

## RUNNING HEAD: Human Connectome Project- Aging

### The Lifespan Human Connectome Project in Aging: An Overview

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## **Highlights**

- The Lifespan Human Connectome Project-Aging (HCP-A) project will collect multimodal MRI and behavioral assessments from 1200+ participants aged 36-100+.
- MRI will include structural (whole brain and high-resolution hippocampal), resting state fMRI, task fMRI, diffusion, and arterial spin labeled perfusion imaging.
- Bio-behavioral assessments will include cognitive, psychiatric, metabolic, socioeconomic, and systemic health characterization.
- 600+ participants will receive a longitudinal follow-up at 20 – 24 months.
- These data will become a public resource to enable in depth studies of the effects of typical aging on the structural and functional connectome.

## **Abstract**

The original Human Connectome Project yielded a rich data set on structural and functional connectivity in a large sample of healthy young adults. Follow up efforts increase the value of these data by extending the age range to include infants, children, older adults, and brain disorders. Here we describe the Human Connectome Project in Aging (HCP-A), which is in the process of recruiting 1200+ healthy adults of ages 36 to over 100, with a subset of 600+ returning for longitudinal assessment. The HCP-A takes advantage of recent advances in acquisition and analysis of MRI, specifically multiband sequences, high-resolution structural imaging, and sequences particularly important for revealing processes known to be affected in aging. Four acquisition sites using matched Siemens Prisma 3T MRI scanners with centralized quality control and data analysis are enrolling participants: Washington University in St. Louis, University of Minnesota, Massachusetts General Hospital (MGH), and University of California Los Angeles (UCLA) School of Medicine. Data are acquired across multimodal imaging and behavioral domains with a focus on factors that are known to be altered in advanced aging. MRI acquisitions include structural (whole brain and high resolution hippocampal), resting state functional (rfMRI), task fMRI (tfMRI), diffusion, and arterial spin labeling (ASL). Behavioral characterization includes cognitive (such as processing speed and episodic memory), psychiatric, metabolic, and socioeconomic measures as well as assessment of systemic health (with a focus on menopause via hormonal assays). This dataset will provide a unique opportunity to examine how brain organization and connectivity differs across normal aging, and how these differences relate to key characteristics of aging including alterations in hormonal status and declining memory and general cognition. A primary goal of the HCP-A is to make these data freely available to the scientific community, supported by the Connectome Coordination Facility (CCF) platform for data quality assurance, preprocessing and basic analysis, and shared via the NIH Data Archive (NDA).

**Key Words.** Neuroimaging, Brain, MRI, Connectivity, Connectomics, fMRI, diffusion imaging, morphometry, functional connectivity

## 1. INTRODUCTION

The years between mature adulthood and advanced aging are accompanied by many changes in cognition (Craik and Salthouse, 2011; Schaie, 1994; Verhaeghen and Salthouse, 1997) and brain structure, function and connectivity (Buckner, 2004; Cabeza et al., 2004; Chan et al., 2014; Fjell et al., 2014; Grady, 2012; Greicius et al., 2004; Hedden and Gabrieli, 2004; Madden et al., 2009; Park and Reuter-Lorenz, 2009; Raz et al., 2010; Resnick et al., 2003; Salat et al., 2004). Even in the absence of disease processes, it is typical for older individuals to experience declines in cognition, particularly perceptual abilities and speed of processing (Baltes and Lindenberger, 1997; Jagust, 2013; Salthouse, 1996). Early stages of disease that are difficult to separate from normal aging can augment these cognitive declines and preferentially affect certain domains including memory (Bennett et al., 2006; Dubois et al., 2016; Jagust, 2013; Weiner et al., 2012). These declines are accompanied by changes in hormones, metabolic processes, and health-related biometrics such as cardiac function and blood pressure, and are affected by numerous lifestyle factors.

The goal of the Human Connectome Project in Aging (HCP-A) is to acquire a large, normative dataset that includes a breadth of brain, cognitive and biometric data, and to make these data freely available to the scientific community to answer critical questions about healthy brain aging. This manuscript describes the rationale, procedures, and protocols used in the HCP-A. The paper by Somerville et al (2018) describes components specific to the companion project -- the Human Connectome Project in Development (HCP-D) -- while information on scan selection, image acquisition, and analysis methods common to both projects are described in the overview paper by Harms et al. (2018). Here we focus on elements that are specific to the HCP-A.

The original Human Connectome Project focused on healthy young adults ('HCP-YA') was initiated in 2010 (U01-MH93765) and collected behavioral and multimodal imaging data in 1100+ participants, led by a collaboration between Washington University, the University of Minnesota and Oxford (the 'WU-Minn' HCP consortium). Another separate consortium, led by researchers at Massachusetts General Hospital and University California Los Angeles (later, University of Southern California: the 'MGH-USC' HCP consortium) focused on diffusion imaging in a smaller number of participants at extremely high gradient strength. These two consortia were successful in their initial missions to develop next generation image acquisition procedures, to acquire and disseminate a large database of publicly available structural and functional connectomics data (WU-Minn), and to engineer new MRI hardware with advanced capabilities for connectomics neuroimaging (MGH-UCLA). Detailed descriptions of this first phase of the HCP and resulting research are found in many existing publications (Barch et al.,

2013; Fan et al., 2016; Finn et al., 2015; Glasser et al., 2016; Glasser et al., 2013; Marcus et al., 2013; Setsompop et al., 2013; Smith et al., 2013; Sotiropoulos et al., 2013; Ugurbil et al., 2013).

Data from the over 450 publications that credit HCP-YA (as of December 2017) provide a foundation for research directions of the HCP-A. Several of these publications suggest associations between connectivity and intact cognitive features. Stronger, or more stable connectivity has been associated with protein turnover (Hellyer et al., 2017), memory (Suri et al., 2017), manipulation of semantic representations (Moss and Schunn, 2015), and response to error (Neta et al., 2015; Neta et al., 2014), which may reflect intact underlying biochemistry and preserved cognition. Also, positive lifestyle, demographic, and psychometric features have been linked to specific patterns of connectivity (Smith et al., 2015). Person-specific traits and behaviors such as large-scale brain systems (Gordon et al., 2017), sustained attention (Rosenberg et al., 2016), fluid intelligence (Finn et al., 2015), and body mass index (BMI) (Park et al., 2015) have been detected using fMRI, as have individual-specific connectivity profiles (Finn et al., 2015). These advances offer the prospect of using the HCP-A data to discover means to preserve quality of life throughout aging and to identify patterns that suggest a departure from a healthy trajectory.

With the accomplishments of this initial phase of the HCP-YA, new NIH efforts were initiated to further expand understanding of brain connectomics, particularly with regard to how brain connectivity is altered with disease (Connectomes Related to Human Disease U01; PAR-14-281) and to map dynamic changes in the connectome across the human lifespan. These include studies of the formation of brain connections in babies (Lifespan Human Connectome Project: Baby Connectome U01; RFA-MH-16-160), progression of connectivity during development (Lifespan Human Connectome Project: Development U01; RFA-MH-16-150), and the modifications of those connections with aging (Lifespan Human Connectome Project: Aging U01; RFA-AG-16-004). Here we describe the specific multisite consortium efforts for the Aging study, which includes a central coordinating site at Washington University, three additional data acquisition sites at UCLA, University of Minnesota, and MGH, and a consulting site at Oxford University. Protocols and operating procedures for the HCP-A were established in close coordination with the HCP-D to produce a harmonized data acquisition across a broad portion of the entire human lifespan with HCP-D enrolling individuals from 5-21 years of age and HCP-A enrolling individuals from 36 years of age to >100 years. The HCP-A aims to acquire unique data that will inform our understanding of alterations in the human connectome with aging and provide a rich resource for future explorations and comparisons with the disease-specific connectome initiatives.

## 1.1. Aims

The Aims of the HCP-A are fourfold:

Aim 1: To optimize data acquisition to the practical challenges of studying older adults. HCP-A takes advantage of newer MRI sequences and the Siemens Prisma platform to collect high-quality data. We designed both MRI and behavioral protocols to reveal age-related cognitive, behavioral, and brain differences. Meeting this aim involved extensive testing of different MRI scan parameters and establishing a behavioral battery that was as comprehensive as possible while conforming to the constraints of subject burden. The final protocol will be disseminated to the public (<http://protocols.humanconnectome.org>).

Aim 2: To obtain cross sectional data from 1200+ participants with matched protocols across four acquisition sites. The sample excludes major diagnosed disease but with the goal of otherwise being ‘typical’ regarding health and representative of gender, race and ethnicity, and socio-economic status of the United States for the age range. The HCP-A characterizes the sample for major factors relevant to general health and brain aging, including vascular burden (e.g., obesity, hypertension, smoking), genetic status with a focus on risk genes for age-associated disease (e.g., APOE), diet, physical activity, systemic health, (insulin, hemoglobin A1c, glucose, creatinine, cholesterol, total protein), hormonal status (estrogen, testosterone, luteinizing hormone, follicle stimulating hormone), and life history of factors including stress, depression, sleep patterns, social/community engagement, and adversity.

Aim 3: To collect longitudinal data from 600+ participants with a focus on understudied and scientifically interesting groups. Specifically, ages 36-44 (when late maturational and early aging processes may co-occur), ages 45-59 (peri-menopausal, when rapid hormonal changes can affect cognition and the brain), and ages 80 –100+ (the ‘oldest old’, whose brains may reflect a ‘healthy survivor’ state) will be targeted for longitudinal assessment at 20-24 months after their baseline imaging sessions. An administrative supplement expanded the longitudinal component to include ages 60-79 to allow better assessment of ages often characterized by the appearance of white matter lesions and onset of dementia.

Aim 4: Optimize data processing schemes for middle age and older adults, and make the data and analytic tools publicly available for the scientific community while providing consistency with HCP-D. This work is described in the companion overview paper by Harms et al (Harms et al., 2018).

## 1.2 Brain Aging and Neuroimaging

The brain undergoes complex and substantial changes throughout the lifespan. The dynamic processes influencing neural integrity continue throughout life and are modified by a range of genetic, biological and environmental factors. Much of our current understanding of

these processes has been achieved via post-mortem investigation and neuroimaging research. With regard to the most deleterious neural modifications associated with aging, there is great variation in the degree of deterioration across individuals. Although there is general public awareness of the devastating neurodegenerative processes that occur with known age-associated diseases such as Alzheimer's disease (AD; e.g. recent reviews in Bloom, 2014; Krstic and Knuesel, 2013; Spires-Jones and Hyman, 2014), it is generally less appreciated that the brain undergoes alterations even in the absence of clinically defined disease that begin early in life. Brain volume decreases by about 0.1% to 0.2% per year in young adults accelerating to about 0.5% in advanced aging, even in the absence of detectable disease (Fotenos et al., 2005). In pathological aging, the changes become substantially more dramatic.

