, & Takkouche, 2006), and
less occupational complexity (Y. Stern et al., 1994) are associated with increased risk of dementia. A meta-analysis of 22 studies found that high cognitive reserve was associated with a 46% decrease in the risk of incident dementia (Valenzuela & Sachdev, 2006). A neuroimaging study of younger (age 70-80) and older (age 90 and older) adults showed that group differences in atrophy of the brain were larger than group differences in performance on cognitive tests, suggesting that there is a cognitive reserve process occurring in longer-lived adults (Beeri et al., 2009). A study of healthy elders investigated the association of proxies of cognitive reserve including premorbid IQ, educational and occupational attainment, and lifetime participation in creative, physical, and social activities with structural and functional imaging (Sole-Padulles et al., 2009). They found that higher cognitive reserve proxies were associated with larger whole-brain volume and decreased activation suggesting better brain function in healthy elderly.

Several factors have been shown to be proxies of cognitive reserve including education, occupational complexity, and leisure activities. Those with higher education were found to have a decreased risk of cognitive impairment but an increased risk of 2-year mortality (Langa et al., 2008). This suggests a protective effect of education in preventing the onset of cognitive impairment but a sharper decline after its onset. One must also be aware that older birth cohorts, particularly those before 1915, generally had less than 12 years of education. Furthermore, education is obtained from lifetime experiences in
addition to formal education. Therefore, quality of education, rather than years of education, may be a more reliable substitute for estimating baseline functioning and higher cognitive reserve in older persons. A study of quality of education as measured by reading level found that low literacy was associated with lower baseline function and greater decline in cognitive functions over time (Manly, Schupf, Tang, & Stern, 2005; Manly, Touradji, Tang, & Stern, 2003). Additionally, literacy was a better predictor of decline than years of education.

Consideration of occupational demands and complexity during one’s lifetime is essential in assessing the level of cognitive reserve. Occupations often involve additional vocational training as well as physical demands, interpersonal relations, intellectual capacity, and interaction with people, data, and things such as machines, tools, and substances. A study of occupational complexity found better cognitive performance in older adults who had occupations with greater reliance on general intellect and interpersonal relations even when controlling for education and intelligence in young adulthood (Potter, Helms, & Plassman, 2008). Using the commonly accepted practice of coding occupational complexity as complexity of interactions with data, people, and things, it was found that complexity with data and people were associated with better MMSE scores at an average age of 83 (Andel, Kareholt, Parker, Thorslund, & Gatz, 2007). Similarly, a decreased risk of dementia was found for those with high lifetime job complexity with people or things compared with low complexity among a sample of people over age 65 (Kroger et al., 2008). In
contrast, two studies have shown that occupations with higher physical activity are associated with increased risk of dementia. Perhaps this is because occupations with higher levels of physical activity also have low levels of complexity in interacting with people, data and things (Kroger et al., 2008; Potter et al., 2008). The beneficial effect of complexity in one’s occupation may not affect all workers equally. Potter and colleagues (2008) found that those with lower intellect in young adulthood had a stronger association between occupations with high intellectual demands and better performance on cognitive tests later in life compared to those with higher intellect as young adults. Duration of occupation is also important in assessing cognitive reserve as increased complexity with people and things was associated with decreased risk of dementia only in those with more than 23 years in their principal occupation (Kroger et al., 2008).

Engaging in activities with intellectual, creative, physical, and social aspects during leisure time can also increase cognitive reserve. Those with greater participation in leisure activities perform better on tests of memory, processing speed, executive function, and visuospatial ability (Saczynski et al., 2008; Wilson, Barnes, & Bennett, 2003) and show less of a decline in global measures of cognition, memory and perceptual speed over time (Wilson, Bennett et al., 2003; Wilson, Mendes de Leon et al., 2002; Wilson, Scherr, Schneider, Tang, & Bennett, 2007). Participation in a greater variety of leisure activities was found to be associated with reduced risk for dementia even when controlling for
education, occupation, and health conditions and limitations (Scarmeas, Levy, Tang, Manly, & Stern, 2001). However, it seems that not all leisure activities have the same effect. A 95% decreased risk of AD was found for people who had higher levels of novel activities such as learning new skills and hobbies, and a 30% decreased risk for those with higher levels of engaging in discussions (Fritsch, Smyth, Debanne, Petot, & Friedland, 2005). However, no change in AD risk was found for social activities in this study. Similarly, participation in leisure activities with a cognitive component was associated with a reduced risk of AD but participation in physical activities and passive activities was not (Akbaraly et al., 2009; Verghese et al., 2003; Wilson, Mendes de Leon et al., 2002; Wilson et al., 2007). Frequency of participation in leisure activities has an important role as those with the highest frequency of leisure activities have been shown to have a 50% or greater reduced risk for AD compared to those with the lowest frequency (Akbaraly et al., 2009; Verghese et al., 2003). Furthermore, it appears that participation in activities in early and late life are independently associated with cognitive performance (Wilson et al., 2005) and dementia risk (Wilson et al., 2007) such that those with a lower frequency of activities with a cognitive component at either time point have more cognitive impairment and an increased risk of dementia in late life. Associations between leisure activities and pathology have also been noted. Saczynski and colleagues (2008) examined a subgroup of participants with the highest levels of subcortical or periventricular white matter lesions on imaging and found that those with higher levels of leisure activity had
better processing speed than those with low levels of leisure activity. Their research suggests that cognitive reserve created by participating in leisure activities can modify the effects of pathology. Although pathology and preclinical dementia may be responsible for lower leisure activity involvement, studies omitting participants with an onset of dementia at the first follow-up or mild cognitive impairment (MCI) at baseline still found that increased leisure activity was associated with reduced risk of AD, suggesting that preclinical AD may not be causing the observed lower levels of leisure activity (Akbaraly et al., 2009; Verghese et al., 2003). Another study found that measures of cognitively stimulating leisure activities at baseline were not related to levels of neuropathological hallmarks of dementia at autopsy (Wilson et al., 2007). Additionally, the presence of MCI at baseline was not predictive of decreases in cognitive activity over time providing evidence that decreased leisure activity is not simply a result of the dementia course. These studies of cognitive reserve support the notion that cognitive ability is a malleable entity that continues to develop throughout the adult lifespan.

A buildup of cognitive reserve is believed to delay the onset of incident dementia by allowing preservation of function in the presence of substantial pathology. Those with a similar amount of pathology and lower cognitive reserve would experience levels of cognitive dysfunction warranting a diagnosis of dementia. Studies of the association between neuropathology in AD and cognitive reserve have found that years of formal education modifies the
relationship between neuritic and diffuse plaques and cognitive impairment, such
that those with more years of formal education have less cognitive impairment for
a given amount of pathology compared to those with fewer years of formal
education (Bennett et al., 2003). Additionally, pathology as indicated by lower
cerebral blood flow particularly in the temporal lobe and parietotemporal region is
associated with indices of higher cognitive reserve including higher education,
higher premorbid IQ, greater occupational complexity, and more leisure activities
when controlling for clinical severity (Hanyu et al., 2008; Scarmeas et al., 2003;
Y. Stern et al., 1995). Similarly, in patients with MCI or AD it was found that
higher cognitive reserve was associated with smaller brain volume and higher
brain activation when controlling for MMSE score. The reverse was true in
controls, indicating preserved function in the presence of greater
neurodegeneration (Sole-Padulles et al., 2009). In patients with high levels of β-
amyloid deposition there was an effect of education such that only those with
post-college education did not perform significantly worse than those with low
levels of β-amyloid deposition (Roe et al., 2008). This indicates that those with
higher cognitive reserve are able to function at the same level as those with
lower cognitive reserve even though they have more underlying pathology.

Cognitive reserve also affects the trajectory of cognitive decline after
dementia diagnosis. Increasing dementia pathology results in death. As such,
there is a compression of cognitive morbidity in those with higher cognitive
reserve as they postpone the onset of incident dementia toward the stable
endpoint of death. This results in a faster cognitive decline after the onset of diagnosed dementia (Y. Stern, 2009). Studies of cognitive reserve have demonstrated this phenomenon. In those with incident dementia, a greater frequency of participation in leisure activities was associated with a delay in the onset of accelerated memory decline as well as a faster memory decline after onset compared to those with less frequent participation in leisure activities (Hall et al., 2009). Furthermore, higher cognitive reserve has been associated with a faster and more widespread distribution of decrease in cerebral blood flow over time (Hanyu et al., 2008).
CHAPTER TWO: FEASIBILITY OF THE CURRENT STUDY

The New England Centenarian and Long Life Family Study investigators, including this author, hypothesize that long-lived individuals experience a compression of cognitive morbidity and disability by postponing the onset of cognitive impairment and minimizing the clinical impact of underlying neuropathology. However, previous studies of cognition in long-lived cohorts have relied on global measures such as the MMSE or shortened versions of neuropsychological tests which limit the ability to accurately characterize the neuropsychological profile of exceptional longevity. In addition centenarians can be difficult to study due to physical frailty as well as severe and multiple sensory deficits (Motta et al., 2008; Silver et al., 2001).

Previous studies have shown that there is a reduced risk of AD among family members of non-demented very old individuals (age 90+) compared to family members of younger non-demented elderly individuals of various age groups between 60 and 89 years (Silverman et al., 2008). The genetic factors that are protective of cognitive function in the oldest old are likely enriched relative to the general population due to demographic selection. New England Centenarian and Leiden Longevity data suggest that these nonagenarians and centenarians have just as high a prevalence of disease (including dementia) associated genetic variants as the general population. A famous exception to this rule is the APOE e-4 allele which is less common in the extreme old, but several studies have shown that the risk associated with this allele and
Alzheimer’s disease is much less if not negligible in the extreme old compared to people in their 60’s and 70’s. One possibility for the decreased risk could be the presence of protective variants that mitigate the pathological significance of the e-4 allele. More generally, there is growing evidence that the presence of many other disease associated genetic variants in the extreme old is countered by the presence of many protective genetic variants. Such variants are hypothesized to slow aging and decrease risk for many age-related diseases including those that cause dementia. Silverman and colleagues (2008) have proposed that the best sample of humans for studying the genetics of successful cognitive aging is families with reduced rates of dementia. These types of families are the target sample of the Long Life Family Study.

In this study we seek to determine whether participants of the LLFS have a reduced risk of cognitive impairment (not limited to dementia risk). Studying long-lived populations that demonstrate successful aging can help us to identify factors that preserve cognitive function and facilitate the escape from or compression of cognitive morbidity and disability towards the end of life. In addition, findings of a reduced risk of cognitive impairment in families selected for longevity compared to sporadic long-lived individuals would support studying this group to study discover genetic and other familial factors that predispose for successful cognitive aging.
The Long Life Family Study

The Long Life Family Study is a multi-center, National Institute on Aging-funded (grant U01-AG23755) research project founded in 2004 as a collaboration between Boston University Medical Center, Columbia University, University of Pittsburgh, University of Southern Denmark, and Washington University St. Louis to investigate familial factors contributing to exceptional longevity and healthy aging. Enrollment of a family required that siblings of the proband (oldest living) generation exceed a score of at least 7 on the Family Longevity Selection Score (FLoSS). The FLoSS is based upon combined survival probabilities of siblings that are calculated from birth cohort-specific life tables. The resultant 539 families that were enrolled in the LLFS are very rare and fewer than 0.2% of families in the Framingham Heart Study would qualify to be enrolled in the LLFS (Sebastiani et al., 2009). Individuals in the families who died from accident, injury, or war, or before the age of 40 did not contribute to the calculation of the FLoSS. A bonus weight was added to the calculated FLoSS for siblings who were alive at the time of enrollment because they would therefore be available for study.

Additionally, eligibility for the study required at least two living siblings over the age of 79 and an offspring, all of whom were willing to participate in an in-person data collection visit. Mailing lists of people over the age of 79 and who lived within 3-hours driving of each of the study centers were obtained from the Centers for Medicare and Medicaid Services (CMS) and local voter registries. These individuals were administered a screening questionnaire to determine the
ages and vital status of their siblings. FLoSS scores were calculated from these screening data and if the other enrollment criteria were met (the presence of the minimum triad), along with a FLoSS >7, then the family was asked to enroll in the LLFS. Spouses of all participants were recruited as controls. Enrollment consisted of 539 families and 4953 individuals (134 families and 1,285 individuals at the Boston field center) from 2006 to 2009. In-person data collection included sociodemographic and medical history, physical function questionnaires, performance, anthropomorphic, blood pressure, and lung function measurements as well as cognitive, mood, and personality assessments. Blood samples were collected for DNA isolation and standard laboratory analyses. Participants complete a follow-up phone questionnaire to update health, physical, and cognitive status (using the Telephone Interview for Cognitive Status (TICS)) on a yearly basis.

A separate family study of nonagenarian siblings by Westendorp and colleagues (2009) has shown a 0.59 lower mortality risk compared to sporadic nonagenarians further supporting the utility of family studies with long-lived siblings for studying various phenotypes associated with longevity and determining, if possible, their environmental and genetic determinants.

Analyses of data from the short neuropsychological battery administered at the in-home assessment of participants of the LLFS have revealed a cognitive benefit to being part of a long-lived family. Proband generation participants were shown to have better scores on the MMSE and Digit Symbol Substitution Test
compared with participants of the same age-range in the Cardiovascular Heart Study (CHS) as well as better MMSE scores compared with FHS participants of the same age-range (Newman et al., 2011). Offspring generation family members were found to perform better on the MMSE compared with participants from FHS and better on the Digit Symbol Substitution Test compared with CHS participants and offspring spouses enrolled in LLFS. An analysis within the LLFS found that offspring generation family members performed better on forward digit span (DSF), backward digit span (DSB), and verbal fluency for vegetables compared with their spouses (Barral et al., 2012). Another analysis developed an algorithm using tests administered in both the LLFS and as part of the National Alzheimer’s Coordinating Center Uniform Data Set to classify individuals with probable AD and healthy controls (Cosentino et al., 2013). The algorithm was then applied to the LLFS family members and spouse controls to classify participants as having mild cognitive impairment consistent with Alzheimer’s disease. The test scores used in the algorithm were delayed logical memory, orientation to time and place, animal fluency, and the digit symbol test. Application of the algorithm revealed that offspring of the proband had a reduced risk of cognitive impairment compared with their spouses and probands had a reduced non-significant risk of cognitive impairment. More extensive neuropsychological testing of these participants is required to investigate individual domains of cognitive function and preservation of specific cognitive
processes in long-lived individuals, particularly in the domains of attention, working memory, episodic memory, and executive functions.

**Cognitive Impairment in Normal Aging and Dementia**

Although impairments may be seen in various domains and cognitive processes in normal aging and neuropathological conditions such as dementia, the two most common areas of impairment are deficits in episodic memory and executive function. This study assessed these domains in detail.

**Episodic memory**

Impairments in episodic memory remain part of the diagnostic criteria for amnestic mild cognitive impairment and AD, the most common form of dementia (Dubois et al., 2007). Episodic memory involves remembering events with a specific time and place (Lezak, Howieson, Loring, Hannay, & Fischer, 2004). Impairments can arise in immediate recall of information or recall after an intervening time span. Retrieval cues may help recall in some situations. In those with impaired recall of previously presented information after a delay, preserved recognition suggests a deficit in retrieval of memories rather than a loss of information.

