Identifying early-, mid-, and later-life experiences that condition the expression of genetic propensities of cognitive decline and Alzheimer's disease

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Abstract

Of all life-threatening diseases, Americans most fear Alzheimer's disease (AD)—even more than cancer, stroke, heart disease, or diabetes. AD is devastating to individuals, their partners, and other family members as the disease strips people of their identities and ability to function. Estimates suggest that there will be 13.8 million cases of AD by 2050, becoming a public health crisis. Research on AD has not yet yielded a cure but there have been significant advancements in understanding its genetic causes. However, many people who possess genetic markers for AD and even who have measurable AD pathology never develop symptoms of the disease. This discovery has led to a search for clues from early-life experiences and social environments that could either block the genetic propensity of AD to express itself or open a gate to the biological processes that result in AD symptoms. Unfortunately, few large-sample, general-population sources of data on older adults who are at risk for Alzheimer's contain prospective information on early-life experiences. Our proposal requests funding to extend our effort to collect DNA data from participants of The Life & Family Legacies Study. This study began in 1966 with high school students in Washington state from the classes of 1966 and 1967. With participants now approaching 70, we are at a critical time to collect the DNA data before too many participants start becoming unable to participate due to mental or physical health problems or death. We seek funding for the student wages and materials needed to collect and extract DNA from participant saliva samples. We have already secured funding for the sample collection (purchasing saliva kits, mailing the kits, providing respondent incentives). The IDR award would be used to process the kits when they are returned by respondents, including logging them and extracting the DNA from the saliva samples. The final stage of the project will be securing a R01 grant from the National Institute of Aging of about $1 million for the analysis of DNA.

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Introduction

Of all life-threatening diseases, Americans most fear Alzheimer's disease (AD)—even more than cancer, stroke, heart disease, or diabetes (Marist Poll, 2012). AD can also be devastating to partners and other family members as they watch a loved one lose memory of their relationships and the ability to function. Although there are no cures for AD, the search for cures has led to significant advancements in understanding the genetic causes of AD. However, many people who possess genetic markers of AD never develop symptoms of the disease (Breitner et.al., 1999). Many researchers believe that early-life social environment and experiences (e.g., head trauma) may be the key to understanding why and how the genetic markers of AD manifest in symptoms in later life (e.g., Lahiri et al. 2008). However, few large-sample, general-population sources of data on older adults who are at risk for AD contain information on early-life experiences. With DNA available from participants in the on-going Life & Family Legacies study, a study that began in 1966 with high school juniors and seniors from Washington State, the study will become the single-best suited dataset to uncover the early-life environmental triggers of the genetic propensity for AD. Because participants are about age 70, we are at a critical time to collect the DNA data before too many start become unable to participate due to mental or physical health problems or death.

Background

AD is the most common form of dementia among the elderly. Dementia is a broad classification of disorders, of which AD is a part, characterized by a decline in cognition involving one or more cognitive domains (learning and memory, language, executive function, complex attention, perceptual-motor, social cognition) that is severe enough to interfere with daily functioning and personal independence (Larson, 2015). AD diagnoses account for somewhere between 60 and 80 percent of all dementia diagnoses (Alzheimer's Association, 2017).

Dementia, and particularly AD, are linked to age. Fewer than five percent of all people diagnosed with AD develop symptoms before age 65 (Mayo Clinic, 2014). While in 2013 only 14.1 percent of the U.S. population was age 65 or older, that number will grow to 22 percent by 2040 (Administration on Aging, 2015). AD is the only top ten cause of death in the US that cannot be effectively slowed, prevented, or cured (Alzheimer's Association, 2017). Given our aging population and the sharp increase in the incidence of AD at older ages, unless there are new interventions to cure, prevent, or slow the onset of dementia, the number of people diagnosed with AD may nearly triple, from 5.1 million to 13.8 million cases by 2050 (Alzheimer's Association, 2017). A tripling of AD will be extremely taxing on healthcare providers, long-term care facilities, and families caring for relatives with the disease.