Complicating the study of advanced aging, approximately 30% of cognitively normal individuals who are greater than 70 years old have pathological signs consistent with AD. These deteriorating conditions are complexly intertwined with later-stage developmental processes that extend into middle-age (Bartzokis et al., 2012; Lebel et al., 2012). Functionally, reduction in peak cognitive abilities in many domains begins in early adulthood (Craik and Bialystok, 2006), with some domains improving especially those linked to crystallized abilities (Park et al., 1996). At the same time, presumably detrimental changes in the brain including neural and white matter loss are detectable with early adult aging and accelerate with later aging (Raz et al., 2005), and these changes may partially account for the reduction in cognition during this period. With later aging (beginning sometime in the 6<sup>th</sup> to 7<sup>th</sup> decade), deterioration becomes more significant with changes increasing in rate across time and certain types of 'pathologic' brain changes beginning to accumulate even in relatively healthy individuals vascular-associated brain changes (Wardlaw et al., 2013). This is also the period of the lifespan when abnormal cognitive impairment, dementia and in particular AD becomes a high risk. Importantly, current data demonstrates the influence of early and midlife factors on how the brain is modified with later aging (Debetto et al., 2011).

Neuroimaging has been used to study brain aging for decades, dating back to computed tomography research (CT; Huckman et al., 1975), with MRI subsequently becoming a highly prevalent modality in the early 1980s (Brant-Zawadzki et al., 1985; Gado et al., 1982). Initial MR studies utilized magnetic resonance spectroscopy (MRS) to examine metabolic variation as well as 'structural' imaging that qualitatively described patterns of brain atrophy and accumulation of detectable lesions, often in the white matter (Fazekas et al., 1987) in the typically and abnormally aging brain. An early goal was to determine the histopathologic correlates of changes measured with neuroimaging (Awad et al., 1986a; Brun and Englund, 1986) as well as



the health factors such as cerebro/cardiovascular health presumed to be mechanistically causal to the measured changes (Awad et al., 1986b).

The development of semi-quantitative and computerized procedures allowed reliable data analysis at the individual and group level (e.g., volumetrics: Gado et al., 1982; Grant et al., 1987; Jack et al., 1992; Seab et al., 1988). Current procedures for sensitive and reliable computational measurement of a range of structural and functional properties of the human brain -- including procedures for connectomics (Fischl, 2012; Smith et al., 2013; Sotiropoulos et al., 2013; Van Essen et al., 2012) along with advances in data informatics (Marcus et al., 2013) -- have greatly expanded the ways in which imaging can provide insights into mechanisms underlying brain development and aging.

### **1.3 Leadership**

Gathering a sizeable and nationally representative sample of healthy participants for the HCP-A necessitated a multi-site approach. Integrating data across sites requires substantial coordination in multiple domains, and the leadership recognized early on in the process that it would be ideal to have overlap in the sites contributing to both the development and aging Lifespan studies. Doing so created the opportunity for time and effort savings in machine calibration, personnel training, and most importantly for creating datasets that would be maximally comparable across the development and aging projects. The latter goal motivated the leadership to identify centers with identical scanners, and with scientists with expertise working with both developing and aging populations. There were also strong advantages in building on the same research teams involved in the original HCP-YA study of 22-35 year olds, including the same experts in MRI hardware, software, and data analysis. These factors motivated the formation of our current team. The Principal Investigator of the overall HCP-A is David Van Essen, who along with Kamil Ugurbil also led the HCP-YA. The Principal Investigative team consists of members from four acquisition sites, three of which were part of one of the two consortia from the original HCP: Washington University in St. Louis (David Van Essen and Beau Ances), University of Minnesota (Kamil Ugurbil and Melissa Terpstra), and MGH (David Salat and Randy Buckner), and an additional acquisition site for the Lifespan projects, UCLA (Susan Bookheimer and Roger Woods). As in the HCP-YA, Stephen Smith from Oxford University is the lead investigator overseeing data analysis.

The HCP-A also engaged several consultants with special expertise critical to the study. Dr. Lenore Arab of UCLA is an epidemiologist whose knowledge of demographic and recruitment approaches is helping to ensure the samples are both representative of the population overall and well matched across the age bins. Dr. Pauline Maki of University of Illinois, Chicago, adds special expertise in hormonal changes associated with menopause. Drs.

Thomas Perls and Stacey Anderson of Boston University, who have worked on the New England Centenarian Study (NECS) and the Boston Field Center of the NIA-funded Long Life Family Study (LLFS), will aid in recruiting centenarians.

Like the partnered HCP-D, HCP-A has a centralized infrastructure led by Project Manager Sandra Curtiss for IRB, site training, recruitment monitoring, and overall project management. Similarly, each acquisition site has a project coordinator and a team of research assistants responsible for recruitment, data acquisition and transfer, and communicating with similar personnel across sites to ensure ongoing harmonization of procedures. Regular communication among coordinators and RAs takes place in weekly or bi-weekly conference calls that include the central (Washington University) coordinating team. Locally, sites have regular team meetings, and the HCP-D and HCP-A have joint weekly or biweekly conference calls involving PIs, key personnel, and project coordinators. Supplementary Table 1 includes a listing of study personnel who have contributed to the project as of December 2017.

#### **1.4 Relation to other Human Connectome Project efforts**

A primary goal of the Human Connectome Projects as a group is to acquire high-quality data across ages, and for ‘healthy’ participants in addition to those with specific disorders. Aside from the HCP-A presented here and the HCP-D described in the companion paper by Somerville et al. (2018), over a dozen connectome “disorder” projects have been funded covering topics from infant development to a range of neurological and psychiatric disorders. The HCP-A shares many MR modalities including structural, resting state fMRI, and diffusion, and overlaps in biosample acquisition and many cognitive testing domains. However, the project also includes imaging, biosamples and cognitive metrics tailored to acquire data particularly relevant to aging; these are described in detail below. The complete list of cognitive tests and behavioral questionnaires is provided in Supplementary Table 2, while important features are highlighted in the data acquisition section below.

## **2. PARTICIPANTS**

The HCP-A aims to advance prior work in several ways. At the broadest level, the HCP-A will be the first large-scale study to apply recently developed advanced brain imaging techniques to the adult age-span with associated biological, physiological, neuropsychological, and genetic data. In addition to the basic goal of mapping the human connectome across the lifespan, the consortium identified three focus areas to enhance in the HCP-A project. First, women in the pre- and peri-menopausal phase will be oversampled with quantification of hormone levels for examination of how changes during this critical period of life may influence brain connectivity measures and alterations in cognition during this time. Second, individuals in

the ‘oldest-old’ age range, including individuals over 100 years of age (centenarians), are targeted. This end of the age spectrum has been underrepresented in prior work and may provide important insight into ‘successful’ aging (Eyler et al., 2011; Wahlund et al., 1996). The sample will target representation of the population with respect to demographic and socio-economic status (SES). Finally, a large sample of individuals in the 36-44 year age-range, often omitted in aging studies, will be included. We briefly summarize these focus areas and additional motivation and rationale for our studies in the following sections.

## **2.1 Sample rationale, demographics and recruitment strategy**

2.1.1. Rationale - Focus on ‘typical’ aging: It is understood that, although chronological age is a factor contributing to senescence, a multitude of genetic and environmental influences contribute to the variability in health as a function of age in the general population, and the process of aging is more or less a probabilistic set of events and exposures that result in an individual’s ‘biological age’. A central question in the study of aging is what should be considered ‘normal’ (potentially to be considered typical dimensional variation in function) compared to ‘abnormal’ (potentially a qualitatively distinct condition that is not an inevitable consequence of aging). Many terms have been used throughout the research literature in an attempt to classify older adults based on differing enrollment and study inclusion/exclusion criteria. Terms such as ‘healthy aging’ (Bai et al., 2008; Bartzokis et al., 2003; Greicius et al., 2004; Van Der Werf et al., 2001), non-demented aging (Head et al., 2004; Salat et al., 2009), ‘normal’ aging (Gideon et al., 1994), ‘successful aging’ (Wahlund et al., 1996), as well as simply ‘aging’ have all been used with differing degrees of justification. The goal for HCP-A was to study ‘typical’ aging, a term that has also been used in prior work (Borghesani et al., 2013; Jack et al., 2002; Jack et al., 1998).

The definition of typical in the case of HCP-A in general refers to our goal to enroll individuals who exhibit typical health for their age absent identified pathological causes of cognitive decline (e.g., stroke, clinical dementia). The cohort therefore includes individuals with prevalent health conditions such as hypertension and other forms of vascular risk. The major classes of exclusion include less prevalent conditions that are expected to have an impact on the interpretation of the data such as suspected AD (the most common form of atypical cognitive impairment in older adults) and symptomatic stroke. Although these conditions are common in seniors and particularly in the ‘oldest old’ (80 years and older), they are not found in the majority of individuals, even for the oldest old (Writing Group Members, American Heart Association, 2016) and would be antithetical to the study of typical aging of the connectome.

This general approach of examining typical aging permits the study of links between common health conditions (health ‘modifiers’) and connectomics measures. However, specific aspects of this approach require additional consideration. First, as is typical for aging studies, an increase in health conditions in the older adults will result in medically non-matched groups compared to the younger participants. This includes not only the medical condition of interest, but also any medications or other therapeutic processes in progress during this study. Such information is collected as part of the standard HCP-A intake. Second, the oldest old are particularly elevated in health conditions including highly prevalent sensory deficits that may affect cognitive testing. Third, although the oldest old are often less healthy than younger counterparts, survival to this late age may actually place them in a category of ‘successful agers’, and in the case of the centenarians, even ‘super agers’ -- individuals that are not typically aging but in fact represent a biased sample of individuals who escaped common conditions leading to incapacity and mortality. This represents a potential survival bias in the cohort given that we do not know what percentage of the participants less than 80 years of age will persist into this elite club. Survival in this group can be due to several factors. In some cases, this may largely reflect ‘luck’ based on having a low risk genetic profile and/or lack of high-risk environmental exposures linked to death and disease. In other cases, individuals in the oldest old class may be uniquely resilient. For example, APOE genotype is not predictive of cognitive decline or dementia in the oldest old (Juva et al., 2000), potentially suggesting that other factors contribute to resilience against this highly penetrant genetic risk. Additionally, brain pathologies, such as small vessel disease, volume loss, and amyloidosis, are highly prevalent in cognitively normal individuals in this age range (Lopez et al., 2014). These individuals may therefore harbor additional forms of resilience against the expression of cognitive symptoms for a given level of pathology.