Declines in episodic memory are seen in normal aging. In a population of healthy older adults age 50 to 90 increased age was associated with a greater decline in memory after both a short and long delay (Charlton, Barrick, Markus, &
Morris, 2010). Studies of incident dementia have shown an early impairment of episodic memory tasks that is measurable several years before the onset of clinical AD or vascular dementia (Backman & Small, 2007; Blacker et al., 2007). The Religious Orders Study found that impairment on tests of episodic memory at baseline including immediate and delayed recall of story paragraphs and word lists in MCI patients was associated with a 2.45 times increase in risk of AD compared to people with impairment in other domains over a mean follow-up period of 5 years (Aggarwal, Wilson, Beck, Bienias, & Bennett, 2005). Similarly, performance on tests of episodic memory including word lists, complex figures, and visual reproductions was found to be lower in people who progressed to AD compared to controls as well as those with cognitive impairment that did not meet the criteria for dementia over the follow-up period (Albert, Blacker, Moss, Tanzi, & McArdle, 2007). Furthermore, episodic memory declined faster during the follow-up time in converters compared to nonconverters (Albert et al., 2007). A faster rate of cognitive decline in other domains such as semantic memory and visuospatial abilities has also been associated with episodic memory deficits at baseline (Aggarwal et al., 2005).

Episodic memory dysfunction has been associated with increased densities of senile plaques in those without a clinical diagnosis of dementia or mild cognitive impairment (Price et al., 2009). Therefore, decreased episodic memory performance may help reveal the neuropathological process of preclinical AD. In normal aging, deficits in visual and verbal episodic memory
were shown to occur in association with hippocampal atrophy (Head, Rodrigue, Kennedy, & Raz, 2008). However, atrophy of the lateral prefrontal cortex was also shown to be associated with decreased episodic memory using a model in which increasing age is associated with executive dysfunction including decreased inhibition, working memory, and switching leading to impaired episodic memory. Therefore, deficits in episodic memory may occur via different pathways in various populations.

Tests of episodic memory

Performance on list-learning tasks such as the California Verbal Learning Test–Second Edition (CVLT-II, Delis, Kramer, Kaplan, & Ober, 2000) gives information about learning over trials, retention over a delay, and the ability to retrieve information based on cues. Patients with MCI and vascular cognitive impairment (VCI) were found to have impaired immediate and delayed recall and recognition on a word list learning task compared to controls (de Jager, Hogervorst, Combrinck, & Budge, 2003; Thomann, Toro, Dos Santos, Essig, & Schroder, 2008). Impaired initial recall and retention over time was found in patients with very mild AD compared to controls (Baudic et al., 2006). VCI patients also showed reduced rates of learning over trials (de Jager et al., 2003). Lower performance on the CVLT was shown to be associated with increased risk of progression from normal cognition to mild impairment (Blacker et al., 2007). Story recall tests, such as the Wechsler Memory Scale-Third Edition (WMS-III,
Wechsler, 1997) Logical Memory I & II, are commonly used as measures of episodic memory. Normal aging, MCI, and very mild AD have been associated with lower recall of information from a paragraph compared to controls (Baudic et al., 2006; Bennett et al., 2002; de Jager et al., 2003; Weintraub et al., 2009).

Memory of visually presented information has also been used to test episodic memory. Performance on the copy, immediate, and delayed conditions of the Rey-Osterrieth Complex Figure was found to decrease with normal aging (Mitrushina, Boone, Razani, & D'Elia, 2005; Ostrosky-Solis, Jaime, & Ardila, 1998). Those with mild cognitive impairment in the memory domain and in multiple cognitive domains were shown to have impaired immediate and delayed recall of the complex figure compared to healthy older adults with no cognitive impairment (Lopez et al., 2006). Other tests of visual learning and memory have demonstrated impairments in at least 20% of participants with VCI (Sachdev et al., 2004). MCI patients had impaired visuospatial memory for a placing test compared to controls (de Jager et al., 2003).

The Boston Naming Test (BNT, Kaplan, Goodglass, & Weintraub, 2001) is a test of confrontation naming that assesses semantic memory rather than episodic memory. Participants are shown a line drawing of an object and asked to produce the name of the object. Performance on this test has been shown to decrease with both increasing age and lower educational attainment (Zec, Burkett, Markwell, & Larsen, 2007). However, decreases associated with normal aging are much smaller than those associated with AD progression. Patients
with MCI and VCI have shown impaired BNT performance compared to controls without cognitive impairment (de Jager et al., 2003; Thomann et al., 2008).

Executive function

Studies have shown that deficits in executive function are often seen in normal aging (Jurado & Rosselli, 2007; Wilson, Beckett et al., 2002), cognitively impaired groups (Brandt et al., 2009), and early or mild dementia (Lafleche & Albert, 1995), and can precede impairments in other domains such as memory (Carlson, Xue, Zhou, & Fried, 2009). However, the term executive function refers to a heterogeneous group of cognitive processes as well as control over functions in other cognitive domains (Royall et al., 2002). Executive functions comprise the processes that allow us to carry out goal-directed activities which range from complex processes such as organizing, planning, problem-solving, and judgment to more automatic processes of attentional control and inhibition (R. A. Stern, Andersen, & Gavett, 2011). Not surprisingly, neuropsychological tests of executive function are not able to encompass all of the individual processes under the umbrella of executive function, so performance on these tests can be highly variable. Neuropsychological tests have been found to rely on the various processes of executive function to different degrees and these subcomponents of function may differ by age group or clinical population due to different strategies for completing executive tests (Brandt et al., 2009; Burgess, Alderman, Evans, Emslie, & Wilson, 1998; Hull, Martin, Beier, Lane, & Hamilton,
Miyake and colleagues (2000) selected nine executive tasks that were related to one of three theoretical underlying processes: shifting, updating, or inhibiting. Tests that required the same process correlated well with each other but there was a low correlation among all measures collectively. This suggests that there is heterogeneity in executive processes that are required to complete all of the tasks administered (Miyake et al., 2000). Miyake and colleagues then examined the role of shifting, updating, and inhibiting in complex executive tasks. There was a varying reliance upon those specific executive processes such that the number of perseverative responses on a card sorting task required shifting processes, generation of random numbers required inhibiting and updating processes, and performance on a dual task was not significantly predicted by any of the three factors. The selectivity of executive functions for certain tests may result in part from the fact that there are distinct subcortical pathways connecting the frontal lobes and the thalamus that subserve the executive processes (Royall et al., 2002). The dorsolateral prefrontal circuit is associated with performance on more complex executive functions such as planning, organizing, and working memory, the lateral orbitofrontal circuit with inhibition of behaviors and reward decisions, and the anterior cingulate circuit with error detection and correction.

Decline in executive functions is the predominant feature of cognitive change in normal aging presumably due to changes in frontal-striatal systems including degradation of white matter, preferential atrophy of the frontal cortex,
and depletion of dopamine neurotransmitters (for review, see Buckner, 2004; Gunning-Dixon, Brickman, Cheng, & Alexopoulos, 2009). More specifically, tests of working memory, cognitive flexibility, and reasoning have been shown to decline with increasing age (Charlton et al., 2008). Deficits in executive function in normal aging are believed to be the primary cause of deficits in other domains due to decreased executive control (Royall et al., 2002).

Executive dysfunction may also be indicative of MCI or early dementia. MCI patients, even those with single domain amnestic MCI, have been found to have deficits in executive function (Brandt et al., 2009). Furthermore, studies of MCI patients who convert to AD have also shown that executive function impairment is characteristic of prodromal AD (Albert et al., 2007). However, not all executive functions are affected. In investigating specific executive functions, planning/problem solving and working memory tasks were found to be impaired in MCI patients compared to controls, however, there were no differences in judgment (Brandt et al., 2009).

In addition to indicating cognitive function, performance on tests of executive function has been related to other health outcomes. It is a predictor of disability in performing ADLs (Mitchell & Miller, 2008) as well as a predictor of survival (Ghisletta, 2008). In addition, a neuropathological study of participants without dementia or MCI found that poorer performance on a tests of executive functions were associated with increased density of senile plaques and neurofibrillary tangles (Price et al., 2009). These results indicate that executive
dysfunction may be a sign of underlying pathology before a formal diagnosis of cognitive impairment.

Tests of executive function

Various tests have been used to elucidate changes in executive function in normal aging, MCI and incident dementia. Performance on tests of mental control or working memory such as backward digit spans (DSB, Lezak et al., 2004, pp. 359-360) has been shown to decline with increasing age in those without cognitive impairment (Charlton et al., 2008; Weintraub et al., 2009). DSB performance is also lower in older adults with MCI compared to those with no cognitive impairment (Bennett et al., 2002). Interestingly, those who developed probable AD over a span of 13 years performed better on DSB at baseline compared to those who did not develop AD (Linn et al., 1995).

Another process under the heading of executive functions, verbal fluency, is the ability to generate alternative responses based on a phonemic or semantic cue or a given set of letters (Strauss, Sherman, & Spreen, 2006, pp. 499-526). Deficits on tests of verbal fluency have been seen in normal aging, MCI, VCI, AD and in mixed neurological samples (Bennett et al., 2002; de Jager et al., 2003; Iverson, Williamson, Ropacki, & Reilly, 2007; Weintraub et al., 2009). More specifically, impaired phonemic fluency was seen in preclinical AD and vascular dementia compared with controls, and those with preclinical AD also showed impaired semantic fluency (Jones, Laukka, & Backman, 2006). Similarly, another
study showed impaired phonemic and semantic fluency in very mild AD (Gomez & White, 2006). Deficits in phonemic and semantic fluency were seen in at least 30% of those with vascular mild cognitive impairment (Sachdev et al., 2004).

Tests of more complex executive functions such as problem-solving, conceptualization, and abstraction have been used less frequently. Performance on a sorting test was lower in those age 80 or older compared to those younger than 80 (Royall, Chiodo, & Polk, 2003). Additionally, those with very mild AD had impaired performance compared to controls as well as a greater number of perseverations (Baudic et al., 2006).

Although traditionally considered to be a test of visuospatial functioning, the Clock Drawing Test (CDT, Strauss et al., 2006, pp. 972-983) also requires intact executive functioning (Freedman et al., 1994). Planning and organization are required to properly place the numbers on the clock face within the contour, and conceptualization is required to transform a given numeric time into a representation of time displayed by the placement of clock hands of varying lengths. Performance on the CDT has been shown to decrease with increasing age even when controlling for MMSE score or an estimate of premorbid IQ (Hubbard et al., 2008). Older participants without cognitive impairment had impaired placement of the clock components and did not properly distinguish between hand lengths (von Gunten et al., 2008). Performance on the CDT has been shown to be impaired in populations with MCI and vascular cognitive impairment compared with controls without cognitive impairment (de Jager et al.,
2003; Thomann et al., 2008; Zhou & Jia, 2008). In conjunction with the MMSE, it was found to have a 94% specificity. Another test of visuoconstructional ability, the Rey-Osterrieth Complex Figure Test (ROCF, Corwin & Bylsma, 1993; Osterrieth, 1944) can be used for assessing impairments in executive function. Impairments in planning can lead to fragmentation of the figure and poor strategy in the sequence of drawing the figure components (R. A. Stern et al., 1999). Perseverative behavior in drawing the complex figure can also represent executive dysfunction and a deficit in self-monitoring while completing a task. Better organization on the ROCF has been associated with preserved performance on other tests of executive function processes such as working memory, verbal fluency, set shifting, mental flexibility and abstraction (Somerville, Tremont, & Stern, 2000).

**Covariates in the Oldest Old**

**Age**

Although the proposed study is directed at investigating cognitive function in long-lived individuals indicative of a restricted age range, age has been shown to be a confounder in subgroups of nonagenarians and centenarians (Whittle et al., 2007). A negative correlation between age and performance was found on MMSE, Modified Mini-Mental State Examination, BNT, Animal Fluency, CVLT, CDT, and DSB and the Trail Making Test. Several of these tests or alternate
versions will be used in the proposed study indicating the need to account for age in the analyses.

Sex

Sex has been shown to have an effect on neuropsychological test performance in the oldest old. In studies using global measures of cognitive function in centenarians, men have better preserved cognitive function than women, perhaps because male centenarians need to be more robust to reach extreme old age (Calvert et al., 2006; Terry et al., 2008). On more extensive neuropsychological testing, women age 90 and older performed better than nonagenarian and centenarian men on measures of global cognition, learning, memory, and attention (Whittle et al., 2007). The effect of sex on neuropsychological test performance differs in the very old compared to younger old age groups (Proust-Lima et al., 2008). At age 65 women and men had similar cognitive decline, but at older ages women had greater cognitive decline than men specifically on a global cognitive measure and a test of psychomotor speed. Dementia prevalence varies by sex in the oldest old as well (Corrada et al., 2008). Women age 90 and older were found to have a dementia prevalence of 39% whereas in men it was only 18%. Furthermore, the prevalence doubled every five years for women but stayed stable over time for men.
Education

The correlation of education and neuropsychological test performance across ages is well documented. In older cohorts, Whittle et al. (2007) found that higher education was associated with better performance on tests of general cognitive ability, verbal fluency, confrontation naming, and clock drawing in a cohort of people over the age of 90. Performance on a series of learning and episodic memory tests in another sample of nonagenarians showed associations with education only for delayed recall of a word list but not facial recognition, learning measures, or delayed recall of objects (Hassing, Wahlin, & Backman, 1998).

Sensory and motor function

There are several factors that need to be taken into consideration when developing a neuropsychological test battery for the oldest old. Although an extensive test battery yields a more reliable description of cognitive function compared to using only a few, brief cognitive tests, one must also limit the duration of the testing session to reduce fatigue and encourage high participation rates. As sensory disturbances are common in the oldest old, attempts to reduce testing demands on vision, hearing, and motor function must be made. Furthermore, because vision and hearing loss have been shown to be associated with cognitive impairment in older adults (Clay et al., 2009) and in nonagenarians
and centenarians (Yue et al., 2009), both must be assessed at the testing session for possible confounding of the data.

**Study Hypotheses**

Hypothesis 1: Individuals from long-lived families will have better preserved cognitive function compared to referent groups. Proband generation LLFS participants will have better neuropsychological test scores than participants matched on age, sex, and region and not selected for evidence of familial longevity. Offspring generation LLFS participants will have better neuropsychological test scores than their spouses who are not genetically related to long-lived families.

Hypothesis 2: Episodic memory, which is targeted in the early stages of AD and other neurological conditions involving the hippocampus, will be better preserved in participants from long-lived families. LLFS participants will perform better than referent groups on CVLT-II, ROCF, and WMS-III Logical Memory, particularly on the delayed recall portions of the tests. Hypothesis 3: As executive functions show the earliest declines in normal aging and in many pathological conditions, members of long-lived families will show higher overall scores on the Sorting Test from Delis-Kaplan Executive Function System (D-KEFS, Delis, Kaplan, & Kramer, 2001), Word Generation (WGN) test from the Neuropsychological Assessment Battery (NAB, Robert A. Stern & White, 2003), ROCF, DSB, the CDT, and verbal fluency.
Study Aims

Aim 1: Recruit and enroll proband generation participants of the LLFS and age- and region-matched controls for participation in a 2.5-hour neuropsychological evaluation focused on tests of episodic memory and executive functions for characterization of the neuropsychological profile of long-lived individuals. Neuropsychological test scores of the LLFS proband generation will be compared to the controls who represent long-lived individuals not selected for evidence of familial longevity.

Aim 2: Recruit and enroll offspring and spouse controls of the LLFS for a 2.5-hour neuropsychological evaluation. Neuropsychological test scores of the offspring generation will be compared to spouse control participants of the LLFS. Spouse controls reflect participants not selected for longevity who share many environmental factors with LLFS offspring during adulthood and tend to be similar in birth cohort and sociodemographic factors.