The Linkage Between Memory Lapses, Cognitive Decline, Dementia, and Alzheimer's Disease

Memory lapses, to some extent, are normal at all ages–a child forgets to take lunch to school, a middle-aged father forgets his teenage child's birthday, an elderly woman forgets where she placed her glasses. However, it is only the elderly whose forgetfulness has a name—a "senior moment." With age, forgetfulness becomes meaningful as a potential sign of a coming transition between normal aging and dementia. For most, these memory lapses are generally minor causing temporary embarrassment, but do not disrupt daily life. However, a faulty memory or lapses in other cognitive domains can interrupt

normal functioning and then reflect mild cognitive impairment, a diagnosable condition. These initial deficits in memory may be hardly noticeable to the individual, generally do not significantly impact daily functioning, and can often be resolved using memory aids to help compensate. Over the life-course about a fifth of the population develops mild cognitive impairment (Manly et. al., 2008).

While the causes of mild cognitive impairment are not well understood, one potential cause may be changes in the brain that indicate the very early stages of AD or other dementia. A recent study showed that about a fifth of those with cognitive impairment eventually progressed to a diagnosis of AD, about half remained cognitively impaired (Manly et. al., 2008). Overall, however, people with mild cognitive impairment were 2.8 times more likely to develop AD than "normal" elders.

Statement of Need

A New Approach to Understanding Cognitive Decline and Alzheimer's Disease

Given the known linkage between mild cognitive decline and AD, it is critical to identify factors that predict cognitive decline and when it leads to AD. There is evidence of genetic causes of AD, although work continues to better understand those genetic origins (Ridge et al., 2017). However, findings suggest that many with a high genetic risk for AD never develop symptoms of the disease (Breitner et.al., 1999). AD researchers colloquially refer to the connection between genetic disposition and the expression of AD as genetics loading the gun but environment pulling the trigger. Consequently, the search for causes of cognitive decline and AD has evolved to investigating how early-life experiences might trigger the expression of genetically prescribed biological processes that lead to cognitive decline and AD in some people but allow those processes to remain dormant in others. For example, potential social triggers could be something as concrete as a particular kind of traumatic event (e.g., physical abuse, divorce, death of a spouse, an accident, a traumatic brain injury, etc.), prior illness or the onset of a chronic disease, or as abstract as growing up in a neighborhood characterized by social disorganization (e.g., high crime, low employment, etc.).

What is Needed: Better Data on Social and Environmental Triggers

The difficulty is that most studies of cognitive decline or AD include just a year or two of prior life experiences. Studies do not contain detailed life-history information on large groups of people over an extended period of time that would effectively identify environmental triggers of AD. Although studies try to reconstruct life histories, people are often unable to accurately recall most early-life experiences, creating significant bias in retrospective accounts. One major life-event study that has prospective, detailed life-history data from high school years into older years that could be used to identify possible social and environmental triggers of AD—the Wisconsin Longitudinal Study—has participants that are currently near 80 years old. However, too many of the study participants have died or already begun the descent into cognitive decline for the data to be able to reliably examine environmental triggers of AD. The Life & Family Legacies Study began with high school students in 1966, and people in this study are now about age 70. They are at the cusp of when the prevalence of AD sharply increases.

Study Details

The Life & Family Legacies Study is a longitudinal study that began with 6,729 juniors and seniors from 25 randomly selected urban and rural Washington high schools in 1966. This survey examined their family life, their high school achievements and activities, and their plans for the future. These former students were interviewed again in 1980 about their life events up to age 30-35. About half the young

men in the original survey served in the military during the Vietnam era, and all participants entered young adulthood during the turbulent 1960s and 1970s. About 90 percent of the original respondents participated in the 1980 study. In 2010 and 2012, we conducted additional follow-ups with these early "baby boomers" just prior to retirement age. The 2010 and 2012 studies focused on updating their life experiences, their personal well-being, and any health status changes, as well as assessing their access to health care, relationships with children/grandchildren, and retirement plans. About 3,500 respondents participated in these follow-ups.