An additional concern in the selection of the oldest old is that it is challenging to determine the cognitive health of individuals in this age range because there is limited normative testing data for these adults to be used for reference. Although such data do exist (Miller et al., 2015), large performance ranges and limited samples in the upper age and centenarian range do not allow for strong reliance on the use of such performance metrics for conditions that are difficult to accurately diagnose such as early and/or preclinical AD. For pragmatic reasons, we decided to be less conservative (i.e., more inclusive) in the selection criteria for the older individuals (details in Target Age Bands, below). This includes relaxing our initial goal of trying to exclude anyone who may have some cognitive decline and potentially be in the earliest stages of AD. In the oldest old, use of conservative exclusion criteria is not possible given the rarity of individuals in this population and the additional likely exclusions due to contraindications for MRI.

The scope of the program announcement did not allow for acquisition of additional biomarkers such as cerebrospinal fluid (CSF) or positron emission tomography (PET) markers of amyloid and tau pathology. Therefore, it is likely that some of the individuals across the age spectrum may have preclinical AD or other neurodegenerative conditions. It is expected that varied levels of preclinical pathology will be common in the oldest individuals. Additionally, given the aggressive enrollment schedule to meet the study goals, we are not practically able to obtain information from a collateral sources or informant close to the participant for the assessment of any recent changes in status that could be indicative of impairment due to early stages of dementia (as is typically performed). Given these caveats, individuals enrolled in the oldest old and centenarian age range are likely to be representative of high functioning individuals within their demographic, but unlikely to be ‘typical’ as defined for the younger portions of the HCP-A cohort. Special care in interpreting findings in this group will therefore be warranted.

2.1.2. Summary of population recruited: Data will be collected from 1200+ cross-sectional participants between the ages of 36 and 100+ using a matched protocol across four acquisition sites. A subset of the participants (600+) will be scanned longitudinally. While data acquisition (including optimization) was planned over four years (enrollment of the cohort began February 2017), additional longitudinal scanning may extend the project by one year. The main age cohorts are separated into three groups: Mature (36-64), Old (65-79), and Oldest Old (80 Plus). The objective is to have the sample be representative of the current US population by using the US Census Bureau’s 2015 projections to determine the gender, race, and ethnicity targets for each age band. All sites will strive to achieve variation across low, middle and high income SES brackets. Longitudinal data will be collected in each age band, as detailed below. Table 1 summarizes the planned recruitment by age, gender and longitudinal follow-up point.

			MATURE						OLD				OLDEST OLD			TOTALS
			36-44		Peri-menopause								80+			
Age Cohorts		<36	36-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85-89	90+		
Females	T1	10	46	70	70	70	70	46	46	46	46	56	56	28	660	
	T2		26	30	30	30	30	30	30	30	30	20	15	10	311	
Males	T1	10	46	46	46	46	46	46	46	46	46	48	48	28	548	
	T2		26	30	30	30	30	30	30	30	30	20	15	10	311	
Total Scans		20	144	176	176	176	176	152	152	152	152	144	134	76	1830	
“ Subjects		20	92	116	116	116	116	92	92	92	92	104	104	56	1208	

**Table 1:** Recruitment Goals for HCP-A by age, gender, and longitudinal assessments; T1 and

T2 refer to Time 1 (initial visit) and Time 2 (longitudinal follow-up), respectively.

2.1.3. Target Age Bands: The first age band is 36-44 years, which extends the age continuum from HCP-D (5-21) and HCP-YA (22-35). While college age and slightly older individuals have been studied extensively, a relative paucity of neuroimaging data exists in this late maturational and early aging band. Cross sectional data suggest that late developmental processes and early aging processes may be ongoing concurrently (Wang and Young, 2014; Yeatman et al., 2014), making longitudinal data of particular interest in this age group.

The next age band spans the peri-menopausal period in women ages 45-59. Age-related changes in hormone levels occur in both men and women, but are most pronounced in women in the two years before and after their final menstrual period, occurring on average at age 51 (Randolph et al., 2011). When and how cognition may be affected by the reduction of hormones, particularly estradiol, during the menopause transition or by hormone therapy (HT) remains controversial. Women may be more vulnerable than men to cognitive decline in aging (Gur and Gur, 2002) and there is general agreement that women experience memory deficits in peri-menopause (Epperson et al., 2013; Fuh et al., 2006; Greendale et al., 2010; Maki et al., 2010)). It is important to know how HT affects the brain, cognitive function, and dementia risk, but there are mixed findings across studies.

HT treatments may benefit cognition in typical aging and reduce AD risk but results are inconsistent (Maki and Henderson, 2012; Nelson et al., 2002)). The Women's Health Initiative Memory Study (WHIMS) reported that combined estrogen and progestin HT increased AD incidence in post-menopausal women (Shumaker et al., 2003); in contrast there is mixed evidence suggesting that HT may decrease risk when administered in peri-menopausal women (Henderson, 2006). Imaging studies during the menopause transition are scant and limited in scope. In one study, prefrontal fMRI activation in a verbal memory task was reported to be higher in postmenopausal compared to premenopausal women (Berent-Spillson et al., 2012). Increased estradiol correlates with increased hippocampal volume in some but not all studies (Eberling et al., 2003; Lord et al., 2008; Ryan et al., 2014; Wnuk et al., 2012). Functional connectivity may be enhanced by ovarian hormones and decreased by androgens (Peper et al., 2011). For instance, interhemispheric functional connectivity may vary with menstrual stage (Weis et al., 2008); network connectivity may be elevated in women reporting more menopausal hot flashes (Thurston et al., 2015); and functional connectivity between hippocampus and prefrontal cortex was reported to be enhanced by estradiol (Ottowitz et al., 2008).

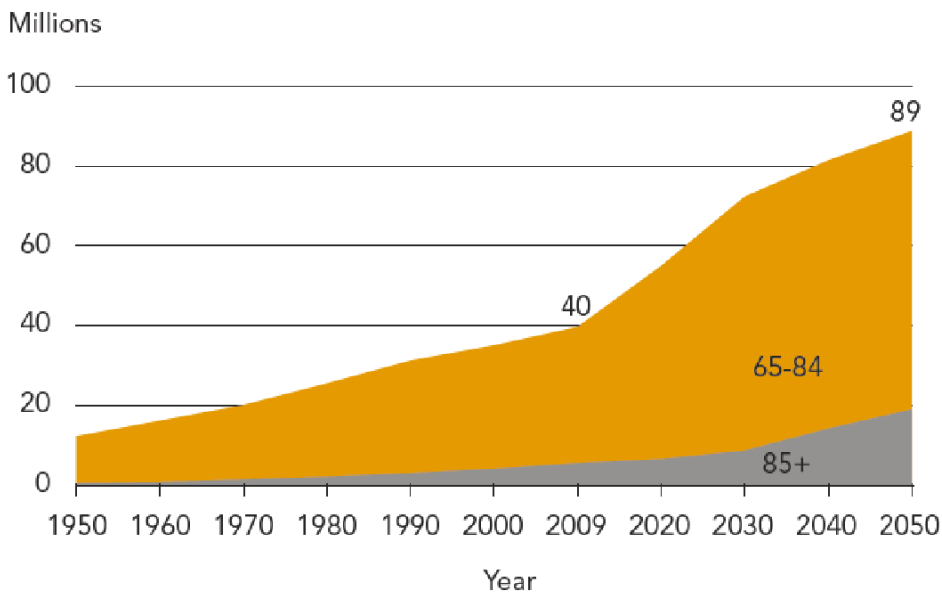
While suggestive that brain circuits may be affected by age-related changes in sex hormones, the paucity of data highlights the need for a more systematic, multimodal, and large-scale exploration of these issues, not only in women but also in men, as estradiol also declines

in males during aging. Hence, HCP-A will recruit an expanded sample in this age range (Table 1). Because of the rapid changes in hormonal levels across the menstrual cycle, participants in the peri-menopausal range are seen within a narrow window in their cycle, 4-7 days past the onset of the last menstrual period. We will also stage menopause objectively using validated criteria (Harlow et al., 2012) and obtain multiple hormonal measures for all participants (across age and gender) for comparison, including serum estradiol (E2), testosterone, luteinizing hormone (LH) and follicle stimulating hormone (FSH), in addition to relevant cognitive, sleep, mood and hormone replacement therapy (HT) factors. Longitudinal assessment will allow us to better characterize how menopausal stage and changing hormone levels affects brain connectivity.

The third age band is 60-79 years. Ages 60 to 79 years represent a period when many participants may develop periventricular and subcortical white matter lesions due to vascular disease that could interfere with network connectivity. Moreover, the prevalence of cognitive impairment due to diagnosed clinical dementia rises after age 65 (Seshadri et al., 1997). Prior research has shown preclinical changes in brain structure and function in this age range prior to mild cognitive impairment (MCI) or AD diagnosis, related to stroke risk factors such as high blood pressure, BMI, and diabetes, as examples (Fennema-Notestine et al., 2009; Habib et al., 2017; Hays et al., 2016; Mak et al., 2017; Neth and Craft, 2017; Rolandi et al., 2016). Thus, this age band will yield key information about early brain changes that accompany pre- and early clinical manifestations of diagnoses related to cognitive decline.

The final age band is the *oldest old* (ages  $\geq 80$ ). For HCP-A, a special emphasis towards enrolling individuals in the ‘oldest old’ age-range is a major focus. The definition of oldest old varies, but tends to refer to individuals  $\geq 80$  years of age (Campion, 1994; Suzman and Riley, 1985). The oldest old represent a unique segment of the population that can be considered a class of ‘survivors’. Individuals in this cohort that are free of degenerative disease can be seen as models of ‘successful’ aging. Although the oldest old are currently rare, this is one of the fastest growing segments of the United States population, projected to increase to 19 million individuals by 2050 and representing one-fifth of individuals aged 65 years and older (Figure 1; (Jacobsen, 2011)).

## U.S. Population Ages 65 and Older, 1950 to 2050



**Figure 1: The growing aging population in the US.** Reproduced with permission from Linda A. Jacobsen, Mary Kent, Marlene Lee, and Mark Mather, "America's Aging Population," Population Bulletin 66, no. 1 (Washington, DC: Population Reference Bureau, 2011).

Modern sanitation, technology, and medical therapies have promoted a general endurance towards later aging while minimizing conditions that contribute to premature mortality. Similarly, advances in health awareness and healthy lifestyle promotion may contribute to prevention of age-related disease. In those who harbor common pathologies such as AD, higher levels of education and premorbid intelligence promote 'cognitive reserve' that staves off cognitive symptom expression, extending the period of functional independence to later in life (Cummings et al., 1998; Stern, 2006, 2012). That said, there is a high incidence of cognitive impairment in this age group: the rate of impairing cognitive deficits is up to 14 times higher in individuals over 85 compared to individuals 65-69 years of age (Hebert et al., 1995). In longitudinal samples, as many as 40% of individuals in this age range show a significant cognitive decline within a 42 month period (Kaye et al., 1997). Thus, examination of factors that contribute to extending optimal cognitive and neural health into this late age-range could provide unique insights into factors that contribute to healthy neural connectivity with aging.