Aim 3: Evaluate the underlying mechanisms of preserved cognitive function in long-lived individuals such as health habits, religiosity and spirituality, and social networks. Proxies of cognitive reserve including estimated intellectual ability, occupational complexity, and leisure activities will also be assessed. Data from LLFS proband generation participants and their referent controls will be combined to assess whether these factors are associated with neuropsychological test performance.
Methods

Study population

Participants were selected from the LLFS Boston field center cohort. Participants in the older generation (probands and siblings over age 79) are administered a yearly extended follow-up questionnaire after their initial participation. The offspring generation is administered a short form yearly follow-up and the extended follow-up questionnaire every third year after their initial participation in the LLFS. The extended follow-up consists of questionnaires to update physical and health status as well as administration of a brief global measure of cognition, the TICS, and a dementia questionnaire. Proband generation, offspring generation, and offspring spouse participants living within 3 hours of Boston were asked at the conclusion of the extended telephone follow-up to participate in an in-home neuropsychological assessment study within the following six weeks. Recruitment began in December 2010 and is ongoing. Participants who were unable to hear over the phone sufficiently to complete the TICS or unable to read due to vision impairment were excluded from participation in order to minimize sensory impairments in the study sample. Participants with a neurological diagnosis known to significantly impair neuropsychological test performance other than stroke were omitted. Participants who were willing to participate within one month and determined to have capacity to consent were enrolled into the study at the in-person visit.
As normative neuropsychological test data for very old ages (90+) are limited, age-, sex-, and region-matched participants were recruited for the referent cohort to the LLFS proband generation. Potential participants of the LLFS who were screened for participation in the main study but found to be ineligible due to a low FLoSS score (<7) were contacted for participation in this ancillary study. Beginning in July 2011, those living within 3 hours of Boston with a FLoSS of less than 5 at the time of screening for LLFS were mailed an introductory letter describing the study with a reply form to indicate interest. Those that did not reply within two weeks were followed up with by telephone to determine interest. Following confirmation of interest in participating in the study, participants for the proband generation referent cohort were described the study in detail and a capacity to provide consent was determined. Those without the capacity to consent, inability to conduct the conversation by telephone due to hearing impairment, or self-reported inability to read due to vision impairment were ineligible for participation in the cognitive function study. Those who were interested and able to provide informed consent were mailed consent forms for enrollment in to the study. After receiving a properly signed consent form by mail, a telephone interview was conducted to collect sociodemographic and medical history information and to administer the TICS. These items were obtained from LLFS participants at the baseline interview and follow-up.

As of March 2013, 68 proband generation and 91 offspring generation participants, 32 proband referents, and 41 offspring referents had been enrolled
and tested. Data analysis was performed to determine the need to continue recruitment. A lack of significant findings was speculated to be due to low power resulting from small sample sizes, particularly in the referent cohorts. Therefore, it was necessary to expand the definitions of the referent groups at the expense of increasing the diversity within each group and introducing more error. Two additional sources of potential participants for the referent cohorts were identified. To increase the size of the proband referent cohort, age- and sex-matching was dropped and instead these covariates are adjusted for in the analyses. All potential participants from the pool of LLFS-ineligible participants with a FLoSS of less than 5 within the age-range of the already enrolled LLFS proband generation participants (age 75-103 years) were contacted by introductory letter. Recruitment was performed in the same manner as the original proband referent group. We also recruited proband generation spouses of the LLFS to participate in the study. The FLoSS scores of the spouses were calculated based on the date of LLFS enrollment to ensure that spouses did not have evidence of familial longevity. Recruitment and enrollment into the cognitive study followed the procedures for participants of the LLFS.

The offspring referent sample size was increased by contacting referent participants of the New England Centenarian Study (NECS) at Boston Medical Center and Boston University School of Medicine. The NECS enrolls centenarians, their siblings, their offspring, and referent controls for the offspring generation. The referent controls consist of spouses of enrolled offspring
participants and as well as septuagenarian controls. The septuagenarian controls were offspring of a parent who was born between 1897 and 1899 and died at average life expectancy for the 1900 birth cohort, which is 73 years. Septuagenarian controls with a second parent who died at age 95 or older were omitted due to evidence of familial longevity. NECS offspring spouse controls as well as septuagenarian controls were contacted in April 2013. Potential subjects had to live within 3 hours of Boston and have been able to complete the TICS by telephone at their annual NECS follow-up. Potential subjects were screened for interest in participating and capacity to consent. Enrollment occurred at the in-person visit.

**Power calculations**

Normative data from Whittle and colleagues study of non-demented nonagenarians (Whittle et al., 2007) were used to conduct power calculations to determine the required population size of proband generation participants from LLFS and matched controls for this neuropsychological study. Of the tests used in this study, Whittle and colleagues provide normative data for animal fluency, CVLT, CDT, DSF, and DSB. Given that the average age of the eligible proband generation LLFS participants was 92, normative data from the 92-94 subgroup were used for these calculations. Participants of LLFS are hypothesized to perform at a better than average level on neuropsychological test measures. Therefore, the values for the 75th percentile of the normative data were chosen to
represent the LLFS participants and the 50th percentile was chosen for the reference group. Power was determined by performing a one-tailed two sample t-test for a sample size of 100 participants in each group assuming an alpha of 0.05. All power calculations were conducted in R version 2.15.2 accessed via RStudio version 0.98.490. As shown in Table 1, power for the matching tests ranged from 83% to more than 99%.
The same or very similar versions of animal fluency, F fluency, DSF, and DSB were used in our study. However, a different protocol for the CDT and a more cognitively demanding version of the CVLT (a 16-word versus 9-word list) were administered. As more difficult tests are believed to elicit larger differences between groups, it is expected that the power is greater in the current study compared to the results in the table above. A power of at least 80% is preferred so it was determined that a sample of at least 100 participants in each group would be sufficient to detect differences between the two populations.

Power calculations for the offspring generation participants of LLFS were performed using preliminary data from the brief neuropsychological exam administered to participants at the initial in-person assessment (Barral et al.,

<table>
<thead>
<tr>
<th>Test</th>
<th>50th Percentile</th>
<th>75th Percentile</th>
<th>SD</th>
<th>Power</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>Mean</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CDT</td>
<td>6</td>
<td>7</td>
<td>1.9</td>
<td>98%</td>
</tr>
<tr>
<td>DSF</td>
<td>9</td>
<td>10</td>
<td>2.1</td>
<td>96%</td>
</tr>
<tr>
<td>DSB</td>
<td>6</td>
<td>7</td>
<td>1.9</td>
<td>98%</td>
</tr>
<tr>
<td>Animal fluency</td>
<td>13</td>
<td>16</td>
<td>4.1</td>
<td>&gt;99%</td>
</tr>
<tr>
<td>F fluency</td>
<td>11</td>
<td>15</td>
<td>4.2</td>
<td>&gt;99%</td>
</tr>
<tr>
<td>CVLT Trials 1-4</td>
<td>23</td>
<td>27</td>
<td>6.2</td>
<td>&gt;99%</td>
</tr>
<tr>
<td>CVLT Delayed Recall</td>
<td>5</td>
<td>6</td>
<td>2.7</td>
<td>83%</td>
</tr>
</tbody>
</table>

Table 1. Power Calculations for the Proband Generation.
Barral and colleagues provide data showing better performance of LLFS offspring on DSF, DSB, and category fluency for vegetables. Similar versions of DSF and DSB as well as an alternate semantic category for fluency were administered during the current study. Power was determined by performing a one-tailed two sample t-test in using the means for LLFS offspring generations compared to LLFS offspring generation spouses assuming a population size of 100 participants in each group and an alpha of 0.05.

<table>
<thead>
<tr>
<th></th>
<th>Offspring Mean (SD)</th>
<th>Control Mean (SD)</th>
<th>Power</th>
</tr>
</thead>
<tbody>
<tr>
<td>DSF</td>
<td>8.7 (2.1)</td>
<td>7.7 (2.1)</td>
<td>96%</td>
</tr>
<tr>
<td>DSB</td>
<td>6.9 (2.3)</td>
<td>6.0 (1.9)</td>
<td>92%</td>
</tr>
<tr>
<td>Vegetable fluency</td>
<td>15.7 (4.6)</td>
<td>14.5 (4.1)</td>
<td>61%</td>
</tr>
</tbody>
</table>

Table 2. Power Calculations for the Offspring Generation.

Although the power calculations for one of the tests for the offspring generation is lower than desired, the current study is intended to build upon these preliminary results. The tests in this neuropsychological battery were selected to represent more complex versions of tasks previously administered to these participants. For example, the NAB Word Generation test was selected as an alternate and potentially more difficult verbal fluency task to the animal and vegetable fluency tasks administered in the initial in-home assessment of the LLFS.
Recruitment

The Boston field site of the LLFS enrolled 284 probands and siblings, 391 offspring, and 136 offspring spouses who live within 3 hours of Boston. At the start of the cognitive function study in December 2010, 72% of probands and siblings, 99% of offspring, and 100% of offspring spouses were still living. Figure 3 shows the recruitment tree for the proband generation. Out of 284 potential participants, 101 were unable to be contacted because 8 had withdrawn from the LLFS and 93 had died. Fifty-one participants were determined to be ineligible (76% were unable to complete the TICS due to hearing impairment, 14% due to blindness, 10% refused the annual follow-up (AFU)). The remaining 136 (48%) participants were screened for interest in the study. Of those, 62 refused, 3 were determined to lack capacity to provide consent, and 71 (52%) were enrolled.
Recruitment for the LLFS offspring generation participants is shown in Figure 4. Out of 276 potential participants, 14 were not able to be contacted because 11 had withdrawn from the study and 3 had died prior to the start of the cognitive function study. From the remaining 262 participants, 15 were ineligible for the study (47% could not be reached, 27% had a neurological condition, 20% refused the annual follow-up, and 7% due to blindness). The 4 participants omitted due to neurological conditions were diagnosed with multiple sclerosis, hydrocephalus, amyotrophic lateral sclerosis, and Down syndrome. Those eligible to be screened consisted of 247 participants (89% of the sample). Of
those screened, 147 refused the study and 100 (40%) enrolled, thus meeting the enrollment goal for the offspring generation participants.

The LLFS offspring spouse referent cohort had a potential pool of 136 participants as shown in Figure 5. Three participants withdrew from LLFS prior to the cognitive study and 15 were ineligible to participate (53% were not able to be reached, 40% refused the annual follow-up, 7% had a neurological condition). The participant omitted due to a neurological condition had been diagnosed with early-onset Alzheimer’s disease. The remaining 118 (87%) were screened. Of those, 64 refused participation and 54 (46%) were enrolled. Screening and enrollment rates were similar in both offspring generation participants and
offspring referents (89% vs. 87% for screening eligibility; 40% vs. 46% for enrollment).

Figure 5. Recruitment flowchart for the Long Life Family Study offspring referent participants.

As shown in Figure 6, the recruitment pool of those who were screened for LLFS but were determined to be ineligible due to a low FLoSS score consisted of 397 potential participants living within 3 hours of Boston. Of those 397 participants, 181 were unable to be contacted because 19 could no longer be located and 162 had died since the screening for LLFS. An additional 38 refused the study by mailed response card or did not return our phone message and 16 were determined to be ineligible prior to screening (31% moved out of the area, 50% had hearing impairments that prevented communication by phone, 19% due
to blindness). The remaining 162 potential participants (41%) were screened. Of those, 108 refused to participate, 6 lacked the capacity to provide consent, and 3 did not return the consent form by mail for enrollment in to the study. The remaining 45 potential participants (28%) were enrolled. Enrollment rates were lower in the proband referent cohort than in the proband generation participants (28% vs. 52%). This is likely due to the fact that participants of the LLFS had already agreed to participate in an in-home assessment for the main study and thus were from a recruitment pool of individuals more willing to take part in lengthy exams. Another issue to note is that the rate of deceased participants from the proband generation selection pool was slightly lower among LLFS participants (33%) compared with the proband referent selection pool (41%). However, recruitment for the proband referent cohort began seven months later than recruitment for the proband generation participants.
After the decision to increase the sample size, recruitment of LLFS proband generation spouses began. As seen in Figure 7, the recruitment pool consisted of 40 proband generation spouses enrolled in LLFS and living within three hours of Boston. Of those 40 individuals, 13 died prior to the cognitive study, 5 withdrew from LLFS, and 22 (55%) were screened. Of the 22 who were screened 64% were enrolled. The screening and enrollment rates were higher than those for the proband generation participants (55% vs. 48% for screening; 64% vs. 52% for enrollment). Rates for those who died prior to screening were similar, however, more LLFS proband generation participants were ineligible for screening due to inability to complete the cognitive measure by phone, blindness,
and unwillingness to complete the AFU, whereas none of the proband generation spouses were ineligible for screening.

In order to increase the sample size of the offspring referent group potential participants from the offspring referent cohort of the NECS were contacted for participation in the cognitive study. There were 76 potential participants from the NECS offspring referent cohorts living within three hours of Boston as seen in Figure 8. Of those 76 individuals, 14 were ineligible for participation (36% had parental longevity, 29% refused the TICS, 36% were unable to be reached) and 62 (82%) were screened. Of those screened, 32
refused and 30 (48%) were enrolled. Enrollment rates were similar to the LLFS offspring referent cohort (48% vs. 46%).

![Recruitment Flowchart](Image)

Figure 8. Recruitment flowchart for the offspring referent cohort participants from the New England Centenarian Study.

Testing sessions analyzed in this study were completed from December 2010 to November 2013. Of the 71 proband generation participants enrolled in the study, 70 completed the testing session. One female participant withdrew after completing the first half of the testing. Of the 59 proband referents who enrolled in the study, 57 were tested. One male participant withdrew prior to the in-home testing session and one female participant was found to be legally blind prior to in-home testing. All of the 100 offspring generation participants and 84 offspring referent participants who were enrolled completed the testing session.
Following testing, one male proband generation participant was omitted from the analysis as a severe outlier across testing. He also had an MMSE score of 15 which was significantly below the next lowest score of 21. One female proband referent was omitted from the analysis because of a significant lack of effort and information received at the in-home session that she had a neurological diagnosis (normal pressure hydrocephalus).

As enrollment goals were not reached for three out of four participant groups, power analyses were recalculated using the same normative data and procedures as described above but using group specific sample sizes. For the proband generation, power to detect differences between participants with and without familial longevity (N=69, N=56) was 90% for the CDT, 84% for DSF, 90% for DSB, more than 99% for animal fluency, more than 99% for F fluency, 97% for CVLT recall of trials 1 through 4, and 66% for the long delayed recall of CVLT. In the offspring generation, power calculations were performed for group sizes of 100 participants in the familial longevity group and 84 in the referent group. Power was determined to be 94% for DSF, 89% for DSB, and 58% for vegetable fluency.

Testing validity

Prior to the study it was unknown whether an aged cohort would have the ability to complete a 2.5 hour in-home neuropsychological exam due to concerns of fatigue and sensory impairments. Furthermore, this study aimed to use more difficult tests than have been used in previous studies of familial longevity to elicit
greater differences between groups and provide a more in-depth investigation of
cognitive domains. Therefore, test difficulty was high. To address fatigue,
sessions were designed to be able to be performed on two separate days, and
on rare occasions, three days, at the request of the participant or the discretion of
the examiner. Due to the high prevalence of sensory impairments in the proband
generation in particular, tests were selected to minimize demands on visual,
auditory, and motor systems. In addition, recruitment aimed to reduce severe
auditory and visual impairments in the selected sample. However, sensory
demands cannot be completely eliminated. To determine the validity of the
testing sessions in light of these concerns, examiners rated each testing session
on a scale of 1 to 4, with 1 indicating that all tests were invalid and 4 indicating
that all tests were valid. Visual, auditory, and motor capacity were each rated on
a scale of 1 to 5, with 1 indicating excellent sensory capacity and 5 indicating
complete deafness, blindness, or inability to use hands. Analysis of validity data
was performed with Mann-Whitney-Wilcoxon tests in R comparing proband
generation participants to the proband referents and offspring generation
participants to the offspring referent group. Results of the validity measures by
participant group can be seen in Figures 9 through 11 and Table 3. Similar
proportions of participants from the LLFS proband generation and the proband
referent cohorts completed the testing in one session. Two participants from the
LLFS proband generation required testing to be completed in three sessions,
whereas no participants in the proband referent cohort required three sessions.
In both the LLFS offspring generation and the offspring referent cohort, almost all participants completed the testing in one session. Testing validity was high in all cohorts with almost all testing sessions reported as all tests valid. Visual, auditory, and motor capacity was lower in the proband generation compared with the offspring generation but not significantly different compared with their respective referent cohorts. Visual capacity in the offspring generation was significantly lower in the offspring referent cohort before removal of one offspring referent who had a recent ophthalmological procedure which interfered with her performance on the ROCF. Her data was omitted from analysis of the ROCF, and therefore, her data was omitted from the analysis of the visual capacity ratings.
Figure 9. Number of testing sessions by cohort.