The 2016-2018 follow-up includes a questionnaire, a telephone interview, and the DNA component that is the subject of this proposal. The questionnaire updates life histories and assesses the Australian National University Alzheimer's Disease Risk Index and other major social, physical injury, and health antecedents of cognitive decline previously identified in the literature. A broad group of faculty throughout the university worked together to identify these measures. The faculty involved in the development of the questionnaire include the faculty named on this proposal as well as the following:

Blaine Winters; School of Nursing
Brent Nielsen; Microbiology & Molecular Biology in the College of Life Sciences
Brock Kirwan; Psychology in the College of Family, Home, and Social Sciences
Craig Nuttall; School of Nursing
Jeremy Yorgason; School of Family Life in the College of Family, Home, and Social Sciences
Michael Larson; Psychology in the College of Family, Home, and Social Sciences
Richard Miller; Sociology in the College of Family, Home, and Social Sciences
Ronald Hager; Exercise Science in the College of Life Sciences

Each of these faculty are important to the overall design of the study of social and environmental triggers to AD that we present here but are not included on the proposal as investigators because the funding we are asking for will specifically be used for the collection and processing of the saliva samples to generate DNA data. We are currently collecting questionnaire data are approaching 2,500 responses.

As respondents return their questionnaire, they are contacted by our study staff by telephone to participate in a short telephone interview. The purpose of the interview is to establish a baseline measure of cognitive decline using the Minnesota Cognitive Acuity Screen (MCAS; Knopman et al., 2000). The MCAS was developed as a telephone administered screening tool to measure cognitive function and, primarily, memory impairment, which is typically the first cognitive symptom associated with the onset of AD. Respondents also complete a number of cognitive tasks as part of the MCAS, which increases its sensitivity to cognitive decline. The MCAS takes approximately 15 minutes to administer and has been standardized for use over the telephone. With such a large sample as ours, the MCAS is an appropriate tool to use to assess cognitive functioning because it can be reliably done over the telephone. In addition, more recent studies have demonstrated that the MCAS can differentiate between healthy older persons with intact cognition, those with early symptoms of dementia, and those diagnosed with AD (Tremont et al., 2011). The telephone assessment also includes a measure of semantic fluency that takes 60 seconds to administer and has been shown to be particularly sensitive to AD (Henry et al., 2004). In addition to the MCAS and semantic fluency test, we ask basic demographic and health related questions, which have been shown as predictors for risk of developing cognitive decline and AD (Pankratz et al., 2015; Xu et al., 2015). Respondents receive a $20 incentive payment for completing the telephone assessment.

We have secured the $300 thousand funding needed to collect saliva samples from the study participants. Once respondents have completed their cognitive functioning assessment by telephone, they become eligible for the DNA component of the study. We are scheduled to begin sending Oragene DNA (OG-500) saliva collection kits to participants during February. Participants will be mailed a letter notifying them about their opportunity to participate in the saliva collection along with a consent form. Once we receive their consent form, we will send them the collection kit with instructions on how to

provide the sample and return it to us. Once we receive the saliva sample, we will mail the respondents a $50 incentive payment and store the saliva samples.

The IDR award will be used to extract the respondents' DNA from the saliva samples. This will be done in Dr. Kauwe's lab using the prepIT L2P reagents and protocols designed by the provider of the saliva kits (DNA Genotek Inc. Kanata, Ontario, Canada). Once the DNA are extracted, they will be stored in a locked freezer at -20° Celsius. The DNA samples will be stored in Dr. Kauwe's lab until funding is secured for the DNA analysis. Dr. Kauwe has considerable experience with these processes. The volume of extractions that will be involved will keep a steady flow of work for two years for the students that the IDR grant will fund.