Although the oldest old have been recognized as a valuable cohort for study for some time (Suzman and Riley, 1985) and have been described in several prior cohort studies (Davis et al., 2012; Gonzales Mc Neal et al., 2001; Green et al., 2000; Hickman et al., 2000; Howieson et al., 1997; Howieson et al., 1993; Kaye, 1997; Kaye et al., 1994; Lautenschlager et al., 1996;



Soldo et al., 1997), representation of individuals in this age-range is limited in the neuroimaging literature on aging. When the age-span under study does include the oldest old, this segment of the data is often limited, with relatively few participants, and is typically not analyzed separately in the cohort. Prior imaging work in cognitively healthy oldest old and AD found different patterns of volumetric changes suggesting differential pathologic processes in these groups (as opposed to a simple acceleration of age-related processes in AD) (Salat et al., 1999). These studies have linked cognitive preservation and decline in this population to imaging markers of AD pathology (Dekhtyar et al., 2017), demonstrated associations between progression of white matter disease to blood pressure variability (Liu et al., 2016), and have described age-associated variation in white matter in demented and non-demented oldest old (Bennett et al., 2017). To date, limited advanced connectomics have been examined in this age band.

## **2.2 Screening**

2.2.1: Exclusionary criteria: The goal of screening is to include individuals showing patterns of ‘typical’ aging and to rule out those with diagnosed conditions associated with diseases that span the lifespan as well as neurodegenerative diseases that become more common in advanced aging. In that sense, our screening aims to identify ‘atypical’ conditions (those that do not affect a large portion of the population likely to participate). As a first step, a phone screen is performed for all potential participants to rule out major exclusionary health conditions. In individuals of 60 years of age and older, we also exclude those with impaired cognitive abilities using a cognitive screener, the Telephone Interview for Cognitive Status (TICS-M) (de Jager et al., 2003). Potential participants must score 30 or greater on the TICS-M to be eligible. TICS-M scores are adjusted to reflect different educational backgrounds: for instance, individuals receive 5 points if they have <8 years of school, 2 points if they have 8-10 years of school, and lose 2 points if they have 16 or more years of school.

In addition to the TICS-M, we administer the Montreal Cognitive Assessment (MOCA) (Nasreddine et al., 2005) during intake. Participants must meet the determined threshold for their age bracket on the MOCA to be considered eligible for the study. The screening process involves MR exclusion questions to assure participant safety. Additionally, to achieve a study sample that reflects ‘typical’ aging and not a ‘supernormal’ sample, participants are not excluded based on medication use alone. Instead participants are asked about any medications they are taking at intake; this information is captured in Redcap, so that users can investigate or avoid specific medication confounds. Participants returning for longitudinal assessment will be screened again but only excluded for two reasons: changes resulting in a contraindication to safe MRI scanning, such as implantation of a pacemaker, and reduction in cognition severe enough that the subject no longer has the capacity to give informed consent.

Given the common changes in health status with advanced aging, certain conditions were screened on a sliding scale with provisions allowing individuals of 80 years of age and older to have certain conditions that are not permitted in the younger sample. Table 2 shows the tiered cut-off criteria by age range. The tiered cutoffs allow inclusion of individuals who may have low scores for other reasons beside mild cognitive impairment or dementia, and in the later age range of 80 years of age and older, a primary goal is to assure capacity to consent.

<b>Exclusion Criteria for Older Adults</b>						
	<b>Age Bin</b>	<b>36-59</b>	<b>60-79</b>	<b>80</b>	<b>81-89</b>	<b>90+</b>
	<b>Criteria</b>					
Phone Screening	<b>TICS-M</b>	--	29	If less than 30, screened for capacity		
	<b>Macular Degeneration</b>	Diagnosis excludes			Record and Enroll	
	<b>Hearing</b>	Exclude if hearing loss prevents communication via telephone			Exclude if unable to communicate via microphone when in the scanner (i.e. without hearing aids)	
Visit Intake	<b>MoCA Score</b>	19	19	17	17	16

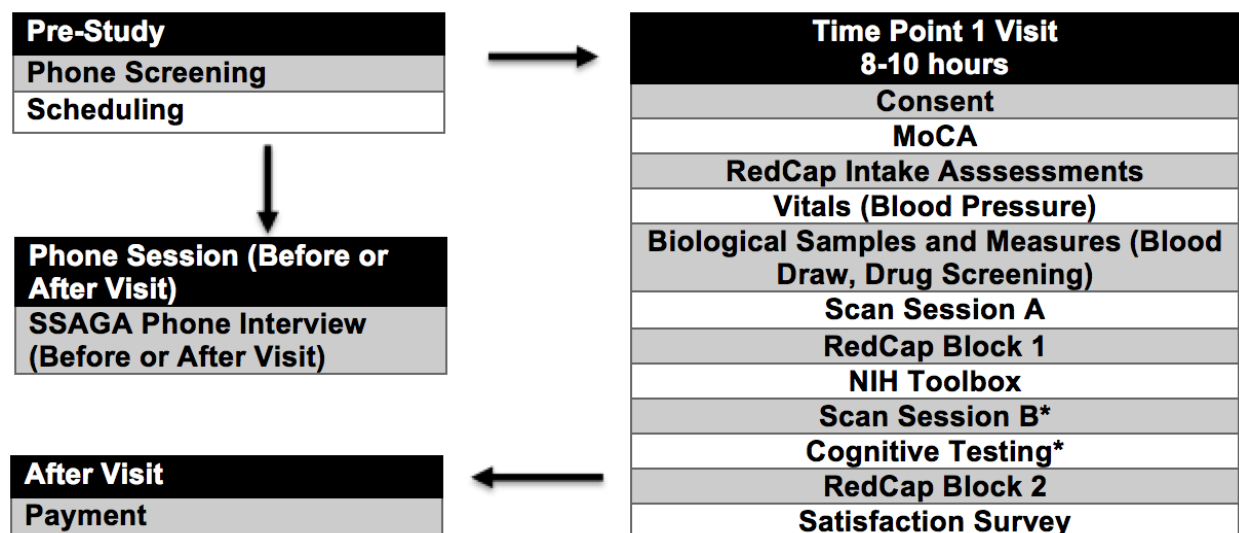
**Table 2:** Tiered cutoff scores by age for the TICS-M, the MoCA and presence of macular degeneration.

There are two major areas where this tiered scale has impact. First, as noted above, we used criteria for cognitive exclusion based on clinical scales that are well-verified in the typical age-range for which they are employed and for which normative data exist. However, the same scales are less appropriate for individuals in the oldest old group where only limited normative data exist. Additionally, pathologies associated with AD may begin to accumulate decades prior to when symptoms appear and could be present before overt clinical signs manifest (Jack et al., 2010). We have used a liberal threshold for inclusion of participants to reflect the true population. We acknowledge that these criteria may lead to including individuals with mild to moderate cognitive deficits. Furthermore, it is highly likely that some individuals in the older age ranges harbor some degree of AD or other neurodegenerative pathologies. Approximately 30% of cognitively normal older adults (65-85 years of age) exhibit amyloid positivity on positron emission tomography (PET) imaging (Sperling et al., 2009) and we expect this prevalence to be greater in the oldest adults. Second, we are less conservative in exclusion of oldest old for auditory or visual deficits. Practically, such deficits are common in this population (Gussekloo et al., 2005) and coupled with the many potential additional exclusion factors that increase in prevalence with aging (including contraindications for MRI), using conservative criteria would make it extremely challenging to meet enrollment goals. Given the constraints of the study, we decided it would be best to assure enrollment of an adequate number of oldest old, allowing for

at least brain measurements from neuroimaging data, but with the potential caveat of auditory or visual deficits impacting performance (although auditory impairment will likely be less of a concern than visual impairment (Gussekloo et al., 2005)). Our protocol is therefore to include the oldest old who do not meet criteria for being legally blind (with or without vision correction) and to include individuals with auditory deficits as long as they do not have substantial difficulty carrying out a conversation in person. A complete list of inclusion and exclusion criteria is found in Supplementary Table 3.

**2.2.2: Assessing Capacity to Consent:** At both the initial and longitudinal visits, we assess the potential participants' capacity to give informed consent. Particularly in the older participants when rates of cognitive decline are high, it is important to determine whether participants who are able to pass the reduced cognitive screening threshold are able to comprehend the nature of a research study. Capacity to consent is defined as "a threshold requirement for persons to retain the power to make decisions for themselves" (Appelbaum and Gutheil, 1991). There are four principles guiding assessment of capacity to consent: Understanding, Appreciation, Reasoning, and Expression of a Choice. These are assessed formally using a brief version of the MacArthur Capacity to Consent Scale (Appelbaum, 2007) which was designed for AD clinical trials. Three critical questions have been found sufficient for understanding the nature and purpose of research participation (1) "What is the purpose of the study?" (2) "What are the risks?" and (3) "What are the benefits?". Participants who can answer each question correctly are considered competent to participate as research participants.

**2.2.3: Scheduling and Timing:** Following phone screening, participants are scheduled for imaging, cognitive testing, and biosample collection, described in detail in the next sections. Figure 2 below shows a typical example of the subject activities.



**Figure 2: HCP-A Screening and testing outline.** \*The timing for the second scan session and cognitive testing alternate across participants. While this order is meant to be consistent across participants, in some cases it may be altered to accommodate specific subject needs, scheduling conflicts or other circumstances.

## **2.3 Longitudinal Scanning**

In the initial proposal, we aimed to select a subset of participants for longitudinal examination. NIH subsequently awarded a supplement that will allow us to expand longitudinal acquisition to all age bands and a total of 600+ longitudinal participants (Table 1). Participants in all age bands will be invited for a 20-month longitudinal follow-up, with latest follow-up being 24 months. There is evidence that a two-year interval is sufficient to identify brain structural changes generally as a result of aging (Barrick et al., 2010; Jiang et al., 2014) and based on genetic risk for AD in the 60-79 year old range (Donix et al., 2010). Table 1 shows the distribution of cross-sectional and longitudinal participants by age and gender.

An ongoing recruitment database will guide completion of the planned cohort sizes. We planned for an attrition rate of ~10% in keeping with our prior experience with longitudinal studies with older adults. Participants chosen for longitudinal analysis will include any completers with good quality scans from their first visit who continued to meet inclusion criteria at the end of the first timepoint; we will not exclude participants at longitudinal follow-up if they have developed age-related disorders which would have excluded them at study entry, with two exceptions: 1) they can no longer be scanned safely (for example, had a pacemaker implanted), and 2) no longer have the capacity to consent (see section 2.2.2).

## **2.4 Retention**

To increase retention and incentivize continued participation, we will use a multifaceted approach that has proven successful in our prior longitudinal investigations: (a) obtain the contact information of someone who will be able to reach participants even if they move; (b) contact participants every 3 months to remain in touch and inquire about potential moving plans; (c) send holiday and birthday cards every year; (d) send a semi-annual newsletter with study progress and updates; (e) provide “swag” with logos and contact information; and (f) provide bonus payment for participating in the longitudinal session. Our budget also provides travel reimbursement as needed.