Notes: PG refers to proband generation participants, PR to proband referents, OG to offspring generation participants, and OR to offspring referents.
Figure 10. Testing validity by cohort.

Notes: PG refers to proband generation participants, PR to proband referents, OG to offspring generation participants, and OR to offspring referents. Testing sessions were rated on a scale of 1 (all tests invalid) to 4 (all tests valid).
Figure 11. Sensorimotor capacity ratings by cohort.

Notes: PG refers to proband generation participants, PR to proband referents, OG to offspring generation participants, and OR to offspring referents. All
sensorimotor modalities were rated on a scale of 1 (excellent) to 5 (complete deafness, blindness, or inability to use hands)

<table>
<thead>
<tr>
<th></th>
<th>PG</th>
<th>PR</th>
<th>p</th>
<th>OG</th>
<th>OR</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td># of visits</td>
<td>1 (1-3)</td>
<td>1 (1-2)</td>
<td>0.9</td>
<td>1 (1-2)</td>
<td>1 (1-2)</td>
<td>0.7</td>
</tr>
<tr>
<td>Testing validity</td>
<td>4 (3-4)</td>
<td>4 (3-4)</td>
<td>0.3</td>
<td>4 (3-4)</td>
<td>4 (3-4)</td>
<td>0.4</td>
</tr>
<tr>
<td>Hearing capacity</td>
<td>2 (1-4)</td>
<td>2 (1-4)</td>
<td>0.2</td>
<td>1 (1-3)</td>
<td>1 (1-3)</td>
<td>0.1</td>
</tr>
<tr>
<td>Visual capacity</td>
<td>2 (1-4)</td>
<td>2 (1-4)</td>
<td>0.2</td>
<td>1 (1-2)</td>
<td>1 (1-4)</td>
<td>0.2*</td>
</tr>
<tr>
<td>Motor capacity</td>
<td>1 (1-3)</td>
<td>1 (1-4)</td>
<td>0.4</td>
<td>1 (1-2)</td>
<td>1 (1-3)</td>
<td>0.4</td>
</tr>
</tbody>
</table>

Table 3. Test validity ratings by cohort.

Notes: Data are presented as median (range). PG refers to proband generation participants, PR to proband referents, OG to offspring generation participants, and OR to offspring referents. *One offspring referent participant with a score of 4 was omitted from the analysis due to a recent ophthalmologic procedure. Her data was omitted from the analysis of the Rey-Osterrieth Complex Figure.

Several individual tests (less than 1% of all tests administered) had to be omitted from analysis due to sensorimotor impairments (N=8), refusals (N=5), environmental distractions (N=3), examiner errors (N=7), and other reasons that made the tests invalid (N=8). The ROCF (N=9), BNT (N=5), and WGN (N=4) tests were the most commonly omitted tests). See Appendix 4 for a detailed
listing of the omitted tests. Appendix 5 lists test examination, omission, refusal, and administration error rates by examiner.

Feasibility outcomes

Recruitment shows that long-lived individuals and cohorts with familial longevity are willing to take part in extended neuropsychological examinations. The sessions were completed in the participants’ homes, eliminating the burden of travel which may have otherwise prevented many participants, particularly in the proband generation, from participating. Analysis of validity measures shows that eligibility criteria, described previously, resulted in a cohort of participants with high sensorimotor capacity ratings and without sensorimotor impairments significant enough to prevent neuropsychological testing. The very low refusal rate and number of tests omitted due to lack of effort indicate that participants are willing to complete tests, even when tests of high difficulty are included in the battery.
CHAPTER THREE: THE NEUROPSYCHOLOGICAL ASSESSMENT

Method

Neuropsychological battery

A 2.5-hour neuropsychological battery was administered within six weeks of the telephone interview in the participant’s home or an alternate chosen location. Multiple testing sessions were administered when requested by the participant or at the discretion of the examiner. Tests were selected based on previous research showing their usefulness in detecting cognitive changes in normal aging, cognitive impairment, and incident dementia as well as their emphasis on episodic memory and executive function. We also considered the potential for both quantitative and qualitative data analysis of each test. In addition, preference was given to tests that minimize motor, vision, and hearing demands due to the high prevalence of sensory deficits in this study population.

The North American Adult Reading Test (NAART, Blair & Spreen, 1989) was administered as a proxy for quality of education. Mood was assessed with the 10-item Center for Epidemiologic Studies Depression Scale (CES-D, Andresen, Malmgren, Carter, & Patrick, 1994; Radloff, 1977). The MMSE was used as a brief measure of global cognitive function for comparison with other studies.

The CVLT-II, Wechsler Memory Scale-Third Edition Logical Memory I & II (WMS-III, Wechsler, 1997) and the ROCF were administered as measures of episodic memory. All subtests of the CVLT-II were administered including
Immediate Free Recall Trials 1 through 5 of List A, Immediate Free Recall of List B, and Short-Delay Free and Cued Recall of List A. Long-Delay Free Recall, Cued Recall, and Yes/No Recognition were administered after a 15-minute delay. The Forced-Choice Recognition format was administered following a subsequent 10-minute delay. The Copy, Immediate, and 20-minute Delayed Recall Conditions of the ROCF were administered and scored following the protocol from the Boston Qualitative Scoring System (BQSS, R. A. Stern et al., 1999). Administration of WMS-III Logical Memory I and II followed standard administration procedures including delayed recall and recognition formats. WMS-III Logical Memory II was administered 25-35 minutes after Logical Memory I. In addition to the episodic memory tests, semantic memory was tested with the Standard Form 60-item BNT (Kaplan et al., 2001). The multiple choice format was given for all items not correctly named following administration of all 60 items.

Tests of executive function included forward and backward digit spans, phonemic and semantic fluency, the NAB Word Generation test, the CDT, and the D-KEFS Sorting Test. The WMS-III version of DSF was administered to examine attention and DSB was administered to examine working memory components of executive function. The Controlled Oral Word Association (COWA) test for phonemic fluency for the letters F, A, and S and semantic fluency for the category of animals were administered following the protocol of Strauss and colleagues (Strauss et al., 2006). The NAB Word Generation test
was administered as another test of verbal fluency and generativity. The CDT was administered and scored following the FHS protocol (Nyborn et al., 2013), except for the designated time used in the time setting condition (described below). Participants were given command and copy conditions, each with a time setting of “10 after 11,” and two pre-drawn conditions. In the first two conditions the participant was given a blank sheet of paper on which to draw the clock, first without a stimulus and then following a stimulus to copy. In the third condition the participant was given the outer contour of the clock and asked to fill in the numbers of a clock. A piece of paper with a pre-drawn outer contour and preplaced numbers was given to the participant in the fourth condition with instructions to set the time to “20 after 7.” This specific time was selected to reduce practice effects from the previous conditions requiring time setting and because it requires the participant to use both lower quadrants of the clock which has the potential to reveal left neglect. Problem solving and conceptualization were examined with the Free Sorting and Sort Recognition subtests of the D-KEFS Sorting Test.

In addition to the neuropsychological battery, participants completed a sociodemographic questionnaire to collect data on height, weight, smoking and alcohol intake, loss of consciousness, head trauma, fainting, and hallucinations, handedness, primary and other language fluencies, parental education and causes of death, family history of dementia diagnosis, social networks, occupation of longest duration, frequency and type of leisure activities, and
frequency and type of exercise activities. Sleep quality was assessed with the Pittsburgh Sleep Quality Index (PSQI, Buysse, Reynolds, Monk, Berman, & Kupfer, 1989). The Duke University Religion Index (DUREL) (Koenig, Parkerson, & Meador, 1997) and the Overall Self-Ranking questions from the National Institutes of Health/Fetzer Brief Multidimensional Measure of Religiousness/Spirituality questionnaire (Fetzer Institute and National Institute on Aging working group, 1999) were used to assess religion and spirituality for inclusion as a social connectedness variable. A cognitively stimulating activity questionnaire (Wilson, Barnes et al., 2003; Wilson et al., 2005) was used to assess frequency of participation in cognitively demanding activities with limited physical and social components at ages 6, 12, 18, 40, and at the present time. Social activities were measured using the Social Disengagement Index (Bassuk et al., 1999).

At the midpoint of the testing session, seated, resting blood pressure of the right arm (or if not possible, in the left arm) and a semi-recumbent ankle-arm blood pressure was assessed using a BPTru Digital Sphygmanometer and a handheld 8 megahertz Doppler Probe with built-in speaker for assessment of vascular risk factors. Visual acuity was assessed with a Snellen chart set at a distance of 10 feet from the participant. The participant was asked to read the lowest line on the chart possible for him/her using both eyes simultaneously. The lowest line read accurately was recorded. Lower lines indicate better visual acuity. Auditory acuity was assessed with a finger rub test. The participant was
asked if she/he could hear a noise in each ear and had to describe the sound accurately. Ability to hear the rub in one ear, both ears, or neither ear was recorded.

A proxy designated by the participant was asked to complete the Functional Assessment Questionnaire (FAQ) (Pfeffer, Kurosaki, Harrah, Chance, & Filos, 1982) as a measure of functional disability in IADLs, the Neuropsychiatric Inventory (NPI) (Cummings et al., 1994) to detect psychiatric features of dementia, and the Behavior Rating Inventory of Executive Function – Adult Version (BRIEF-A) (Roth, Isquith, & Gioia, 2005) to quantify behavioral features of executive dysfunction.

All testing sessions were recorded with a digital voice recorder and transcribed. Testing sessions were completed by SA and four research assistants. Training on neuropsychological test measures was performed by SA in a group setting on multiple occasions to ensure consistency in administration. Demonstration of mastery in conducting the test battery was performed on an individual basis. SA completed 34% of all testing sessions with research assistants ranging from 9% to 28% of the administrations. Tests were double-scored by a research assistant and SA individually, except for ROCF which was scored only by SA due to the intricate and time-consuming nature of the scoring system. Differences in scoring were discussed until a consensus could be reached. Test scores and questionnaire data were entered into a database and double-checked for accuracy.
All participants provided informed consent to participate in this ancillary study. This study was approved by the Boston University Institutional Review Board and the LLFS Ancillary Studies Committee.

Data analysis

Descriptive statistics including means and standard deviations for normal data and medians and ranges for skewed data were generated for the proband generation, offspring generation and both referent groups for demographic information and MMSE, physical function, neuropsychiatric, and mood scores. LLFS participants were compared to their respective referent cohorts for demographic variables and raw neuropsychological test scores using parametric analyses for normal data and nonparametric analyses for skewed or categorical data. Episodic memory test scores used in this study were CVLT-II Trials 1 to 5 score (CVLT15), CVLT-II short-delay free recall score (CVLT-SD), CVLT-II long-delay free recall score (CVLT-LD), ROCF immediate and delay presence and accuracy scores from the BQSS scoring system (ROCF-I and ROCF-D respectively), WMS-III Logical Memory I Story B trials 1 and 2 recall (LMIB), and WMS-III Logical Memory II Story B recall (LMIIB). Story A from the WMS-III Logical Memory was not used because participants from the LLFS have previously been administered that version. Executive function test scores included the COWA score, Animals score, NAB Word Generation subtest score (WGN), CDT Command Condition error score (CDT-F), CDT Copy Condition
error score (CDT-C), WMS-III Digits Forward score (DSF), WMS-III Digits Backward score (DSB), D-KEFS Sorting Test Description Score, D-KEFS Sorting Test Confirmed Correct Sorts score, ROCF copy presence and accuracy score from the BQSS scoring system (ROCF-C). The BNT spontaneous correct score was used for language and semantic memory. The Global Executive Composite score of the BRIEF-A was used for analysis.

Skewed neuropsychological test scores were transformed using log, square root, or cubic root transformations and the generalized estimating equations (GEE) approach was used to compare proband generation participants to proband referents and offspring generation participants to offspring referents adjusting for age, sex, and estimated intellectual ability with clustering for familial relatedness. Analyses were not adjusted for education as it is correlated with the estimated intellectual ability measure included in the model ($r=0.48$, $p<.0001$). A lowered p-value of 0.005 to account for multiple comparisons was used to determine significance.

Results

Proband generation

Table 4 shows the participant characteristics of the proband generation participants (N=69) and the proband referents (N=56). Participants in both groups had an average age of approximately 91 years and had similar percentages of females in the sample. Education and IQ as estimated by
performance on the NAART were both significantly higher in the proband referent group (p=.03 and p=.004 respectively). Only 14% of proband generation participants had an advanced degree compared with 27% of the proband referents. Those with less than a high school education accounted for 13% of the proband generation participants but only 5% of the proband referent participants. Figure 12 shows the proportion of each cohort that falls within four education levels: less than high school, high school diploma, college degree, and advanced degree. There were no significant differences between the groups in MMSE, FAQ, NPI, or CES-D scores.
<table>
<thead>
<tr>
<th></th>
<th>Probands</th>
<th>Referents</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>69</td>
<td>56</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>90.8 ± 6.0</td>
<td>90.9 ± 4.9</td>
<td>0.9</td>
</tr>
<tr>
<td>% Female</td>
<td>51 (N=35)</td>
<td>63 (N=35)</td>
<td>0.2</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>%&lt;HS</td>
<td>13</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>% HS diploma</td>
<td>49</td>
<td>41</td>
<td></td>
</tr>
<tr>
<td>% College degree</td>
<td>23</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>% Advanced degree</td>
<td>14</td>
<td>27</td>
<td>0.03</td>
</tr>
<tr>
<td>Race (% white, not Hispanic)</td>
<td>100</td>
<td>96 (N=54)</td>
<td></td>
</tr>
<tr>
<td>NAART Estimated IQ</td>
<td>107.1 ± 9.5</td>
<td>111.5 ± 7.2</td>
<td>0.004</td>
</tr>
<tr>
<td>MMSE Score</td>
<td>26.6 ± 2.6</td>
<td>26.6 ± 2.5</td>
<td>0.9</td>
</tr>
<tr>
<td>FAQ Score</td>
<td>2 (0-22)*</td>
<td>2 (0-22)*</td>
<td>0.4</td>
</tr>
<tr>
<td>NPI Score</td>
<td>0 (0-5)*</td>
<td>0 (0-3)*</td>
<td>0.2</td>
</tr>
<tr>
<td>CES-D Score</td>
<td>5 (0-18)*</td>
<td>6 (0-21)*</td>
<td>0.6</td>
</tr>
</tbody>
</table>

Table 4. Participant characteristics for the proband generation.