Anticipated Outcome of IDR funding

Once we extract the DNA using the IDR funding, the final stage of the DNA portion of the project is to do the genetic analysis. Whole genome mapping identifies the complete genetic makeup of each subject. This remains a time-intensive and costly endeavor and will potentially require close to $1 million for a sample as large as ours. We anticipate that the DNA extraction will be near completion at the end of two-year IDR funding period. However, at the beginning of the second funding year, we will prepare and submit an R01 proposal to the National Institute of Aging. Having the DNA samples prepared, the novel nature of the data and research questions, and considering the funding history of the investigators, we feel like the likelihood of being funded is very good.

The three investigators have successfully collaborated on academic papers in the past. However, the IDR funding would significantly strengthen the collaborative relationships that we have as we work through the DNA extraction process and pursue funding from the NIA. Dr. Erickson is the Project Director of The Life & Family Legacies Study and has worked with the dataset since 2009. His familiarity with the sample and the survey research process are critical for the collection of these data. Dr. Kauwe's experience with the genetics of AD provide the needed expertise for processing the saliva samples to producing usable DNA data. As a physician and neuroscientist, Dr. Hedges' role as investigator on this project is as an expert on the social correlates of cognitive functioning.

Potential Impacts of Project

Using the multidimensional, longitudinal design of this study—now spanning 50 years—and its associated large number of subjects, we anticipate being able to identify social, medical, and demographic factors over the lifespan that are associated with cognitive function in late life and that trigger the expression of the genetic propensity for AD. We anticipate that the knowledge generated by this project will prove valuable in at least four ways.

First, the identification of both lifetime risk and protective factors for cognitive function in late life will improve our theoretical understanding of cognitive aging.

Second, it is likely that some of the triggers we identify will be modifiable giving individuals power to decrease their risk of AD. Specifically, a more complete characterization of environmental triggers may lead to more effective prognostic or diagnostic testing. This could provide a mechanism for earlier interventions with existing therapies and open the door to developing additional preventive interventions. For example, drug development can be accelerated by the identification of appropriate therapeutic targets.

Third, because we will be connecting genetic propensities for AD with early-life triggers, public health campaigns could be designed to target specific groups of people who are particularly at risk for dementia.

Finally, as work on AD continues to explore its genetic causes and potential medical treatments,

a better understanding of the environmental and genetic interplay leading to the disease will inform selection of at risk samples for clinical trials. This knowledge could make the path to a cure faster and more efficient and may illuminate novel biological pathways that can be developed as therapeutic targets for AD.

Conclusion

The IDR funding is a critical piece to our project. By adding a genetic component to The Life & Family Legacies Study, it will be uniquely positioned to make a significant contribution to the investigation of AD. By looking at environmental triggers and the onset of AD disease using surveys, phone assessments, and DNA, valuable new insights could be discovered that identify options for a way forward with efforts to prevent and treat AD.

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Budget

Year 1

$10,000: Genotek prepIT L2P reagents
$49,920: 4 students at $11.50/hour for 20 hours/week for 52 weeks

Total: $59,920

Year 2

$10,000: Genotek prepIT L2P reagents
$49,920: 4 students at $12/hour for 20 hours/week for 52 weeks

Total: $59,920

Justification

As described in our proposal, the saliva kits will only be sent to respondents who have completed previous components of the study. However, a large number of participants already satisfy this criterion. Consequently, we anticipate that there will be an immediate need for the DNA extraction reagents in Year 1. The student wages for Year 1 are also needed to immediately begin processing the samples and extracting the DNA.

While the students process the early returned saliva samples, we will continue to pursue respondents who do not immediately return their collection kits and who have not completed the questionnaire and telephone assessment. As respondents complete these components, we will invite these additional respondents to participate in the saliva collection. Consequently, we anticipate a steady receipt of saliva samples through the middle of the second funding year. Therefore, continued funding for student wages is necessary.