## **3.0 THE HCP-A IMAGING PROTOCOL**

Here we briefly describe the scanning protocol for HCP-A and the intended use of the different scan types. More complete treatment of the scanning protocol can be found in Harms et al. (2018). A downloadable protocol is available on the Human Connectome Project website (<http://protocols.humanconnectome.org/>). All imaging for HCP-A is performed on Siemens Prisma scanners running the VE11C operating system and using the Siemens Prisma 32-channel head coil. The HCP-A protocol and hardware differ from that used in the original HCP-YA owing to the change to the Prisma scanner and also burden constraints of scanning older adults. The differences and their implications are discussed in detail in Harms et al, (2018).

The HCP-A protocol includes high spatial resolution structural and diffusion imaging, and high spatial and temporal resolution functional imaging. New to the Lifespan projects is a high spatial resolution arterial spin labeling (ASL) perfusion scan. The scanning protocol was limited by the amount of time that could be allocated for imaging to keep the scan sessions tolerable for older adults. The final protocol consists of two imaging sessions each including approximately 45minutes of scanning that can be performed in a single day or across two days depending on site-specific procedures and constraints. The total scanning session length was capped based on preliminary experience with these cohorts. Highly compelling justification was needed to add imaging modalities to the extant HCP-YA protocol. A comparable restriction was placed on overall participant burden. MRI scans particularly important for aging or specific to HCP-A are described below. More details on all scans can be found in the companion paper by Harms et al, (2018).

A simulated ‘mock scanner’ is available at each site. For HCP-A participants, the use of the mock scanner is optional and decided on a case-by-case basis depending on factors such as whether the participant has previously been in an MRI scanner and whether they have questions or concerns about the scanner environment. During the imaging session, pulse oximetry and respiratory belt data are acquired for possible future use in cleaning functional data. Eye monitoring using infrared cameras is a planned addition for all sites in early 2018 to determine compliance during resting functional scans.

Certain scan types, although desirable, were not included in the final protocol. Most notably for aging, fluid attenuated inversion recovery (FLAIR) is a common clinical sequence used to visualize a range of brain pathologies including small vessel ischemic changes and multiple sclerosis plaques, as well as in research quantifying white matter lesion volumes (Hajnal et al., 1992). FLAIR imaging was excluded primarily for time constraints with the rationale that much of what is detected on FLAIR can also be revealed to some extent via the other imaging modalities (T1, T2, diffusion) but that the other modalities provide greater anatomical and microstructural contrast relative to FLAIR. In addition, we did not include susceptibility weighted imaging (SWI) to evaluate hemorrhages or contrast scans with contrast

agents to evaluate for possible tumors, as this was not a clinical study. The clinical conditions of concern are expected to be minimally incidental in the HCP-A cohort, and pilot data from one of our sites (D. Salat, MGH) found that quantification of white matter lesions via T1 and/or T2 imaging is highly correlated with values from FLAIR imaging.

Table 2 shows the HCP-A imaging protocol. Below we describe in more detail the HCP-A specific scans, the rationale for choosing them, and some preliminary data.

**TABLE 2: Imaging protocol for HCP-A<sup>a</sup>**

Session 1					
Modality	Scan	Resolution (mm) <sup>b</sup>	fMRI volumes	Duration (min:sec) <sup>c</sup>	Participant action
Spin echo field maps	AP & PA	2.0		0:18	NA
BOLD Resting state	Run 1 AP	2.0	488	6:41	Fixation
	Run 2 PA	2.0	488	6:41	Fixation
Multiecho T1w MPRAGE	T1 vNav Setter <sup>d</sup>	8		0:01	Movie <sup>e</sup>
	T1	0.8		8:22	Movie
T2w SPACE	T2 vNav Setter <sup>d</sup>	8		0:01	Movie
	T2	0.8		6:35	Movie
T2w TSE	HighRes Hipp	0.4 x 0.4 x 2.0		3:31	Movie
Spin echo field maps	AP & PA	2.0		0:18	NA
BOLD Task -VisMotor	Run 1 PA	2.0	194	2:46	Task
BOLD Task -Go/NoGo	Run 1 PA	2.0	300	4:11	Task
BOLD Task -Facename	Run 1 PA	2.0	345	4:47	Task
Cumulative scan duration				45 min	
Session 2					
Modality	Scan	Resolution (mm) <sup>c</sup>	fMRI volumes	Duration (min:sec) <sup>d</sup>	Participant action
Spin echo field maps	AP & PA	2.0		0:18	NA
BOLD Resting state	Run 1 AP	2.0	488	6:30	Fixation
	Run 2 PA	2.0	488	6:30	Fixation
Spin echo field maps	AP & PA	2.0		0:18	NA
Diffusion	Run 1-98 dir AP	1.5		5:38	Movie
	Run 2-98 dir PA	1.5		5:38	Movie
	Run 3-99 dir AP	1.5		5:42	Movie
	Run 4-99 dir PA	1.5		5:42	Movie
ASL Field Map	AP & PA	2.5 <sup>f</sup>		0:18	NA
ASL	PCASL	2.5 <sup>f</sup>		5:29	Fixation
Cumulative scan duration				43 min	



<sup>a</sup> For conciseness, a “Localizer block”, consisting of brief localizer and AutoAlign scout scans is omitted.

<sup>b</sup> Isotropic spatial resolution (voxel size), unless noted.

<sup>c</sup> Durations reflect what is listed on scanner, which includes calibration and discarded scans. For the T1w MPRAGE and T2w SPACE scans, the listed durations also include up to 80 s of *k*-space reacquisition.

<sup>d</sup> The “T1/T2 vNav setter” scans are very short scans that write the imaging parameters for the volumetric navigators to a file that is then read by the main T1w/T2w scans for setting the navigator parameters.

<sup>e</sup> Participant selects a movie/documentary or music from options provided by each site.

<sup>f</sup> Nominal slice thickness of 2.27 mm with a 10% gap (yielding 2.5 mm between slices).

AP = anterior to posterior phase encoding direction; PA = posterior to anterior; TSE = turbo-spin-echo; ASL = arterial spin labeling; PCASL = Pseudo-continuous ASL.

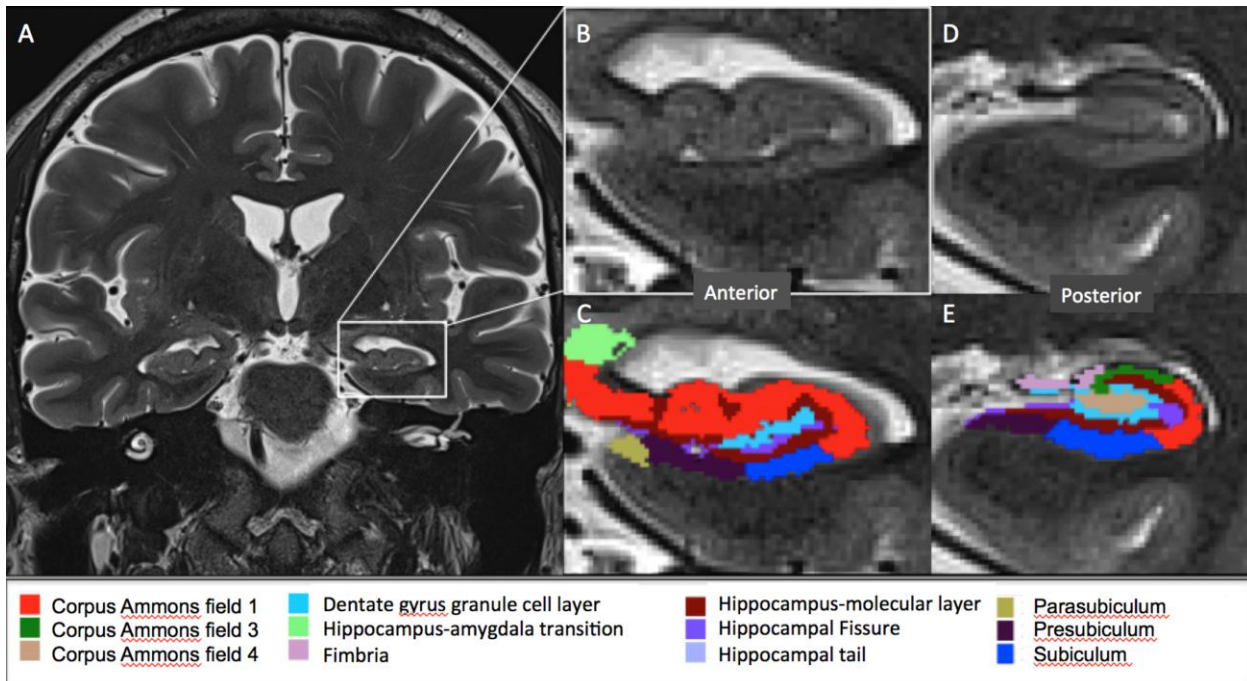
### 3.1 High resolution hippocampal scan

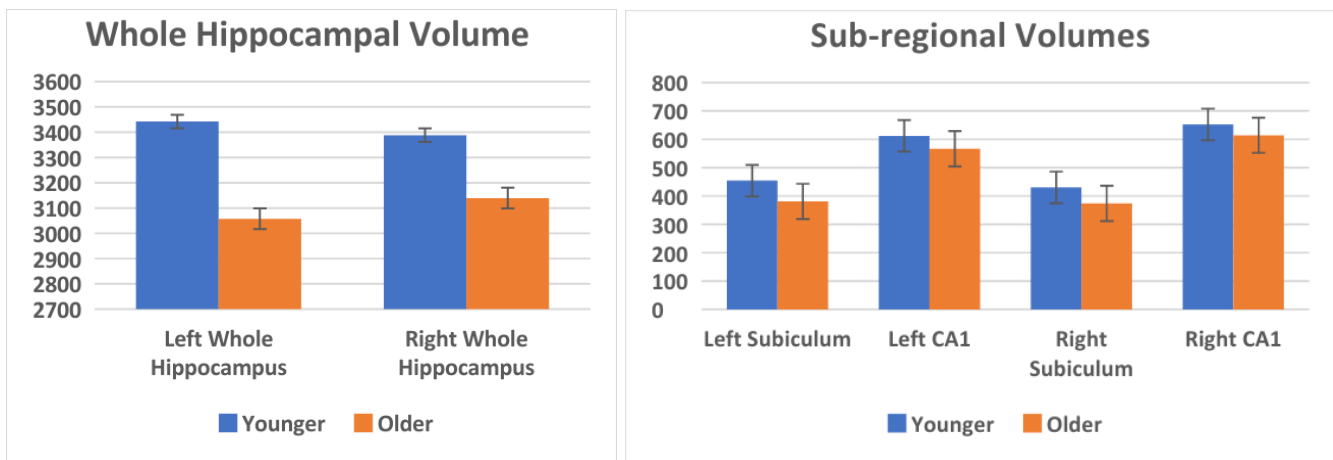
The HCP-A protocol includes a high-resolution 2D T2-weighted, turbo-spin-echo (TSE) structural scan centered on the hippocampus (HC) and extending to the adjacent gray matter, particularly entorhinal, perirhinal and parahippocampal cortex, and the amygdala in most participants. These medial temporal regions are critical for episodic memory and are particularly important in aging, as they are affected early in incipient AD and also in a range of other age-related disorders. Prior research has noted medial temporal changes associated with aging, and in particular, in early stages of AD (Dickerson et al., 2009; Jack et al., 1997; Scheltens et al., 1992; Singh et al., 2006).