Note: All values are mean ± SD unless otherwise noted. Results noted by * were skewed and thus are reported as median (range). HS=high school, NAART= North American Adult Reading Test, MMSE=Mini-Mental State Examination, FAQ=Functional Activities Questionnaire, NPI=Neuropsychiatric Inventory, CES-D=Center for Epidemiologic Studies Depression Scale.
Figure 12. Educational attainment in the proband generation.
<table>
<thead>
<tr>
<th>Test Type</th>
<th>Probands</th>
<th>Referents</th>
<th>p</th>
</tr>
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<tbody>
<tr>
<td><strong>Episodic memory</strong></td>
<td></td>
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</tr>
<tr>
<td>CVLT15</td>
<td>28.8 ± 10.9</td>
<td>29.4 ± 9.8</td>
<td>0.8</td>
</tr>
<tr>
<td>CVLT-SD</td>
<td>4 (0-16)*</td>
<td>5 (0-12)*</td>
<td>0.4</td>
</tr>
<tr>
<td>CVLT-LD</td>
<td>4 (0-14)*</td>
<td>5 (0-15)*</td>
<td>0.3</td>
</tr>
<tr>
<td>ROCF-I</td>
<td>8.2 ± 3.3</td>
<td>8.0 ± 2.9</td>
<td>0.6</td>
</tr>
<tr>
<td>ROCF-D</td>
<td>8.2 ± 3.6</td>
<td>7.5 ± 3.2</td>
<td>0.3</td>
</tr>
<tr>
<td>LMIB</td>
<td>20.2 ± 8.0</td>
<td>22.1 ± 8.1</td>
<td>0.2</td>
</tr>
<tr>
<td>LMIIB</td>
<td>8.9 ± 4.8</td>
<td>9.7 ± 5.3</td>
<td>0.4</td>
</tr>
<tr>
<td><strong>Executive function</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Animals</td>
<td>13.6 ± 4.5</td>
<td>13.6 ± 4.6</td>
<td>1.0</td>
</tr>
<tr>
<td>COWA</td>
<td>32 (10-72)*</td>
<td>34.5 (13-76)*</td>
<td>0.6</td>
</tr>
<tr>
<td>WGN</td>
<td>7 (0-21)*</td>
<td>8 (0-20)*</td>
<td>0.4</td>
</tr>
<tr>
<td>CDT-F</td>
<td>2.5 (0.75-10.75)*</td>
<td>2.25 (0.75-9.75)*</td>
<td>0.7</td>
</tr>
<tr>
<td>CDT-C</td>
<td>2.1 ± 1.1</td>
<td>2.0 ± 1.0</td>
<td>0.6</td>
</tr>
<tr>
<td>DSF</td>
<td>8.8 ± 1.9</td>
<td>9.1 ± 2.1</td>
<td>0.4</td>
</tr>
<tr>
<td>DSB</td>
<td>5.5 ± 1</td>
<td>5.9 ± 1.8</td>
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<tr>
<td>DKEFS-CS</td>
<td>5.8 ± 2.7</td>
<td>6.1 ± 3.0</td>
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<tr>
<td>DKEFS-DS</td>
<td>20.2 ± 10.0</td>
<td>22.1 ± 11.3</td>
<td>0.3</td>
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<tr>
<td>ROCF-C</td>
<td>15.6 ± 2.4</td>
<td>16.0 ± 2.4</td>
<td>0.4</td>
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<tr>
<td><strong>Other tests</strong></td>
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<td></td>
<td></td>
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<tr>
<td>BNT</td>
<td>51 (27-59)*</td>
<td>52 (32-58)*</td>
<td>0.4</td>
</tr>
<tr>
<td>BRIEF-A</td>
<td>74 (70-159)*</td>
<td>79 (70-134)*</td>
<td>0.3</td>
</tr>
</tbody>
</table>

Table 5. Unadjusted test descriptives for the proband generation.
Note: All values are mean ± SD unless otherwise noted. Results noted by * were skewed and thus are reported as median (range). CVLT15 = CVLT Trials 1 to 5 score, CVLT-SD = CVLT Short-Delay score, CVLT-LD = CVLT Long-Delay score, ROCF-I = ROCF Immediate Presence and Accuracy score, ROCF-D = ROCF Delayed Presence and Accuracy score, LMIB = WMS-III Logical Memory I Story B Immediate Recall Trials 1 and 2 score, LMIIB = WMS-III Logical Memory II Story B Delayed Recall score, CDT-F = Clock Drawing Test Command Condition error score, CDT-C = Clock Drawing Test Copy Condition error score, DKEFS-CS = D-KEFS Sorting Test Confirmed Correct Sorts score, DKEFS-DS = D-KEFS Sorting Test Description Score, ROCF-C = ROCF Copy Presence and Accuracy score

Table 5 shows the unadjusted test scores in the proband generation by group. Transformations to normalize skewed data were not successful for the BRIEF-A and data were determined not to be informative due to lack of sensitivity of the measure in this population. Therefore, it was omitted from further analysis. See Appendix 6 for histograms of the transformed data for the BRIEF-A. Tables 6 and 7 show the results of the GEE adjusted for age, sex, and estimated intellectual ability with clustering for familial relatedness in the proband generation for the episodic memory tests and executive function tests, respectively. The BNT results were added to Table 6 even though it is a measure of semantic memory. No differences were seen between groups. Word
generation showed a tendency toward better performance in the proband generation without accounting for adjustment for multiple comparisons.

<table>
<thead>
<tr>
<th></th>
<th>Estimate</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVLT15</td>
<td>0.72</td>
<td>0.4</td>
</tr>
<tr>
<td>CVLT-SD^</td>
<td>-0.01</td>
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</tr>
<tr>
<td>CVLT-LD^</td>
<td>-0.04</td>
<td>0.4</td>
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<tr>
<td>ROCF-I</td>
<td>0.41</td>
<td>0.2</td>
</tr>
<tr>
<td>ROCF-D</td>
<td>0.72</td>
<td>0.1</td>
</tr>
<tr>
<td>LMIB</td>
<td>-0.42</td>
<td>0.4</td>
</tr>
<tr>
<td>LMIIB</td>
<td>-0.08</td>
<td>0.5</td>
</tr>
<tr>
<td>BNT</td>
<td>-0.55</td>
<td>0.3</td>
</tr>
</tbody>
</table>

Table 6. Proband generation episodic memory performance: GEE adjusted for age, sex, and intellectual ability with clustering for familial relatedness.

Note: A ^ indicates a square root transformed variable.
<table>
<thead>
<tr>
<th></th>
<th>Estimate</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Animals</td>
<td>0.54</td>
<td>0.3</td>
</tr>
<tr>
<td>COWA*</td>
<td>0.07</td>
<td>0.1</td>
</tr>
<tr>
<td>WGN^</td>
<td>0.20</td>
<td>0.08</td>
</tr>
<tr>
<td>Clock-F*</td>
<td>-0.01</td>
<td>0.5</td>
</tr>
<tr>
<td>Clock-C</td>
<td>-0.06</td>
<td>0.4</td>
</tr>
<tr>
<td>DSF</td>
<td>0.24</td>
<td>0.2</td>
</tr>
<tr>
<td>DSB</td>
<td>0.01</td>
<td>0.5</td>
</tr>
<tr>
<td>DKEFS-CS</td>
<td>0.42</td>
<td>0.2</td>
</tr>
<tr>
<td>DKEFS-DS</td>
<td>1.19</td>
<td>0.2</td>
</tr>
<tr>
<td>ROCF-C</td>
<td>-0.15</td>
<td>0.4</td>
</tr>
</tbody>
</table>

Table 7. Proband generation executive function performance: GEE adjusted for age, sex, and intellectual ability with clustering for familial relatedness.

Note: A * indicates a log transformed variable, ^ indicates a square root transformed variable.

**Offspring generation**

Table 8 shows the participant characteristics of the offspring generation participants and the referent cohort. The offspring referent participants were significantly older than the offspring generation participants (p<.001). This was due to the higher ages of the referent participants recruited from NECS compared with the offspring spouses from the LLFS (mean age 76.1 ± 4.3 vs.
Table 8. Participant characteristics for the offspring generation.

<table>
<thead>
<tr>
<th></th>
<th>Offspring</th>
<th>Referents</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>100</td>
<td>84</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>63.0 ± 7.5</td>
<td>68.1 ± 7.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>% Female</td>
<td>57 (N=57)</td>
<td>51 (N=43)</td>
<td>0.7</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>%&lt;HS</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>% HS diploma</td>
<td>18</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>% College degree</td>
<td>41</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>% Advanced degree</td>
<td>41</td>
<td>36</td>
<td>0.7</td>
</tr>
<tr>
<td>Race (% white, not Hispanic)</td>
<td>99 (N=99)</td>
<td>99 (N=83)</td>
<td></td>
</tr>
<tr>
<td>NAART Estimated IQ</td>
<td>116 (90-125)*</td>
<td>115 (83-122)*</td>
<td>0.05</td>
</tr>
<tr>
<td>MMSE Score</td>
<td>30 (25-30)*</td>
<td>29 (21-30)*</td>
<td>0.08</td>
</tr>
<tr>
<td>FAQ Score</td>
<td>0 (0-19)*</td>
<td>0 (0-4)*</td>
<td>0.09</td>
</tr>
<tr>
<td>NPI Score</td>
<td>0 (0-5)*</td>
<td>0 (0-3)*</td>
<td>0.4</td>
</tr>
<tr>
<td>CES-D Score</td>
<td>4 (0-20)*</td>
<td>3 (0-16)*</td>
<td>0.7</td>
</tr>
</tbody>
</table>

Note: All values are mean ± SD unless otherwise noted. Results noted by * were skewed and thus are reported as median (range). HS=high school, NAART= North American Adult Reading Test, MMSE=Mini-Mental State Examination, FAQ=Functional Activities Questionnaire, NPI=Neuropsychiatric Inventory, CES-D=Center for Epidemiologic Studies Depression Scale.
63.7 ± 8.1, p<.0001). Both groups had similar percentages of females in the sample and did not differ in educational attainment or estimated intellectual ability. MMSE, FAQ, NPI, and CES-D scores were similar in both groups.

Table 9 shows the unadjusted neuropsychological test scores of the offspring generation participants and the offspring referents. Transformation to normalize the data in the offspring generation could not be achieved for the BNT and the BRIEF-A. The BNT and BRIEF-A were dropped from further analysis because they also had ceiling effects and floor effects respectively which prevented them from being informative. See Appendix 7 for the transformations of the BNT and BRIEF-A. Results of the GEE adjusted for age, sex, and intellectual ability with clustering for familial relatedness for episodic memory test and executive function tests are shown in Tables 10 and 11, respectively. After correcting for multiple comparisons offspring generation participants had a tendency toward fewer errors on both the command and copy conditions of the CDT and a tendency toward better performance on DSF. No statistically significant differences were seen between offspring generation participants and offspring referents.
<table>
<thead>
<tr>
<th></th>
<th>Offspring</th>
<th>Referents</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Episodic memory</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVLT</td>
<td>48.2 ± 11.7</td>
<td>43.6 ± 11.6</td>
<td>0.008</td>
</tr>
<tr>
<td>CVLT-SD</td>
<td>9.7 ± 3.5</td>
<td>8.6 ± 3.9</td>
<td>0.04</td>
</tr>
<tr>
<td>CVLT-LD</td>
<td>10.2 ± 3.6</td>
<td>8.8 ± 3.9</td>
<td>0.009</td>
</tr>
<tr>
<td>ROCF-I</td>
<td>13.2 ± 2.7</td>
<td>11.9 ± 3.9</td>
<td>0.01</td>
</tr>
<tr>
<td>ROCF-D</td>
<td>12.9 ± 2.5</td>
<td>11.7 ± 3.8</td>
<td>0.01</td>
</tr>
<tr>
<td>LMIB</td>
<td>32 ± 7.0</td>
<td>29.3 ± 7.5</td>
<td>0.01</td>
</tr>
<tr>
<td>LMIIB</td>
<td>16.3 ± 4.4</td>
<td>14.7 ± 4.9</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>Executive function</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Animals</td>
<td>21.9 ± 5.1</td>
<td>19.7 ± 5.7</td>
<td>0.009</td>
</tr>
<tr>
<td>COWA</td>
<td>44.1 ± 12.8</td>
<td>41.8 ± 12.6</td>
<td>0.2</td>
</tr>
<tr>
<td>WGN</td>
<td>12.9 ± 5.0</td>
<td>11.1 ± 4.6</td>
<td>0.01</td>
</tr>
<tr>
<td>CDT-F</td>
<td>1.25 (0.25-6.25)*</td>
<td>1.75 (0.25-8.25)*</td>
<td>0.005</td>
</tr>
<tr>
<td>CDT-C</td>
<td>1.25 (0.25-5.25)*</td>
<td>1.5 (0.25-4.25)*</td>
<td>0.02</td>
</tr>
<tr>
<td>DSF</td>
<td>11 (7-15)*</td>
<td>9 (7-16)*</td>
<td>0.003</td>
</tr>
<tr>
<td>DSB</td>
<td>7.6 ± 2.3</td>
<td>6.6 ± 2.2</td>
<td>0.006</td>
</tr>
<tr>
<td>DKEFS-CS</td>
<td>10.8 ± 2.3</td>
<td>9.9 ± 2.7</td>
<td>0.01</td>
</tr>
<tr>
<td>DKEFS-DC</td>
<td>41.7 ± 9.1</td>
<td>37.4 ± 11.3</td>
<td>0.006</td>
</tr>
<tr>
<td>ROCF-C</td>
<td>18.1 ± 1.4</td>
<td>17.6 ± 1.8</td>
<td>0.05</td>
</tr>
<tr>
<td><strong>Other tests</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BNT</td>
<td>57 (49-60)*</td>
<td>57 (34-60)*</td>
<td>0.4</td>
</tr>
<tr>
<td>BRIEF-A</td>
<td>74 (70-161)*</td>
<td>74 (70-154)*</td>
<td>0.6</td>
</tr>
</tbody>
</table>

Table 9. Unadjusted test descriptives for the offspring generation.
Note: All values are mean ± SD unless otherwise noted. Results noted by * were skewed and thus are reported as median (range). CVLT15 = CVLT Trials 1 to 5 score, CVLT-SD = CVLT Short-Delay score, CVLT-LD = CVLT Long-Delay score, ROCF-I = ROCF Immediate Presence and Accuracy score, ROCF-D = ROCF Delayed Presence and Accuracy score, LMIB = WMS-III Logical Memory I Story B Immediate Recall Trials 1 and 2 score, LMIIB = WMS-III Logical Memory II Story B Delayed Recall score, CDT-F = Clock Drawing Test Command Condition error score, CDT-C = Clock Drawing Test Copy Condition error score, DKEFS-CS = D-KEFS Sorting Test Confirmed Correct Sorts score, DKEFS-DS = D-KEFS Sorting Test Description Score, ROCF-C = ROCF Copy Presence and Accuracy score

<table>
<thead>
<tr>
<th></th>
<th>Estimate</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVLT</td>
<td>0.41</td>
<td>0.4</td>
</tr>
<tr>
<td>CVLT-SD</td>
<td>0.09</td>
<td>0.4</td>
</tr>
<tr>
<td>CVLT-LD</td>
<td>0.41</td>
<td>0.2</td>
</tr>
<tr>
<td>ROCF-I</td>
<td>-0.01</td>
<td>0.5</td>
</tr>
<tr>
<td>ROCF-D</td>
<td>0.75</td>
<td>0.1</td>
</tr>
<tr>
<td>LMIB</td>
<td>0.54</td>
<td>0.3</td>
</tr>
<tr>
<td>LMIIB</td>
<td>0.06</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Table 10. Offspring generation episodic memory performance: GEE adjusted for age, sex, and intellectual ability with clustering for familial relatedness.
Table 11. Offspring generation executive function performance: GEE adjusted for age, sex, and intellectual ability with clustering for familial relatedness.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimate</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Animals</td>
<td>0.46</td>
<td>0.3</td>
</tr>
<tr>
<td>COWA</td>
<td>-0.73</td>
<td>0.3</td>
</tr>
<tr>
<td>WGN</td>
<td>0.53</td>
<td>0.2</td>
</tr>
<tr>
<td>Clock-F*</td>
<td>-0.11</td>
<td>0.09</td>
</tr>
<tr>
<td>Clock-C*</td>
<td>-0.10</td>
<td>0.09</td>
</tr>
<tr>
<td>DSF*</td>
<td>0.06</td>
<td>0.03</td>
</tr>
<tr>
<td>DSB</td>
<td>0.34</td>
<td>0.2</td>
</tr>
<tr>
<td>DKEFS-CS</td>
<td>0.04</td>
<td>0.4</td>
</tr>
<tr>
<td>DKEFS-DS</td>
<td>0.29</td>
<td>0.4</td>
</tr>
<tr>
<td>ROCF-C</td>
<td>0.10</td>
<td>0.3</td>
</tr>
</tbody>
</table>

Note: * indicates a log transformed variable.