Although we are not entirely certain how many saliva samples we will receive, we believe that the reagents we will purchase over the course of both IDR funding years will cover what we need for a generous estimate of the response we are likely to have based on previous research experience with the study participants.

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Education

2005 Ph.D., Sociology, University of North Carolina at Chapel Hill
2001 M.S., Sociology, Brigham Young University
1999 B.S. with University Honors, Sociology, Brigham Young University

Teaching and Research Positions

2013 – present Associate Professor, Department of Sociology, Brigham Young University.
2006 – 2013 Assistant Professor, Department of Sociology, Brigham Young University.
2002 – 2005 Pre-Doctoral Trainee, Carolina Population Center, University of North Carolina at Chapel Hill.

Grants and Awards

2014 – 2017 Hinckley Young Scholar, College of Family, Home, and Social Sciences, Brigham Young University.
2011 – 2012 Lance D. Erickson and Vaughn R.A. Call, "Montana Health Matters Follow-up," US Department of Veterans Affairs, $293,325.
2010 – 2011 Vaughn R.A. Call, Lance D. Erickson, Jeremy Yorgason, and Carol Ward, "Vietnam Veteran Study Follow-up," US Department of Veterans Affairs, $276,633.
2009 – 2010 Lance D. Erickson and Vaughn R.A. Call, "Veteran Health in Urban and Rural Communities," US Department of Veterans Affairs, $233,024.

Selected publications

Berrett, AN, SD Gale, LD Erickson, BL Brown, DW Hedges. (Forthcoming). "Helicobacter pylori moderates the association between 5-MTHF concentration and cognitive function in older adults." *PLoS ONE.*

Erickson, LD, S Sanders, MR Cope. (Forthcoming). "Lifetime Stayers in Urban, Rural, and Highly Rural Communities in Montana." *Population, Space and Place.*

Gale, SD, AN Berrett, LD Erickson, BL Brown, DW Hedges. (2018). "Association between Virus Exposure and Depression in US Adults." *Psychiatry Research*. 261:73-79. DOI: 10.1016/j.psychres.2017.12.037.

Berrett, AN, LD Erickson, SD Gale, A Stone, BL Brown, and DW Hedges. (2017). "Toxocara seroprevalence and associated risk factors in the United States." *American Journal of Tropical Medicine and Hygiene*. 97(6):1846-1850. DOI:10.4269/ajtmh.17-0542

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Current Position

Associate Professor	2014-present	Brigham Young University Provo, UT	Department of Biology
Associate Chair	2016-present	Brigham Young University Provo, UT	Department of Biology

Education

Postdoc	2008	Washington University St. Louis, MO	Alzheimer's disease biomarkers and genetics
Ph.D.	2007	Washington University St. Louis, MO	Evolution, Ecology and Population Biology
M.S.	2003	Brigham Young University Provo, UT	Population Genetics
B.S.	1999	Brigham Young University Provo, UT	Molecular Biology

Extramural Research Grants (current grants only)

2017 National Institutes of Health National Institute on Aging R01
Modeling of Cognitive Resilience to AD (B. Zhang PI)
Role: Subcontract Principal Investigator
Direct Costs: $146,888 Funding Period: 09/01/2017-08/03/2022

2016 National Institutes of Health National Institute on Aging RF1 AG054052
Epidemiology of Alzheimer's disease resilience and risk pedigrees
Role: Principal Investigator
Direct Costs: $2,484,211 Funding Period 08/01/2016-12/31/2021

2012 National Institutes of Health National Institute on Aging R01 AG042611
Pleiotropic and Interaction Effects on Alzheimer's disease Risk and Progression
Role: Principal Investigator
Total Funding: $1,318,126 Funding Period: 09/01/2012-12/31/2018

Editorial Positions

Senior Editor, **Alzheimer's & Dementia**

Ad Hoc Reviewer: More than 20 journals including **Alzheimer's & Dementia, Nature Medicine, PLoS Genetics, Proceedings of the National Academy of Sciences**

Publications (selected from 101 total)

Ridge, PG, Karch CM, Hsu S, Arano I, Teerlink CC, Ebbert MT, Farnham JM, et al, Kauwe, JSK (2017). “Linkage, whole genome sequence, and biological data implicate variants in RAB10 in Alzheimer’s disease resilience.” Genome Medicine. 9:100.