We targeted an approximately 3 min acquisition duration and piloted a 2D TSE scan with 0.39x0.39x2 mm<sup>3</sup> resolution with slices oriented perpendicular to the long axis of the hippocampus. The anisotropic voxel size allows for maximum sub-regional differentiation within the cross section of the HC perpendicular to its long axis, where sub-regional resolution is most needed. Lower spatial resolution in the slice thickness axis is necessary to maintain sufficient signal-to-noise ratio (in a limited scan duration) and is acceptable because the sub-regional architecture of the hippocampus varies little along the long axis of the HC.

Sub-regional analysis of the hippocampal complex and surrounding neocortex will be performed using a version of Freesurfer that is currently being optimized for the HCP-D. Preliminary data show excellent parcellation of HC sub-regions, with expected age-related

volumetric changes observed in HC volume. Figure 3 shows an example of the imaging data acquired with this scan and the resulting labeling of hippocampal subfields; initial results on 10 younger (mean age 38.8) and 10 older (mean age 71.5) participants from automated segmentation of the hippocampal high resolution scan are shown in Figure 4.





**Figure 4: Preliminary volumetric data from the HCP-A high resolution HC scans.** Whole and sub-regional volumes in 10 younger (mean age 38.8 years) vs. 10 older participants (mean age 71.5 years) HCP-A participants. Error bars are standard deviations; y-axis values are cubic millimeters.

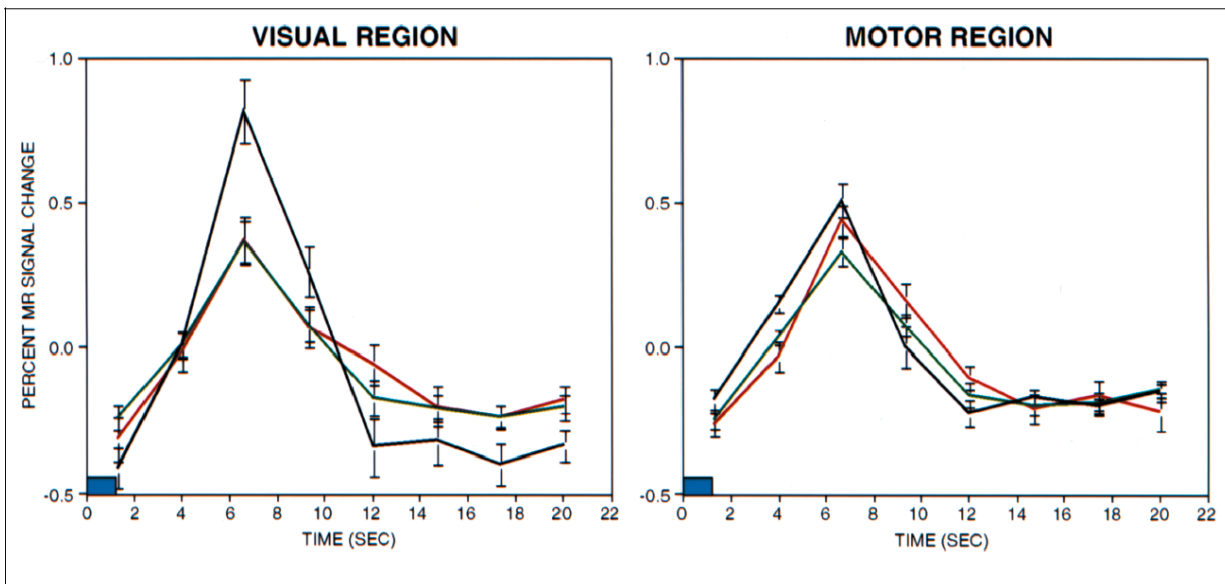
### 3.2 Task fMRI

**3.2.1. Inhibitory Control task (a shared task with HCP-D):** HCP-A participants will perform a Go/NoGo task that taps into inhibitory control processes. This “CARIT” task (Conditioned Approach Response Inhibition Task) is the same Go/NoGo task used in the HCP-D to assess inhibitory control, described in the companion paper by Somerville et al. (Somerville et al.). Specifically, the participants are instructed to rapidly press a button in response to seeing all shapes except two target shapes. In HCP-D, but not HCP-A, this task has a conditioned reward-history component wherein a different reward value is attached to one of the shapes during an immediately preceding “Guessing” task. Foregoing the Guessing task in HCP-A (thus rendering the reward-history component of the CARIT task inoperative) was a strategic decision based on subject burden while also prioritizing the functional domain most relevant for studying aging, episodic memory. However, the response-inhibition aspects of the CARIT task nonetheless address an important function that can decline in older participants, particularly if there is white matter impairment affecting fronto-striatal circuits (Fjell et al., 2010).

**3.2.2 Visuomotor task:** Visual and sensory-motor responses can be consistently generated through simple stimuli and task paradigms. Such sensory-motor tasks are therefore useful for assessment of the hemodynamic response in individuals and groups. Assessment of hemodynamic response characteristics can be used to assess potential vascular compromise in an individual as has been performed in prior work (Buckner et al., 2000; Dumas et al., 2012).

For example, Buckner et al. (2000) used a paradigm of repeated presentation of visual flickering checkerboards paired with a simple motor response. They demonstrated that, although response properties were altered in older adults and individuals with dementia (e.g.,

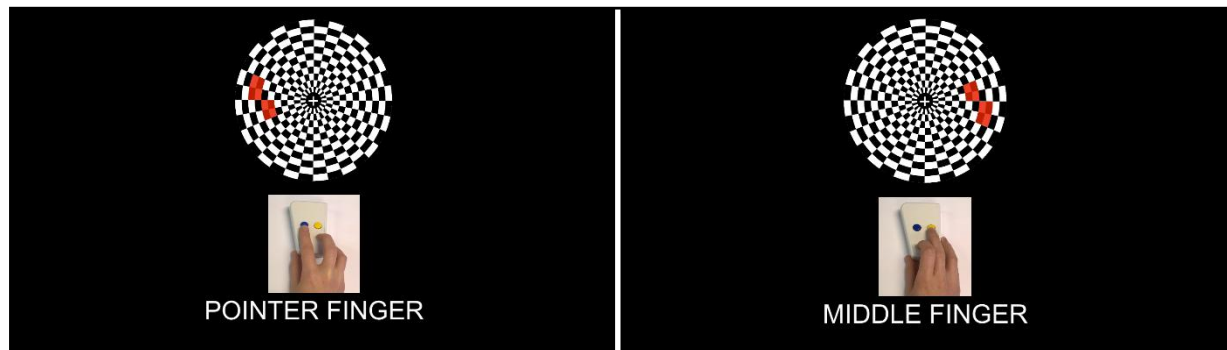
reduced amplitude in visual cortex), paired events resulted in an expected summation response in both groups and that qualitatively comparable activation maps could be derived in each group. Thus, such data may provide information useful in the interpretation of results from cognitive or resting fMRI data (Figure 5) and could be used in multivariate analyses aiming to control for non-neural physiological factors.



**Figure 5: The hemodynamic response in older adults.** Excerpt from Buckner et al., (2000) shows mean age-related differences in the hemodynamic response in younger vs. older adults in primary visual (left panel) and motor (right panel) regions using a standard (non-multiband) TR of 2.68s. Black lines = young adults; green = non-demented older adults; red = demented older adults. Error bars are standard error of the mean; the blue square in the lower left corners indicates the stimulus presentation. Reprinted with permission from Randy L. Buckner, Abraham Z. Snyder, Amy L. Sanders, Marcus E. Raichle, John C. Morris, 'Functional Brain Imaging of Young, Nondemented, and Demented Older Adults,' *Journal of Cognitive Neuroscience*, 12:2 (2000), pp. 24-34. © 2000 by the Massachusetts Institute of Technology, published by the MIT Press.

The Visuomotor task in HCP-A is a single run of 155 seconds (Figure 6). Participants are presented with a black and white circular checkerboard, with red flickering square targets. The red squares appear in pairs, either LEFT or RIGHT of a central fixation point. Participants are instructed to respond as quickly as they can with either their index finger (left button press) for red squares on the left or middle finger (right button press) for red squares on the right. The task begins with a countdown and an 18 second fixation block followed by 3 active blocks each lasting 27 seconds with 9 trials, separated by an 18 second fixation block. The location of the targets (LEFT vs. RIGHT) are randomized between trials. The checkerboard flickers at a frame-

rate of 4 Hz. As a cueing facilitator, a green fixation cross turns white 1s before the start of each block and stays white during the active block. It turns green and stays green during the fixation blocks. Preliminary analysis in 10 participants shows the Visuomotor task robustly activates motor and visual cortices at the group level.



**Figure 6: Depiction of the visuomotor test stimuli and response.**

3.2.3 Face-Name task: Forgetting names is among the most common memory complaints of older adults. Formation of face-name associations has been used as a cognitive probe since early behavioral studies in the 1980s (McCarty, 1980) and subsequently adapted for imaging (Sperling et al., 2001). The FaceName task is a single run of 276 seconds with encoding, distractor and recall blocks repeated twice for each set of faces. Participants are instructed to memorize the names for a series of faces and try to remember them for later. The task begins with a countdown followed by the first encoding block lasting 22 seconds: a 2 second cue to MEMORIZE followed by 5 face/name pairs that are shown for 4 seconds each (Figure 7). The distractor block comes next with a 2 second cue and 20 seconds of Go/NoGo task. The recall block follows with a 2 second cue to RECALL and 20 seconds where the same faces are shown with “???” (without their paired names) for 4 seconds each. Participants are instructed to press their index finger button (left button press) when they see a new face/name pair appear on the screen in encoding blocks. For recall blocks, they are instructed to press their index finger button (left button press) when they believe they have correctly remembered the name of a face.

To minimize head motion contamination of the data and to maintain integrity of the retrieval components of the task, we opted against an in-scanner recognition test; instead, participants indicate with a button press whether they knew the response and are tested

immediately after the scan for retrieval accuracy. This task is always the last task performed during the session, therefore minimizing and standardizing the retrieval interval.