Discussion

In the proband generation there were no significant differences between participants with and without familial longevity in the neuropsychological test measures administered in this study. However, we also found that the proband referents had significantly more education and higher estimated intellectual ability scores than participants with familial longevity and yet, they performed similarly to the familial longevity proband participants. Higher education and intellect have
frequently been associated with decreased cognitive impairment and mortality. Environmental and genetic factors associated with familial longevity may help proband generation participants to reach exceptionally old ages in spite of lower educational attainment and intellectual ability. Conversely, higher educational attainment and intellectual ability may be more essential for the proband referent participants to achieve exceptional survival, as they do not have genetic or environmental advantages associated with familial longevity.

It must be noted that there is a significant survivor effect in the referent group. The proband referent group consisted of spouses of proband generation participants and participants of the same age-range as the proband generation participants but who were ineligible to participate in LLFS due to lack of evidence of familial longevity. The fact that these participants were living and able to take part in the study at an average age of 91 indicates that they have longevity even though it may not be familial longevity. Therefore, this group of exceptional survivors may not be an appropriate referent group as they are not part of the "normal" population.

It is also possible that more difficult tests of cognitive function need to be administered to this long-lived cohort. Tests with a high difficulty level are more likely to show differences between groups that have only minor disturbances in cognitive function. Since a tendency toward better cognitive performance on the NAB Word Generation task was demonstrated, it should be investigated whether more difficult tasks of generativity would show differences between cohorts.
Although not considered to be more difficult tasks than the NAB Word Generation, two other tests of generativity were used in this study, the COWA test and semantic fluency for animals. No differences between groups were seen on these tests. This indicates that tests that purport to assess the same process may, in fact, rely on different processes or have differential susceptibility to impairment.

As recruitment and enrollment goals were not met, it is possible that there may not have been enough power to detect differences between the cohorts, especially after adjusting for multiple comparisons. It is believed that this is not a substantial factor for the lack of differences because the power should have been high enough to detect differences on verbal fluency and CVLT Immediate Recall before adjusting for multiple comparisons.

Analysis of the offspring generation found only a tendency toward better performance on the command and copy conditions of the CDT and the DSF of the offspring family-member participants compared with the offspring referents. The lack of significant findings in the offspring generation after adjusting for multiple comparisons within cognitive domains is surprising given that previous studies have demonstrated better cognitive performance in the offspring generation of the LLFS compared with referent cohorts using some of the same tests used in this study. For example, Barral et al. (2012) found significantly better performance on the DSF and DSB in offspring family members compared with their spouses, however, they had a much larger data set of 739 participants.
from across the four field centers of the LLFS. Similarly, offspring with parental longevity in the FHS were found to have better attention scores on a different task than used in this study (Murabito et al., 2013). Smaller sample sizes and differences in task demands that purport to test the same domain may account for the lack or replication in the current study. Barrel and colleagues (2012) also found significantly better performance of the offspring family members on vegetable fluency, which was not administered in this study. In contrast, they did not find a difference on animal fluency similar to this study. This also suggests that various fluency tests may have different underlying processes or susceptibility to cognitive dysfunction. Another study of familial longevity with similar recruitment criteria of families with at least two long-lived siblings, The Leiden Longevity Study, found better performance of the offspring generation compared with their spouses on immediate and delayed recall of a picture learning task and an inhibition task (Stijntjes et al., 2013). In addition to the use of a different learning task, they also had a larger study population of 250 offspring and 250 spouses which may account for differences between studies.

Scores on the DSF are indicative of attention and short-term retention capacity. Faster decline in DSF scores over time has been shown to be associated with impending death when controlling for preclinical dementia status (Laukka, MacDonald, & Backman, 2008). Therefore, DSF performance has important implications for daily life and the ability to attend to process incoming information as well as for survival.
The CDT is a more multifactorial test. Performance on the command and copy conditions of the CDT relies on the executive function processes of planning and organization to be able to arrange the numbers around the circumference of the clock properly as well as abstraction to be able to convert verbal time to a conceptual representation. Executive processes are considered to be higher order cognitive functions that allow one to plan and carry out goal-directed behavior. Due to these higher level processes, executive dysfunction can have detrimental effects on the ability to engage and complete tasks in daily life. Daily activities that are relevant to exceptional survival that may be affected by executive dysfunction are health habits, including medication adherence, ability to plan for and engage in daily activities, and maintenance of social and occupational roles. The CDT also requires intact visuospatial function to properly place the numbers and hands within space. Impaired visuospatial function even at high levels of function can result in decreased driving ability and loss of independence. Certainly, impaired performance on the CDT is likely to be incompatible with successful aging.

Even though other studies suggest that age-related cognitive decline occurs as early as 50 years of age (Singh-Manoux et al., 2012), our relatively young offspring cohorts may not yet be experiencing cognitive decline. It may also be that some domains of cognitive function which were not studied may be more informative or may show earlier decline such as processing speed. Study results published after the start of the current study indicated that LLFS probands
and offspring had better scores on the Digit Symbol Substitution Test, a test of symbol coding and processing speed, compared with similarly aged participants from the Cardiovascular Health Study (Newman et al., 2011). Another study of offspring of nonagenarian siblings found better performance of offspring compared with their spouses on the Stroop, a test of inhibition, but did not find differences on the Digit Symbol Substitution test (Stijntjes et al., 2013).

Rate of change over time may be a more informative measure in the offspring generation. As the offspring generation ages they can be repeatedly tested to determine age of onset of cognitive impairment and trajectories of cognitive decline can be assessed. Murabito and colleagues (2013) found a slower decline in tests of attention, working memory, and visual memory over a follow-up interval for offspring with parental longevity compared with offspring without parental longevity. Delay of onset of cognitive impairment as well as a stable trajectory would be a sign of successful aging.

Certainly the difficulty of the tests used in this study may not have been high enough to elucidate differences in the offspring generation. Since the same test battery was administered to significantly different aged cohorts, some tests may have been too easy. The ceiling effects on the BNT resulted in omission of the test from analysis for this reason.

There are several limitations of the analysis of the neuropsychological test performance in this study. The offspring referent group was comprised of participants from several sources resulting in less homogeneity of the
participants as follows. The offspring referent participants recruited from the NECS were significantly older than offspring referents recruited from LLFS which could lead to false positive results. Also, the NECS referents included spouses of centenarian offspring as well as a different type of cohort-matched control specifically selected for lack of familial longevity. The septuagenarian controls had one parent who died at average life expectancy and a second parent who died under the age of 95. Spouse controls had no requirements concerning parental age at death but were assumed to be part of the general population in which parental longevity would be highly unlikely. Spouse controls are representative of a control group which shares environmental exposures with the offspring cohort and generally has the same sociodemographic and geographic background. The heterogeneity of the offspring referent cohort could lead to biases that could lead to either false positive or false negative results.

Power calculations did not account for multiple comparisons so the study may be underpowered (though multiple comparisons were accounted for in the analysis and therefore such comparisons were not a source of error in the conclusions of the study). Given the refusal and enrollment rates of the study, it is unlikely that the sample sizes could have been substantially increased beyond the sample that was finally established. Decreased power could lead to false negative results, however the positive results in this study are likely real. Larger samples of experimental and referent groups would be necessary to decrease the risk of false negative results.
Examination conditions were not as standardized as test session taking place in a clinic so there were interruptions by family members, neighbors, pets, and most commonly, telephone calls. However, in-home examination likely led to less test anxiety and higher participation rates. As there was no incentive beyond helping to advance science, participants may not have had a motive to provide full effort, however, test session validity ratings provided by the examiners suggest that this was not a major limitation.
CHAPTER FOUR: FACTORS UNDERLYING COGNITIVE PERFORMANCE IN LONG-LIVED INDIVIDUALS

The findings of similar cognitive performance levels in the proband generation participants compared to the proband referents who do not have familial longevity led to an analysis of other factors that may underlie cognitive performance in the proband generation. Specifically, factors associated with health habits, social connectedness, and cognitive reserve were investigated for their role in preserving cognitive function.

Method

Assessments

Measures of health habits included self-reported current physical activity level and physical activity level at age 40 as indicated by the number of hours of weekly participation in mildly energetic, moderately energetic, or vigorous physical activity as described by Singh-Manou, Hillsdon, Brunner, and Marmot (2005). Mildly energetic physical activity includes activities such as gardening and general housework. Moderately energetic physical activity is described as activities such as dancing or cycling. Vigorous physical activity includes running and hard swimming. Physical activity levels of less than two hours per week of moderately energetic activity and less than one hour per week of vigorous physical activity was scored as low. At least 2.5 hours per week of moderately energetic physical activity or at least one hour per week of vigorous physical activity
activity was scored as high physical activity. Physical activity levels in between these ranges were scored as medium. Sleep quality was assessed with the Pittsburgh Sleep Quality Index and scored following the standard protocol (Buysse et al., 1989). Social connectedness was measured with the Social Disengagement Index (Bassuk et al., 1999). This questionnaire assesses six types of social ties: spousal, monthly visual contact with relatives and close friends, yearly non-visual contact with relatives and close friends, religious, other groups, and participation in social leisure activities. Although standard scoring recodes the number of social ties in a reverse index of social disengagement, scores were left as the number of social ties for ease of interpretation in this study. The Duke University Religion Index measures participation in organizational and non-organizational religious activities as well as religious beliefs (Koenig et al., 1997). Index 1 scores how often the participant attends religious meetings with ratings from 1 (more than once per week) to 6 (never). Index 2 scores the frequency of time in private religious activities on a scale of 1 (more than once a day) to 6 (rarely or never). Index 3 is a composite measure of three statements about organizational and non-organizational religious belief or experience, such as "My religious beliefs are what really lie behind my whole approach to life." Items are rated on a scale of 1 (definitely true of me) to 5 (definitely not true of me). The two questions from the Overall Self-Ranking section of the NIH/Fetzer Brief Multidimensional Measure of Religiousness/Spirituality (BMMRS) questionnaire (Fetzer Institute and National
Institute on Aging working group, 1999) were also used to assess religiosity and spirituality. The religiosity questions ask to what extent the participant considers him/herself to be a religious person with four options of very religious, moderately religious, slightly religious, or not religious at all. The same question is asked in terms of spirituality. The questions were coded on a scale from 1 (very religious/spiritual) to 4 (not religious/spiritual at all). A cognitively stimulating activity questionnaire (Wilson, Barnes et al., 2003; Wilson et al., 2005) was used to assess frequency of participation in cognitively demanding activities with limited physical and social components at ages 6, 12, 18, 40, and at the present time. Frequency of participation in playing board games, reading books, magazines, and newspapers, writing letters, visiting a library, visiting a museum, and attending concerts, plays, or musicals was recorded for each time point as appropriate for that age. Duration for participation in homework and reading each day was recorded for appropriate ages. Each item was scored on a 5-point scale with higher scores indicating greater frequency or duration. Participation in foreign language instruction, music lessons, art, dance or theater lessons, and journal writing by the age of 18 was recorded. Occupational complexity was determined by using detailed information about each participant’s longest-held job and specific job duties obtained in the health and sociodemographics questionnaire to find a matching job title in the Dictionary of Occupational Titles (DOT, National Academy of Sciences, 1977). The DOT assigns a code to each job title in which the four, fifth, and sixth digits refer to complexity of interaction
with data, people, and things, respectively. Complexity is coded with higher scores indicating lower complexity. Specifically, complexity with data ranges from 6 (comparing) to 0 (synthesizing), complexity with people ranges from 8 (taking instructions/helping) to 0 (mentoring), and complexity with things ranges from 7 (handling) to 0 (setting up).

**Data analysis**

Composite measures of cognitive activities were calculated by averaging scores on the cognitive activities questionnaire for questions pertaining to ages 6, 12, and 18 for early life cognitive activity, age 40 for mid-life cognitive activity, and current activity for late-life cognitive activity. Descriptive statistics of medians and ranges were generated for the proband generation participants and the proband referents for measures of health habits (current exercise, exercise at age 40, and sleep habits), social connectedness (SDI, DUREL, BMMRS Overall Self-Ranking), occupational complexity (with data, people and things), and participation in cognitively stimulating activities at different stages of life (early, mid, and late). LLFS proband generation participants were compared to the proband referent participants using nonparametric analyses as all data were ordinal. Factors with significant differences between groups were analyzed for correlation with test scores using Spearman rank-order correlations. A cutoff of $r \geq 0.3$ and $p<0.005$ were used to determine which tests were significantly correlated with the selected modifying factors.
Z-scores for each neuropsychological test score were generated based on proband generation performance by sex. A composite score of episodic memory was created by averaging the z-scores for CVLT-II immediate recall, CVLT-II short delay recall, CVLT-II long delay recall, ROCF immediate recall, ROCF delayed recall, LM I Story B recall, and LM II Story B recall. The executive function composite score was created by averaging the z-scores for animal fluency, COWA, WGN, DSF, DSB, D-KEFS Sorting Test Description Score, D-KEFS Sorting Test Confirmed Sorts Score, ROCF copy score, and the reversed error scores for the CDT command and copy conditions. Multiple linear regression analysis was used to develop a model for predicting neuropsychological test performance from lifestyle habits including exercise and sleep quality, as well as social networks, religiosity and spirituality, and participation in cognitively stimulating activities. Due to the high correlation of the BMMRS religiosity and spirituality questions with the DUREL3 index, only the DUREL indexes were used and the BMMRS Overall Self-Rating questions were omitted. All remaining variables as well as estimated intellectual ability were added to the model and stepwise regression was used to determine the variables that were not significant which were removed from the overall model to reach the best model fit. All analyses were conducted in R version 2.15.2 accessed via RStudio version 0.98.490.
Results

Results of the analysis of differences in health habits, social networks and religiosity, occupational complexity, and cognitively stimulating leisure activities are shown in Table 12 through 15. No significant differences were found between proband generation participants and proband referents in current or mid-life exercise, sleep quality, religiosity and spirituality, social connectedness or occupational complexity. Proband referents engaged in significantly more cognitively stimulating activities in mid-life (p=.002) and late-life (p=.0002) than proband generation participants.

<table>
<thead>
<tr>
<th></th>
<th>Probands</th>
<th>Referents</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current Exercise</td>
<td>1 (1-3)</td>
<td>1 (1-3)</td>
<td>0.95</td>
</tr>
<tr>
<td>Exercise at Age 40</td>
<td>3 (1-3)</td>
<td>3 (1-3)</td>
<td>0.5</td>
</tr>
<tr>
<td>PSQI</td>
<td>5 (0-16)</td>
<td>5 (1-18)</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Table 12. Proband generation health habits.

Note: PSQI = Pittsburgh Sleep Quality Index
Table 13. Proband generation social networks, religiosity and spirituality.