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Kauwe, JS and Goate A (2016). "Genes for a 'Wellderly' Life." Trends Mol Med **22**(8): 637-639.

Ebbert, MT, Boehme KL, Wadsworth ME, Staley LA, Alzheimer's Disease Neuroimaging I, Alzheimer's Disease Genetics C, et al, Kauwe JS (2016). "Interaction between variants in CLU and MS4A4E modulates Alzheimer's disease risk." Alzheimers Dement **12**(2): 121-129.

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Personal Data

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Education

Residency (Psychiatry)	University of Utah, School of Medicine, 1992
Internship	University of Utah, School of Medicine, 1989
MD	University of Utah, School of Medicine, 1988
MSc (Epidemiology)	University of London, School of Hygiene and Tropical Medicine, 2011
Bachelors	Weber State College, 1984

Board Certification: Diplomat American Board of Psychiatry & Neurology
Written Examination, March 1993
Oral Examination, April 1994

Professional Experience

Professor of Psychology, Department of Psychology, Brigham Young University, Provo, Utah, 2010 to present

Chair, Department of Psychology, Brigham Young University, 2012 to present

Associate Professor of Psychology, Department of Psychology, Brigham Young University, Provo, Utah, 2003 - 2010

Director, Neuroscience Center, Brigham Young University, 2006 - 2010

Assistant Professor of Psychology, Department of Psychology, Brigham Young University, Provo, Utah, 2000-2003

Assistant Professor of Psychiatry, Clinical, University of Utah, School of Medicine, Salt Lake City, Utah, 1995-1999

University of Utah Hospital, Salt Lake City, Utah, Attending Physician,
1992 - 1998

Select Publications

Berrett AN, Stone A, Erickson LD, Gale SD, Brown BL, Hedges DW (2017), *Toxocara* seroprevalence and associated risk factors in the United States, American Journal of Tropical Medicine & Hygiene, 97:1846-1850.

Berrett AN, Gale SD, Erickson LD, Brown BL, Hedges DW (2017), *Toxoplasma gondii* moderates the association between multiple folate-cycle factors and cognitive function in U.S. adults, Nutrients, doi:10.3390/nu9060564

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Hedges DW, Berrett AN, Erickson ED, Brown BL, Gale SD (2017), Association between infection burden and adult height, Economics and Human Biology, 27: 275-280.

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Woon FL, Farrer TJ, Braman C, Mabey JK, Hedges DW (2017), Meta-analysis of the relationship between symptom severity of posttraumatic-stress disorder and executive function, Cognitive Neuropsychiatry, 22: 1-16.

Berrett AN, Gale SD, Erickson LD, Brown BL, Hedges DW (2016), No association between latent toxoplasmosis and multiple body measures in U.S. adults, Folia Parasitologica, 63: 034.

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Perry CE, Gale SD, Erickson L, Wilson E, Nielsen B, Kauwe J, Hedges D (2016), Seroprevalence and serointensity of latent *Toxoplasma gondii* in a sample of elderly adults with and without Alzheimer's disease, Alzheimer Disease & Associated Disorders, 30:123-126.

Gale SD, Erickson LD, Berrett A, Brown BL, Hedges DW (2016), Infectious disease burden and cognitive function in young to middle-aged adults, *Brain, Behavior, and Immunity*, 52: 161-168.