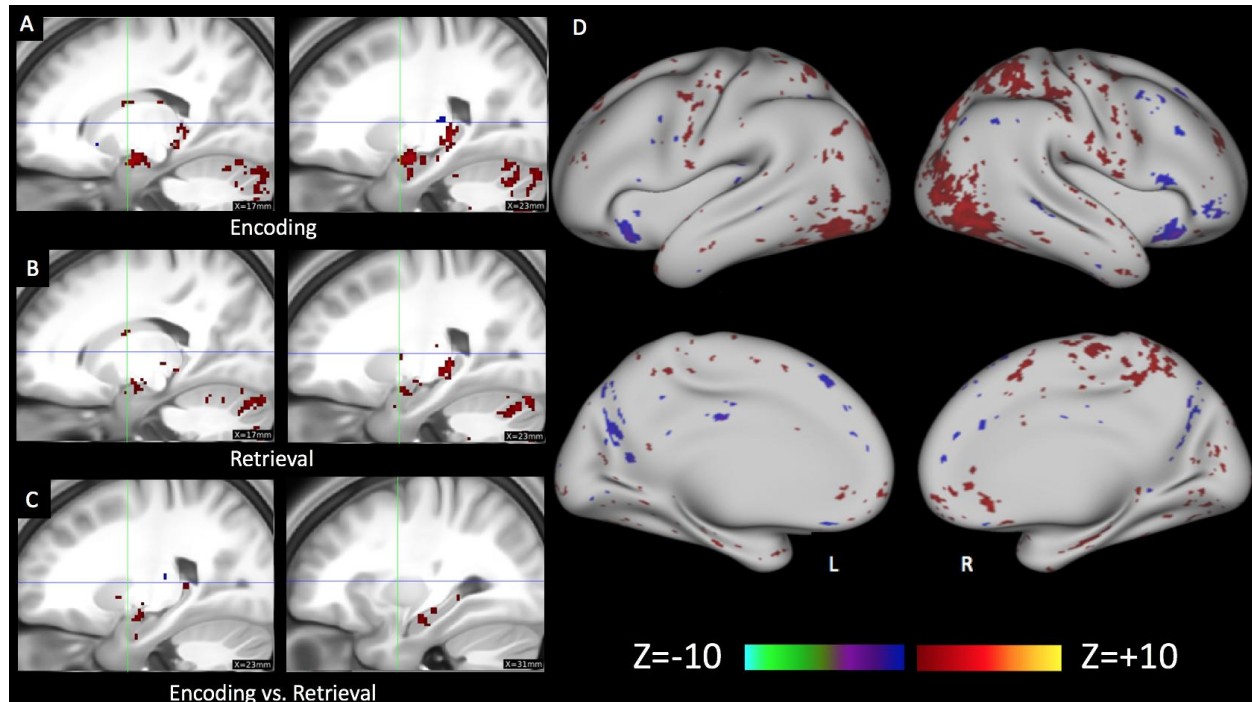
**Figure 7:** Example of face name stimuli; Encoding (left) and Retrieval (right).

3.2.4 Preliminary FACENAME task fMRI Results: We evaluated the activity evoked by the FACENAME task in an early set of 16 participants in the HCP-A study. Initial preprocessing of fMRI data was conducted using the public release HCP Pipelines v3.22. The HCP “fMRIVolume” pipeline includes correction for gradient nonlinearity, motion correction, fieldmap-based EPI distortion correction, brain-boundary-based registration of EPI to structural T1-weighted scan, non-linear (FNIRT) registration into MNI152 space, and grand-mean intensity normalization. The HCP “fMRISurface” pipeline (Glasser et al., 2013) registers the data into a standard grayordinate space by projecting cortical gray matter onto registered surface meshes with a standard number of vertices and projecting subcortical data to a set of subcortical gray matter parcel voxels. The fMRISurface pipeline applies a small amount of spatial regularization using a 2 mm full-width-half-maximum (FWHM) spatial filter (in 2D on the cortical surface and in 3D for subcortical and cerebellar voxels). Following preprocessing, during task fMRI analysis (“TaskfMRIAnalysis” pipeline), additional spatial smoothing was conducted prior to fitting the general linear model (GLM) to bring the applied total smoothing to 4 mm FWHM. Temporal filtering of the 4D time series and the GLM design matrix was conducted with a Gaussian-weighted linear highpass filter with a soft cutoff of 200 s. The 4D time series was prewhitened within FILM to correct for autocorrelations in the fMRI data.

Data were then submitted to a GLM to estimate task effects. The two regressors of interest represented separate time series of stimulus presentation for MEMORIZE blocks and RECALL blocks, convolved with a double-gamma canonical hemodynamic response function. The active distractor blocks (Go/NoGo task between memory blocks) were left unmodeled so that they would become the effective baseline in contrasts of the memory conditions versus baseline.



Data from pilot testing in a small group of 16 healthy volunteers showed that this task significantly activates the hippocampus, in addition to frontal and posterior cingulate cortices, with a dissociation between the magnitude of activation during encoding vs. retrieval, respectively (Figure 8).



**Figure 8: Group activation maps for the Face-Name Association task in an early sample of HCP-A participants (N=16).** Participants (mean age 49.9 years), Z-stat maps, thresholded at  $Z > 2.3$  (uncorrected). **A.** Contrast of Encoding > Distractor; **B.** Retrieval > Distractor; **C.** (subcortical) and **D.** (cortical surface) maps for the direct comparison of Encoding > Retrieval (red); Retrieval > Encoding (blue). Consistent with prior studies (Eldridge et al., 2005; Suthana et al., 2011), there is significant activation seen in the anterior hippocampal region, particularly during encoding compared to retrieval (**Panel C**). Panels A-C are displaying the subcortical voxels from a CIFTI/grayordinate analysis. Fronto-opercular activation is also evident for during retrieval vs. encoding (**Panel D**). Sagittal images show the right hemisphere. Number on bottom right denote the x-slice coordinates (mm) in MNI152 space. L = left, R = right.

### 3.3 ASL

Perfusion imaging holds particular relevance for the aging population. Vascular disruption is common in aging and this is a growing medical concern in this cohort (Heidenreich et al., 2011). Arterial spin labeling (ASL) to measure cerebral blood flow (CBF) is common to both the HCP-D and HCP-A protocols; however ASL holds particular relevance for the aging

population considering the important aspect of vasculature in brain aging and disease (Alsop et al., 2010). CBF is influenced by both vascular and metabolic processes and has been shown to correlate with FDG PET measurement of cerebral glucose metabolism (Cha et al., 2013; Chen et al., 2011; Newberg et al., 2005). A 2D multi-band EPI based pseudo-continuous ASL (pCASL) (Li et al., 2015) is used as it permits the acquisition of higher spatial resolution images, which is not typical for ASL protocols. The 2D slice accelerated approach was chosen (Harms et al., 2018) over conventional 3D ASL techniques due to the desire to have connectome-type spatial resolutions ( $\leq 2.5$  mm) for eventual surface based analysis, which is not feasible with the 3D method due to its high sensitivity to motion and the limited scan time ( $\sim 5$  minutes) allocated to ASL in the HCP-A imaging protocol.

## 4. BEHAVIORAL ASSESSMENTS

### 4.1. General

The cognitive and performance battery includes domains that overlap with those from HCP-D in addition to assessments most relevant for advanced aging, particularly episodic memory, motor speed, sensory acumen (pain tolerance, auditory and visual acuity), and physical fragility. Table 3 lists the complete battery of tests. Some redundant questions were eliminated (see Supplementary Materials for details). We have added a brief discussion of domains and tests unique to HCP-A below.

**Table 3: Behavioral Testing**

<u>Domain</u>	<u>Test</u>
<b>Intake Measures</b>	
Cognition	Telephone Interview for Cognitive Status (TICS-M) Montreal Cognitive Assessment (MOCA)
Demographic and Health Questionnaires (non-standardized; entered into Redcap)	Medication Use Edinburgh Handedness Inventory Dental Work Questionnaires Demographics
<b>NIH Toolbox</b>	
Cognition	Picture Sequence Memory Test (Episodic Memory) Dimensional Change Card Sort Test (Cognitive Flexibility) Flanker Task Control and Attention Test (Inhibition) Picture Vocabulary Test (Language/Vocabulary) Pattern Completion Processing Speed Test (Processing Speed) List Sorting Working Memory Test (Working Memory) Oral Reading Recognition Test (Language/Reading Decoding)
Motor	2-Minute Walk Endurance Test (Endurance) 4-Meter Walk Gait Speed Test (Locomotion) Grip Strength Dynamometry (Strength)



Emotion	Positive Affect Computer-Adaptive Test (CAT) General Life Satisfaction CAT Meaning and Purpose CAT Emotional Support - Full Form (FF) Instrumental Support FF Friendship FF Loneliness FF Perceived Rejection FF Perceived Hostility FF Self-Efficacy CAT Perceived Stress FF Fear-Affect CAT Fear-Somatic Arousal FF Sadness CAT Anger-Affect CAT Anger-Hostility FF Anger-Physical Aggression FF
Sensory	Pain Intensity FF Pain Interference CAT Words-in-Noise Test (Audition) Visual Acuity Test
<b>Additional Behavioral/Cognitive and Health Measures</b>	
Episodic memory	Rey Auditory Verbal Learning Task
Self-regulation / decision making	Delay Discounting
Emotion Recognition	The Penn Computerized Neurocognitive Battery Emotion Recognition subtest
Executive Function/ Switching	Trails A and B
Sleep	Pittsburgh Sleep Quality Index (PSQI)
Stress	Geriatric Adverse Life Events Scale
Emotion	Neuroticism/Extraversion/Openness Five Factor Inventory (Short version of NEO-FFI, all 60 questions as published) Achenbach Adults Self-Report (Short version of ASR plus we cut several questions: see below) Achenbach Older Adult Self-Report (ages 60+) (Short version of ASR)
Psychodiagnostic	Semi-Structured Assessment for the Genetics of Alcoholism (Altered Version of SSAGA) Demographics, Medical History, Depression, Suicide, Eating Disorders, PTSD, OCD, Social Anxiety/Panic/Agoraphobia, Psychotic Episodes, Tobacco, Alcohol, Marijuana, Drugs
TBI	Boston Assessment of Traumatic Brain Injury-Lifetime Questionnaire (BAT-LQ)
Physical Activity, activities of daily living, frailty,	International Physical Activity Questionnaire (Short version of IPAQ) 60+ only: The Lawton Instrumental Activities of Daily Living Scale
Menopause	Menstrual Questionnaire Menopause Screener

## 4.2 Episodic Memory

Episodic memory impairment is of particular concern in aging; some memory decline is expected, but many disorders of aging including AD have prominent effects on hippocampal function, specifically declarative memory including episodic memory. The NIH Toolbox's Picture Sequence Memory test is intended to test episodic memory but there is little data yet using this task in clinical populations. To get a more comprehensive assessment of episodic memory we added a widely used neuropsychological measure, the Rey Auditory Verbal Learning Test (RAVLT, (Rey, 1941)). This test presents a list of 15 unrelated words verbally to the subject who is instructed to repeat each word recalled, with five repetitions to establish a learning curve. This is followed by a second, interference list, of the same length, followed by an additional recall of the initial list. The standard administration of the task has an additional 20-minute delay with another recall trial and a forced-choice recognition test. The RAVLT has multiple alternate forms making it ideal for longitudinal assessment. The HCP-A uses a non-standard RAVLT administration, which omits the additional 20-minute delay-recall that is part of the standard test. This decision was made to reduce the length of the testing battery, a particular concern for older participants, and justified by published data indicating that short term delayed recall is equivalent to long term delayed recall in cognitively relevant clinical samples (Schoenberg et al., 2006; Zhao et al., 2012).