Note: DUREL=Duke University Religion Index, Religious and Spiritual=Overall Self-Ranking section of the NIH/Fetzer Brief Multidimensional Measure of Religiousness/Spirituality questionnaire

<table>
<thead>
<tr>
<th></th>
<th>Probands</th>
<th>Referents</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Social Disengagement Index</td>
<td>3 (0-6)</td>
<td>3 (0-6)</td>
<td>0.5</td>
</tr>
<tr>
<td>DUREL – Church</td>
<td>4 (1-6)</td>
<td>4 (1-6)</td>
<td>0.5</td>
</tr>
<tr>
<td>DUREL – Private</td>
<td>2 (1-6)</td>
<td>3 (1-6)</td>
<td>0.6</td>
</tr>
<tr>
<td>DUREL – Beliefs</td>
<td>11 (3-15)</td>
<td>11 (3-15)</td>
<td>0.4</td>
</tr>
<tr>
<td>Religious</td>
<td>2 (1-4)</td>
<td>2 (1-4)</td>
<td>0.2</td>
</tr>
<tr>
<td>Spiritual</td>
<td>2 (1-4)</td>
<td>2 (1-4)</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Table 14. Proband generation occupational complexity of main occupation.

Note: OC=occupational complexity

<table>
<thead>
<tr>
<th></th>
<th>Probands</th>
<th>Referents</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>OC - Data</td>
<td>2 (0-6)</td>
<td>1.5 (0-6)</td>
<td>0.3</td>
</tr>
<tr>
<td>OC - People</td>
<td>6 (0-8)</td>
<td>6 (0-8)</td>
<td>0.8</td>
</tr>
<tr>
<td>OC - Things</td>
<td>4 (0-7)</td>
<td>4 (1-7)</td>
<td>0.7</td>
</tr>
</tbody>
</table>
Table 15. Proband generation participation in cognitively stimulating activities.

<table>
<thead>
<tr>
<th>Cognitive Activities</th>
<th>Probands</th>
<th>Referents</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early-life</td>
<td>2.7 (1.3-3.9)</td>
<td>3.0 (1.2-4.1)</td>
<td>0.2</td>
</tr>
<tr>
<td>Mid-life</td>
<td>2.8 (1.4-4.0)</td>
<td>3.1 (1.6-4.4)</td>
<td>0.002</td>
</tr>
<tr>
<td>Late-life</td>
<td>2.9 (1.8-4.2)</td>
<td>3.4 (2.0-4.4)</td>
<td>0.0002</td>
</tr>
</tbody>
</table>

Table 16 shows the results of the correlation of each neuropsychological test with mid-life participation in cognitively stimulating activities. No tests in the domain of episodic memory were significantly associated with mid-life cognitive activities. Under the domain of executive functions, the COWA, WGN, DSF, and both D-KEFS Sorting test scores were significantly associated with mid-life cognitive activities with correlations ranging from 0.35 to 0.42 (p<.0001). The correlation between each neuropsychological test and participation in late-life cognitively stimulating activity is shown in Table 17. Similar to mid-life cognitive activity, none of the episodic memory tests were significantly associated with late-life cognitive activity. The COWA, WGN, DSF, DSB, and the D-KEFS Sorting test Description Score under the domain of executive function showed moderate associations (r=.30 to r=.36, p<.001) with participation in late-life cognitive activities.
cognitive activities. Figures 13-22 show plots of the test scores that are correlated with mid- and late-life cognitive activities with regression lines added.
### Episodic Memory

<table>
<thead>
<tr>
<th>Test</th>
<th>R</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVLT15</td>
<td>0.07</td>
<td>0.5</td>
</tr>
<tr>
<td>CVLT-SD</td>
<td>0.06</td>
<td>0.5</td>
</tr>
<tr>
<td>CVLT-LD</td>
<td>-0.05</td>
<td>0.6</td>
</tr>
<tr>
<td>LMIB</td>
<td>0.11</td>
<td>0.2</td>
</tr>
<tr>
<td>LMIIB</td>
<td>-0.02</td>
<td>0.8</td>
</tr>
<tr>
<td>ROCF-I</td>
<td>0.03</td>
<td>0.8</td>
</tr>
<tr>
<td>ROCF-D</td>
<td>-0.12</td>
<td>0.8</td>
</tr>
</tbody>
</table>

### Executive Functions

<table>
<thead>
<tr>
<th>Test</th>
<th>R</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Animals</td>
<td>0.07</td>
<td>0.5</td>
</tr>
<tr>
<td>COWA</td>
<td>0.39</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>WGN</td>
<td>0.36</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CDT-F</td>
<td>-0.07</td>
<td>0.5</td>
</tr>
<tr>
<td>CDT-C</td>
<td>-0.16</td>
<td>0.1</td>
</tr>
<tr>
<td>DSF</td>
<td>0.35</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>DSB</td>
<td>0.27</td>
<td>0.003</td>
</tr>
<tr>
<td>DKEFS-DS</td>
<td>0.39</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>DKEFS-CS</td>
<td>0.42</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ROCF-C</td>
<td>0.16</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Table 16. Correlation of proband generation test performance with mid-life participation in cognitively stimulating activities.
Note: CVLT15 = CVLT Trials 1 to 5 score, CVLT-SD = CVLT Short Delay score, CVLT-LD = CVLT Long Delay score, ROCF-I = ROCF Immediate Presence and Accuracy score, ROCF-D = ROCF Delayed Presence and Accuracy score, LMIB = WMS-III Logical Memory I Story B Immediate Recall Trials 1 and 2 score, LMIIB = WMS-III Logical Memory II Story B Delayed Recall score, CDT-F = Clock Drawing Test Command Condition error score, CDT-C = Clock Drawing Test Copy Condition error score, DKEFS-CS = D-KEFS Sorting Test Confirmed Correct Sorts score, DKEFS-DS = D-KEFS Sorting Test Description Score, ROCF-C = ROCF Copy Presence and Accuracy score
<table>
<thead>
<tr>
<th>Episodic Memory</th>
<th>R</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVLT15</td>
<td>0.07</td>
<td>0.02</td>
</tr>
<tr>
<td>CVLT-SD</td>
<td>0.15</td>
<td>0.1</td>
</tr>
<tr>
<td>CVLT-LD</td>
<td>0.19</td>
<td>0.03</td>
</tr>
<tr>
<td>LMIB</td>
<td>0.23</td>
<td>0.01</td>
</tr>
<tr>
<td>LMIIB</td>
<td>0.16</td>
<td>0.1</td>
</tr>
<tr>
<td>ROCF-I</td>
<td>0.05</td>
<td>0.6</td>
</tr>
<tr>
<td>ROCF-D</td>
<td>-0.02</td>
<td>0.8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Executive Functions</th>
<th>R</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Animals</td>
<td>0.18</td>
<td>0.05</td>
</tr>
<tr>
<td>COWA</td>
<td>0.34</td>
<td>0.0001</td>
</tr>
<tr>
<td>WGN</td>
<td>0.35</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CDT-F</td>
<td>0.001</td>
<td>1.0</td>
</tr>
<tr>
<td>CDT-C</td>
<td>-0.12</td>
<td>0.2</td>
</tr>
<tr>
<td>DSF</td>
<td>0.30</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DSB</td>
<td>0.35</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>DKEFS-DS</td>
<td>0.36</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>DKEFS-CS</td>
<td>0.29</td>
<td>0.001</td>
</tr>
<tr>
<td>ROCF-C</td>
<td>-0.01</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Table 17. Correlation of proband generation test performance with late-life participation in cognitively stimulating activities.
Figure 13. Association of mid-life cognitive activity participation and the Controlled Oral Word Association test in the proband generation.

Figure 14. Association of mid-life cognitive activity participation and Word generation subtest of the Neuropsychological Assessment Battery in the proband generation.
Figure 15. Association of mid-life cognitive activity participation and Digits Forward in the proband generation.

$r=.35, p<.0001$

Figure 16. Association of mid-life cognitive activity participation and the Delis-Kaplan Executive Function System Sorting subtest Description Score in the proband generation.

$r=.42, p<.0001$
Figure 17. Association of mid-life cognitive activity participation and the Delis-Kaplan Executive Function System Sorting subtest Confirmed Correct Sorts Score in the proband generation.

$r = .39$, $p < .0001$

Figure 18. Association of current cognitive activity participation and the Controlled Oral Word Association test score in the proband generation.

$r = .34$, $p = .0001$
Figure 19. Association of current cognitive activity participation and the Word Generation subtest of the Neuropsychological Assessment Battery in the proband generation.

$r = .35, p < .0001$

Figure 20. Association of current cognitive activity participation and Digits Forward in the proband generation.

$r = .30, p = .0006$
**Figure 21.** Association of current cognitive activity participation and Digits Backward in the proband generation.

$r = .35, \ p < .0001$

**Figure 22.** Association of current cognitive activity participation and the Delis-Kaplan Executive Function System Sorting subtest Description Score in the proband generation.

$r = .36, \ p < .0001$
Development of a model to predict episodic memory performance from factors that underlie cognitive performance resulted in a final model consisting of intellectual ability estimated by NAART score, mid-life cognitive activity participation, frequency in attending church and religious meetings, frequency in participating in private religious activities, and number of social network ties. The full model $R^2$ was significantly greater than zero ($F(5, 117) = 4.65$, $p<.001$, $R^2 = .13$) and indicates that the model accounts for 13% of the variance in the composite score for episodic memory. Beta-estimates indicate that higher intellectual ability, lower mid-life cognitive activities, more participation in religious meetings (the DUREL is scored on an inverse scale), less participation in private religious activities and greater social network ties are associated with better episodic memory performance when each of the other variables are held constant. Table 18 shows the results of the final model of the multiple linear regression for the episodic memory composite score. The final model for predicting executive function composite scores included intellectual ability estimated by NAART error score, early- and mid-life participation in cognitive activities, and number of social network ties. The full model accounted for 41% of the variance in episodic memory composite scores ($F(4, 118) = 22.45$, $p<.0001$, $R^2 = .41$). Higher estimated intellectual ability, mid-life cognitive activities, and greater social network ties were associated with better executive function performance, whereas lower early-life cognitive activities was associated with higher executive function composite scores when all other variables were
held constant. The results of the multiple regression for the final model for predicting executive function composite scores are shown in Table 19.

<table>
<thead>
<tr>
<th>Predictor</th>
<th>β</th>
<th>R</th>
<th>CI.95 for r</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAART estimated IQ</td>
<td>.02*</td>
<td>.21*</td>
<td>.03, .37</td>
</tr>
<tr>
<td>Mid-life cognitive activities</td>
<td>-.25*</td>
<td>-.04</td>
<td>-.21, .14</td>
</tr>
<tr>
<td>DUREL1</td>
<td>-.13*</td>
<td>.01</td>
<td>-.16, .19</td>
</tr>
<tr>
<td>DUREL2</td>
<td>.07</td>
<td>.13</td>
<td>-.05, .30</td>
</tr>
<tr>
<td>SDI</td>
<td>.20***</td>
<td>.25**</td>
<td>.08, .41</td>
</tr>
</tbody>
</table>

Table 18. Multiple linear regression results for factors underlying episodic memory performance in the proband generation.

Note: *p<.05, **p<.01, ***p<.001

<table>
<thead>
<tr>
<th>Predictor</th>
<th>β</th>
<th>R</th>
<th>CI.95 for r</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAART estimated IQ</td>
<td>.04***</td>
<td>.60***</td>
<td>.48, .71</td>
</tr>
<tr>
<td>Early-life cognitive activities</td>
<td>-.17*</td>
<td>.23**</td>
<td>.06, .39</td>
</tr>
<tr>
<td>Mid-life cognitive activities</td>
<td>.20*</td>
<td>.36***</td>
<td>.20, .50</td>
</tr>
<tr>
<td>SDI</td>
<td>.08**</td>
<td>.25**</td>
<td>.08, .41</td>
</tr>
</tbody>
</table>

Table 19. Multiple linear regression results for factors underlying executive function performance in the proband generation.

Note: *p<.05, **p<.01, ***p<.001
Discussion

Proband referents had significantly more participation in mid- and late-life cognitive activities compared with proband generation participants. As participation in cognitively stimulating activities is associated with better cognitive function, it suggests that proband referents may be more reliant on higher cognitive reserve to achieve exceptional longevity. Conversely, proband generation participants may have genetic predispositions or environmental exposures associated with familial longevity that result in similar cognitive performance as those with higher cognitive reserve. Brain reserve or brain maintenance may be more applicable concepts in regard to the proband generation participants. Following the concept of brain reserve, they may have neuronal or structural differences, rather than increased cognitive reserve, that account for higher thresholds for functional impairment following brain insult. Alternatively, they may have innate or exposure-related protective factors that prevent damage to neuronal structures and resulting cognitive impairment following the model of brain maintenance. However, without structural imaging or neuropathological assessments conclusive statements cannot be made. Imaging studies of offspring of nonagenarian siblings have found fewer white matter lesions and less degradation of white matter integrity (Altmann-Schneider et al., 2013) Although these studies were done in the offspring generation they suggest that familial longevity is associated with lower susceptibility to white matter damage.
Mid- and late-life participation in cognitively stimulating activities was not found to be associated with performance on tests of episodic memory in the proband generation. In contrast, cognitively stimulating activities had moderate associations with the COWA, WGN, DSF, and D-KEFS Sorting Test Description Score. Mid-life cognitive activity was also associated with the D-KEFS Confirmed Correct Sorts Score and late-life cognitive was associated with DSB. These tests comprise several different processes under the domain of executive functions. The COWA and WGN assess verbal fluency and generativity. The DSB assesses attention and the DSB assesses working memory. The D-KEFS Sorting Test examines abstraction ability for generating categories of similar items.

Better cognitive function in association with engagement in cognitively stimulating activities has significant implications for daily living and maintenance of independence. Better health habits, medication adherence, prevention from falls, and maintained driving ability are only some of the beneficial side effects of preserved cognitive function.

Episodic memory composite scores were best predicted by intellectual ability, mid-life participation in cognitively stimulating activities, attendance at religious meetings, engagement in private religious activities, and size of social networks. Executive function composite scores were predicted by intellectual ability, early- and mid-life cognitive activities and social network size. The predictive value of intellectual ability for neuropsychological test performance is
not surprising as they have been well-documented to be associated. Interestingly, mid-life cognitive activities predicted lower episodic memory function but better executive function. This may indicate that increase of cognitive reserve is more related to building networks associated with executive function but not episodic memory.

Similar to previous studies (Krueger et al., 2009), we found that social networks were significantly associated with neuropsychological test performance even when controlling for proxies of cognitive reserve. The social network questionnaire used in the current study contained similar information about social activities and social network size but did not assess perceived social support. Interestingly, Krueger and colleagues only found an association of social activities and social support but not social network size with cognitive performance. Our measure of social networks, which includes social activities and social network size, was associated with cognitive performance so the results are not completely congruent. However our findings were consistent with a study by James and colleagues (2011) that found an association between participation in social activities and composite scores of episodic memory and additionally perceptual speed.

Social networks are important for well-being and support. Rohr and Lang (2009) noted that for social networks to remain beneficial and promote healthy aging there is a an adaptive requirement to remove negative ties and seek positive relationships, reshape relationships with changing roles, and balance
social support against interdependency. They also note that most assessments of social networks do not assess negative aspects of social ties. The questionnaire used in this study falls into that category. It is possible that assessment of negative qualities of social relationships may also be associated with cognitive performance and longevity, and therefore, warrants future investigation.

We also found that composite measures of episodic memory test performance were predicted by more frequent attendance at religious meetings but lower participation in private religious activities. This may indicate that the social component of religious activities is an important component for preserving cognitive function. However, this may not necessarily indicate that religiosity is associated with cognitive performance. Instead, it may be that ability to attend religious meetings is indicative of better functional status and that greater participation in private religious activities may be the result of functional impairment. These results are also in contrast with a study of Alzheimer’s patients which found participation in private religious activities to be more informative than attendance at religious meetings in predicting decline in MMSE scores (Kaufman et al., 2007).

A limitation to this study of factors underlying cognitive performance is that questionnaires regarding participation in cognitively stimulating activities at mid-life and exercise at age 40 were administered retrospectively, on average 50 years after the time point of interest. This does, however, warrant asking these
questions in the younger generation who are currently closer in age to the time point of interest and expected to be followed longitudinally.

The multifaceted nature of neuropsychological tests should also be considered. Performance on tests traditionally considered to be memory or executive function tests also require intact language and visuospatial functions. The CDT is an example of a test that can be used to examine executive function. Conceptualization is required on the command condition to convert time from a verbal format to representation of time on the clock. Organization and planning are necessary to properly place numbers along the circumference of the circle. However, remembering the stimulus time and the features of the clock utilizes memory functions. Visuospatial functions are necessary to be able to place numbers and hands in the appropriate region of space and intact language functions are required to be able to process the verbal stimulus to draw a clock. Therefore, deficits in these other domains may also result in higher error scores, thereby making the test an impure test of executive function. It is extremely difficult, if not impossible, to develop tests that are pure assessments of a single cognitive domain or process which means that it is also more difficult to study domains and processes in isolation. The creation of composite scores of episodic memory and executive function may have been affected by heterogeneity of tests within the episodic memory and executive function domains.
CHAPTER FIVE: IMPLICATIONS AND FUTURE DIRECTIONS

This study lends further evidence that familial longevity is associated with better cognitive function in the offspring generation. The tendency toward better performance on tests of attention and executive function in this relatively young, small sample suggests the need for further evaluation of neuropsychological test performance, both on data already collected and over longitudinal follow-up. Preservation of cognitive function has substantial public health implications as the population is living longer than ever before. Increased average life expectancy that is associated with more years of physical and cognitive functional disability would have negative ramifications of greater health care and social support costs. However, increased longevity associated with preserved physical and cognitive function fitting the compression of disability paradigm would result in a population that is able to maintain independence and greater life satisfaction.

Successful cognitive aging paradigms are varied. Rowe and Kahn suggest that successful aging is a result of minimal change in function with increasing age (Rowe & Kahn, 1997). As this was not a longitudinal study, cognitive trajectories, and therefore, maintenance of cognitive function with increasing age, cannot be assessed. Although comparisons were not made between the proband generation and the offspring generation in this study, proband generation performance on average was lower than in the offspring generation. It is possible that some individuals in the proband generation are
performing in the average range of the offspring generation and are therefore successful cognitive agers. Alternatively, another definition of successful cognitive aging is performance well above that of age-matched controls, although this definition excludes those who maintain cognitive function at average levels (Daffner, 2010). In this study, the proband generation participants did not perform significantly better than age-matched controls, and thus, would not be considered successful cognitive agers according to this definition. As cognitive function is highly correlated with mortality and both proband generation participants and proband referents have achieved exceptional survival beyond average life expectancy and were able to take part in the study, they are all successful cognitive agers at least to some degree. However, these two cohorts may be using different pathways to achieve successful cognitive aging.

The role of education and cognitive reserve in relation to cognitive performance in the proband generation has useful implications for people without familial longevity. Preservation of cognitive function and compression of cognitive disability has been demonstrated with increasing exceptional longevity. In this study, proband generation participants with an average age of 91 performed similarly to the referent group regardless of the fact that those with familial longevity had lower education. This suggests that higher education and intellectual ability may give people without familial longevity similar cognitive benefits as those with familial longevity. Furthermore, the higher engagement of the proband referent group in cognitively stimulating activities, which has been
shown to be related to increased cognitive reserve, suggests that leisure activities may also help those without familial longevity become successful agers. It has been suggested that participation in cognitively stimulating activities and physical activities provides the most evidence for increasing cognitive reserve and decreasing risk of dementia (Daffner, 2010). However, we did not find evidence of an association of current or mid-life exercise with cognitive performance in this study.

Future studies should analyze qualitative aspects of test performance, particularly in the proband generation. The tests that were administered in this battery were chosen for both their quantitative and qualitative value. Therefore, there is a significant amount of qualitative information about the process used to come to an answer that can be gleaned from these tests. More efficient processes in performing neuropsychological tests may be indicative of the use of different neural networks. Many qualitative processes can reveal information about executive functioning that is generally not testable by direct means. Self-monitoring, the process of double-checking performance and making corrections throughout completion of a task, can lead to improved neuropsychological test performance. Similarly, clustering of words by semantic category on the word list learning tasks or verbal fluency tasks has been related to better test performance. It is possible that although the proband generation participants had lower intellectual ability, they may be using more efficient processes to complete
tasks, and therefore, maintain cognitive function levels comparable to those with higher intellectual ability.

As stated earlier, future studies should investigate the change in cognitive function over time in this cohort with exceptional familial longevity. Cognitive trajectories as the cohort ages, particularly in the relatively young offspring generation, may reveal a divergence in cognitive performance if the offspring generation maintains cognitive stability and the referent group declines. In the proband generation, following participants over time may reveal important information about the phenomenon of terminal decline, the ability to maintain function at a high level followed by a rapid decline at the very end of life. As terminal decline is congruent with the compression of disability hypothesis, it is important to examine whether LLFS participants are able to show preservation of cognitive function until the very end of life compared with participants without familial longevity.

A continuation of the analysis of proxies of cognitive reserve is warranted due to the findings of higher participation in cognitively stimulating activities in the proband referent cohort. Additional analyses could investigate the relationship between specific types of leisure activities and cognitive performance. Creative activities or detail-oriented activities may show better association with neuropsychological test scores than other activities. Length of duration of participation in each activity and mastery of the activity may also be related to increased cognitive performance.
One could also use the data from the neuropsychological test battery to select families with clustering for exceptional cognitive performance. Families with multiple family members scoring well above the mean across multiple tests within the battery may represent a subsample with unique genetic or environmental contributions to cognitive performance. In addition, families with discordant siblings, one scoring well above the mean and one well below the mean could be informative for determining factors associated with successful cognitive aging.
APPENDICES
### APPENDIX 1 – ADMINISTRATION ORDER OF TESTS FOR SESSIONS COMPLETED IN ONE VISIT

**Part 1**

- North American Adult Reading Test
- Mini-Mental State Examination
- Boston Naming Test
- California Verbal Learning Test II Immediate Recall
- Rey-Osterrieth Complex Figure Copy
- Rey-Osterrieth Complex Figure Immediate Recall
- Controlled Oral Word Association test
- Semantic verbal fluency for animals
- Neuropsychological Assessment Battery Word Generation
- California Verbal Learning Test II Delayed Recall
- Rey-Osterrieth Complex Figure Delayed Recall
- California Verbal Learning Test II Forced Choice Recognition

**Part 2**

- Blood pressure measurements
- Ankle/Brachial Index Test
- Visual & auditory acuity assessments
- Clock Drawing Test – Command Condition
- Wechsler Memory Scale III Digit Span
- Wechsler Memory Scale III Logical Memory I
- Clock Drawing Test – Copy Condition
- Delis-Kaplan Executive Function System Sorting Test
- Wechsler Memory Scale III Logical Memory II
- Clock Drawing Test – Pre-drawn (Number Placement)
- Clock Drawing Test – Pre-drawn (Time Setting)
- Center for Epidemiological Studies Depression Scale
### APPENDIX 2 – ADMINISTRATION ORDER OF TESTS FOR SESSIONS COMPLETED IN TWO VISITS

<table>
<thead>
<tr>
<th>Day 1</th>
<th>Day 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>North American Adult Reading Test</td>
<td>California Verbal Learning Test II Forced Choice</td>
</tr>
<tr>
<td>Mini-Mental State Examination</td>
<td>Recognition</td>
</tr>
<tr>
<td>Boston Naming Test</td>
<td>Clock Drawing Test – Command Condition</td>
</tr>
<tr>
<td>California Verbal Learning Test II Immediate Recall</td>
<td>Wechsler Memory Scale III Digit Span</td>
</tr>
<tr>
<td>Rey-Osterrieth Complex Figure Copy</td>
<td>Wechsler Memory Scale III Logical Memory I</td>
</tr>
<tr>
<td>Rey-Osterrieth Complex Figure Immediate Recall</td>
<td>Clock Drawing Test – Copy Condition</td>
</tr>
<tr>
<td>Controlled Oral Word Association test</td>
<td>Delis-Kaplan Executive Function System Sorting Test</td>
</tr>
<tr>
<td>Semantic verbal fluency for animals</td>
<td>Wechsler Memory Scale III Logical Memory II</td>
</tr>
<tr>
<td>Neuropsychological Assessment Battery Word Generation</td>
<td>Clock Drawing Test – Pre-drawn (Number Placement)</td>
</tr>
<tr>
<td>California Verbal Learning Test II Delayed Recall</td>
<td>Clock Drawing Test – Pre-drawn (Time Setting)</td>
</tr>
<tr>
<td>Rey-Osterrieth Complex Figure Delayed Recall</td>
<td>Center for Epidemiological Studies Depression Scale</td>
</tr>
</tbody>
</table>

Performed at the end of Day 1 or Day 2 at the discretion of the examiner

| Blood pressure measurements | Ankle/Brachial Index Test | Visual & auditory acuity assessments |
### APPENDIX 3 – ADMINISTRATION ORDER OF TESTS FOR SESSIONS COMPLETED IN THREE VISITS

<table>
<thead>
<tr>
<th>Day 1</th>
<th>Day 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>- North American Adult Reading Test</td>
<td>- Clock Drawing Test – Command Condition</td>
</tr>
<tr>
<td>- Mini-Mental State Examination</td>
<td>- Wechsler Memory Scale III Digit Span</td>
</tr>
<tr>
<td>- Boston Naming Test</td>
<td>- Wechsler Memory Scale III Logical Memory I</td>
</tr>
<tr>
<td>- California Verbal Learning Test II Immediate Recall</td>
<td>- Clock Drawing Test – Copy Condition</td>
</tr>
<tr>
<td>- Rey-Osterrieth Complex Figure Copy</td>
<td>- Health &amp; sociodemographics questionnaire</td>
</tr>
<tr>
<td>- Rey-Osterrieth Complex Figure Immediate Recall</td>
<td>- Wechsler Memory Scale III Logical Memory II</td>
</tr>
<tr>
<td>- Controlled Oral Word Association test</td>
<td>- Clock Drawing Test – Pre-drawn (Number Placement)</td>
</tr>
<tr>
<td>- Semantic verbal fluency for animals</td>
<td>- Clock Drawing Test – Pre-drawn (Time Setting)</td>
</tr>
<tr>
<td>- Neuropsychological Assessment Battery Word Generation</td>
<td>- Center for Epidemiological Studies Depression Scale</td>
</tr>
<tr>
<td>- California Verbal Learning Test II Delayed Recall</td>
<td>Day 3</td>
</tr>
<tr>
<td>- Rey-Osterrieth Complex Figure Delayed Recall</td>
<td></td>
</tr>
<tr>
<td>- California Verbal Learning Test II Forced Choice Recognition</td>
<td>- Delis-Kaplan Executive Function System Sorting Test</td>
</tr>
<tr>
<td></td>
<td>- Blood pressure measurements</td>
</tr>
<tr>
<td></td>
<td>- Ankle/Brachial Index Test</td>
</tr>
<tr>
<td></td>
<td>- Visual &amp; auditory acuity assessments</td>
</tr>
</tbody>
</table>
## APPENDIX 4 – INDIVIDUAL TESTS OMITTED FROM ANALYSIS

<table>
<thead>
<tr>
<th>Test</th>
<th>Number Omitted</th>
<th>Refused</th>
<th>Vision Impairment</th>
<th>Insufficient Effort</th>
<th>Environmental Distraction</th>
<th>Examiner Error</th>
<th>Non-native English speaker</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAART</td>
<td>2</td>
<td></td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BNT</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVLT-II</td>
<td>3</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ROCF</td>
<td>9</td>
<td>4</td>
<td>1</td>
<td></td>
<td></td>
<td>3</td>
<td></td>
<td>1 Motor Impairment</td>
</tr>
<tr>
<td>Verbal Fluency</td>
<td>2</td>
<td></td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1 Fatigue</td>
</tr>
<tr>
<td>WGN</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td></td>
<td>1 Low Literacy</td>
</tr>
<tr>
<td>Digit Span</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D-KEFS</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>1 Illness</td>
</tr>
<tr>
<td>LM</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>
Note: Verbal Fluency included the Controlled Oral Word Association test and Animal fluency, NAART = North American Adult Reading Test, BNT = Boston Naming Test, CVLT-II = California Verbal Learning Test – Second Edition, ROCF = Rey-Osterrieth Complex Figure, WGN = Word Generation test from the Neuropsychological Assessment Battery, D-KEFS = Delis-Kaplan Executive Function System, LM = Logical Memory from the Wechsler Memory Scale – Third Edition
<table>
<thead>
<tr>
<th></th>
<th># of Sessions</th>
<th># of Omitted Tests</th>
<th># of Refusals</th>
<th># of Examiner Errors</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>312</td>
<td>31</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Examiner 1 (SA)</td>
<td>105 (34%)</td>
<td>8 (26%)</td>
<td>1</td>
<td>0</td>
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<tr>
<td>Examiner 2</td>
<td>88 (28%)</td>
<td>11 (35%)</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Examiner 3</td>
<td>41 (13%)</td>
<td>3 (10%)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Examiner 4</td>
<td>51 (16%)</td>
<td>6 (20%)</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Examiner 5</td>
<td>27 (9%)</td>
<td>3 (10%)</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

Note: Examiner 2 did not correct three participants who drew pentagons from the Mini-Mental State Examination for ROCF Delayed Recall, Examiner 4 did not properly administer two tests and did not correct a participant who misunderstood the instructions on a test (participant gave responses from the Word Generation test when asked to recall the California Verbal Learning Test – Second Edition Delayed Recall).
APPENDIX 6 – HISTOGRAMS OF TRANSFORMED DATA FOR BEHAVIOR RATING INVENTORY OF EXECUTIVE FUNCTION-ADULT VERSION IN THE PROBAND GENERATION

Note: Transformation of the data was performed using the cubic root (upper right), square root (lower left), and log (lower right). BRIEF-A = Behavior Rating Inventory of Executive Function – Adult Version.
APPENDIX 7 – HISTOGRAMS OF TRANSFORMED DATA FOR BOSTON NAMING TEST AND BEHAVIOR RATING INVENTORY OF EXECUTIVE FUNCTION – ADULT VERSION IN THE OFFSPRING GENERATION
Note: Transformation of the data was performed using the cubic root (upper right), square root (lower left), and log (lower right). BNT = Boston Naming Test, BRIEF-A = Behavior Rating Inventory of Executive Function – Adult Version


A, Biological Sciences and Medical Sciences, 63(8), 848-854. doi: 10.1093/gerona/63.8.848


Weintraub, S., Salmon, D., Mercaldo, N., Ferris, S., Graff-Radford, N.R., Chui, H., Cummings, J., DeCarli, C., Foster, N.L., Galasko, D., Peskind, E.,


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Research Assistant, Brandeis University, Wingfield Memory and Cognition Lab, January 1999-May 2000. Supervisors: Karen Kemptes, PhD and Arthur Wingfield, PhD.

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Book Chapters:

Relevant Presentations:


Journal Reviews: Ageing & Society
Archives of Internal Medicine
The Journals of Gerontology: Psychological Sciences

Scientific Meeting Reviews: American Geriatrics Society
Gerontological Society of America

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June 2008 – Faculty nominated participant in the AAAS/Science Program for Excellence in Science
June 2006 – Massachusetts Neuropsychological Society 2006 Laird S. Cermak Poster Session – Honorable Mention

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American Geriatrics Society – 2006 to present
Gerontological Society of America – 2010 to present
Massachusetts Neuropsychological Society - 2006 to present