#### **4.3 Fragility and Activities of Daily Living**

Fragility or frailty in aging describes the tendency for older people to move more slowly, be less coordinated, and thus have a risk of injuries such as falling. The commonly used metrics include recent significant weight loss, weakness, exhaustion, slow gait, and low energy expenditure (Fried et al., 2001). Fragility affects one's ability to perform activities of daily living (ADLs) such as self-care for bathing, dressing and eating, and epidemiology suggests that physical activity is a protective factor against developing AD (Hickman et al., 2000; Rolandi et al., 2016). HCP-A assesses fragility and ADLs with both questionnaires and with a performance test of motor speed and gait quality. These include a short version of the International Physical Activity Questionnaire (IPAQ); participants 60 years and older also complete the Lawton Instrumental Activities of Daily Living Scale (Lawton and Brody, 1969). There are also two performance measures of gait from the NIH Toolbox (Reuben et al., 2013), a four-meter walk gait speed test and a two-minute walk endurance test (Reuben et al., 2013). The four-meter walk gait speed test is adapted from the Short Physical Performance Battery (Guralnik et al., 2000). The participant is asked to walk four meters at their usual pace while being timed. Participants complete one practice and two timed walks. Raw scores are recorded in seconds and the faster of the two walks is used as the official score for each participant. The two-minute endurance walk is adapted from the American Thoracic Society's 6-Minute Walk Test Protocol

(Enright, 2003). Participants are required to walk as far as they can on a 50-foot out and back course. Raw score is measured as the distance in feet and inches walked across the two minutes. Participants are provided instructions and a brief (one 100-foot lap) practice.

#### **4.4 Psychopathology**

HCP-A excludes participants who have been diagnosed and treated for major psychiatric disorders (e.g., schizophrenia, bipolar disorder) or neurological disorders (e.g., stroke, brain tumors, Parkinson's Disease) as well as individuals with severe depression that required treatment for 12 months or longer in the past five years. Supplementary Table 3 lists the complete exclusionary criteria. We document non-exclusionary mental health related symptoms using the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA), a reliable and valid instrument used in numerous studies to examine psychopathology (Bucholz et al., 1994; Ehlers et al., 2013; Gilder et al., 2004; Hesselbrock et al., 1999; Kramer et al., 2009; Lynskey et al., 2005; Munn-Chernoff et al., 2013; Munn-Chernoff et al., 2015; Schuckit et al., 2013). Domains covered are: depression, anxiety, suicidality, trauma, psychosis, eating disorders, and tobacco, alcohol and drug use. Participants are also screened for substance use on entry.

#### **5.0 VITALS AND BIOLOGICAL MEASURES**

Brain aging, particularly brain connectivity, is known to be affected by a range of factors common in aging. A major goal of the HCP-A is to provide data that will identify how these factors affect the brain across the lifespan. In particular, metabolism, vascular health, hormonal status, stress and other environmental factors, have known or suspected relationship to brain circuitry during typical aging as well as in dementia and other diseases (Iturria-Medina and Evans, 2015). In addition to various biological markers of vascular risk, HCP-A will collect information about smoking status and tobacco use history, systolic and diastolic blood pressure, physical activity level, and weight to help characterize vascular health in participants.

Rates and types of brain aging, including age-associated alterations in brain connectivity and connective integrity, may be influenced by a host of biological and environmental factors that shift throughout the lifespan. For example, metabolic, vascular (e.g., blood pressure), and hormonal changes common to aging are all associated with variation in inter-individual neural integrity and specific alterations may promote dementia or neurological disease. Environmental factors such as chronic stress, smoking and tobacco use can also affect the brain and interact with or accelerate typical aging processes. Greater levels of physical activity may promote healthy brain aging whereas greater body mass index is detrimental. Thus, HCP-A will acquire relevant data across these several domains to characterize major factors known to influence brain aging. This will allow modeling of major and interacting factors to more comprehensively

understand the conditions that promote 'healthy' brain aging on one extreme and brain disease on the other (Gorelick et al., 2017; Shatenstein et al., 2015).

## **5.1 Sources**

Participants provide urine, breath alcohol content (BrAC), and blood samples. Each day that participants are scanned a urine sample is collected for a toxicology assessment for the following substances: 1) cocaine; 2) tetrahydrocannabinol; 3) amphetamines; 4) methamphetamines; 5) oxycodone; and 6) opiates. A positive urine assay for any of the aforementioned substances is considered non-exclusionary. A BrAC sample is collected (AlcoHAWK breathalyzer test) at the beginning of each study visit day to collect information about alcohol in the system. A nonzero assay for BrAC is considered non-exclusionary. Shortly after consenting, blood samples for genotyping, metabolic, lipid and hormonal tests are collected from participants, ideally after an 8 hour fasting period. It is noted in the database if a participant did not fast prior to the blood draw, and blood is collected even if the participant did not adhere to the fast. If a blood sample cannot be obtained, saliva is collected for genetic testing. External measures include: height, weight and resting blood pressure examination.

## **5.2. Measures**

5.2.1 Glucose: Glucose metabolism is of particular interest because of its relationship not only to dementia but also to typical aging. Type-2 diabetes mellitus (T2DM) increases risk for cognitive impairment (Biessels and Reijmer, 2014) and the risk (by 2–4 fold) of developing AD dementia (Ohara et al., 2011). Elevated blood glucose increases risk of developing Mild Cognitive Impairment (MCI) (Yaffe et al., 2006), and elevated blood glucose combined with MCI speeds up conversion to symptomatic AD (Yaffe et al., 2006). Importantly, T2DM is associated with alterations in brain structure (Reitz et al., 2017) and functional connectivity similar to those seen with MCI due to AD (Baker et al., 2011).

In particular, T2DM patients have reduced functional connectivity between the hippocampus and other brain regions, and these changes correlate with cognitive performance. Differences in glucose homeostasis may also impact typical aging, as impaired glucose tolerance ('prediabetes') has been associated with lower memory and learning scores in non-diabetic, non-demented older adults (Convit et al., 2003). Metabolic syndrome, a cluster of symptoms including elevated blood pressure, elevated glucose, elevated BMI, and abnormal cholesterol, is prevalent in more than ~25 % of the older adult population (Misiak et al., 2012) and may affect aging brain circuits. To address metabolic syndrome, the HCP-A will measure waist circumference, height, weight, blood pressure, total protein, C-reactive protein,

homocysteine, and glomerular filtration rate and obtain a fasting metabolic panel including glucose, insulin, hemoglobin A1c (HbA1c), triglycerides, LDL, HDL, and total cholesterol.

For the HCP-A, hormonal assays, HbA1C and metabolic analyses will be carried out on blood. Metabolic and lipid assays will be run in batches every 6 months by the Washington University's Core Laboratory, including blood glucose, HbA1c, insulin, a complete metabolic panel, C-Reactive Protein (CRP), a standard lipid profile, and homocysteine. This will help inform investigators of an individual's risk for obesity, diabetes, and other biological markers of vascular risk. Blood/saliva samples for genetics will be stored in the Rutgers University Cell & DNA Repository (RUCDR) in compliance with NIH data and sample sharing policies.

5.2.2. Vascular health/burden: Numerous factors besides genetic risk influence cognitive aging as well as brain structure and function. These include potentially modifiable factors such as smoking, physical activity level, obesity, hypertension, and diet. It has long been recognized that white matter damage (presumably resulting in deterioration of brain structural connectivity) is found in older adults linked to cardio/cerebro-vascular risk factors and is associated with reduced cognitive function (Breteler et al., 1994; Jeerakathil et al., 2004; Longstreth et al., 1996; Reed et al., 2004; van der Flier et al., 2005). Functional MRI studies in typical aging indicate that systolic blood pressure, body mass index (BMI), and total cholesterol are significantly correlated with regional increased activations during cognitive tasks, even over blood pressure and BMI ranges considered normal (Braskie et al., 2010). Variation even in the 'typical' range of variation in older adults (variation in the pre-risk range, e.g., blood pressure/pulse pressure variation in normotensive individuals) is associated with brain structure and cognition (Kennedy and Raz, 2009; Leritz et al., 2010; Salat et al., 2012) and therefore these factors may provide important insight into understanding processes contributing to the 'typically' aging brain. The measurements collected enable calculation of the Framingham risk score for men and women, which also estimates cardiovascular risk (Marma and Lloyd-Jones, 2009).

5.2.3 Menopause and hormone assessment: Age-related changes in hormone levels occur in both men and women, but are most pronounced in women in the two years before and after the final menstrual period -- the defining event of menopause -- occurring on average at age 51 (Randolph et al., 2011). It is controversial when and how cognition may be affected by the reduction of hormones, particularly estradiol, during the menopause transition or by hormone therapy (HT). Women have a higher rate of AD and may be more vulnerable than men to cognitive decline in aging, suggesting a potential relationship between hormones and memory (Candore et al., 2006; Epperson et al., 2013) and there is general agreement that many women experience memory deficits in peri-menopause (Greendale et al., 2010). Longitudinal studies suggest the deficits are transient (late peri-menopausal) and not attributable to age, sleep, or depression confounds (Greendale et al., 2010; Maki et al., 2010). It is obviously

important to know how HT affects the brain, cognitive function, and dementia risk. In healthy aging, some HT treatments may benefit cognition (Maki et al., 2010) and reduce AD risk (LeBlanc et al., 2001), but results are inconsistent. The Women's Health Initiative Memory Study (WHIMS) reported that some but not all HT treatments increased AD incidence (Epperson et al., 2013; Fuh et al., 2006; Greendale et al., 2010). Mechanistically, a menopause-related decrease in estradiol may contribute to cognitive impairment, especially memory, in peri-menopausal women. Estrogen receptors are enriched in hippocampus and frontal cortex (McEwen, 2002), brain areas important for episodic and working memory. In human imaging studies of healthy, premenopausal women, experimental estrogen depletion decreases fMRI activation during verbal memory tasks, and reinstatement normalizes this response (Craig et al., 2008).

Hence, HCP-A oversamples women in this age range. We are staging menopause objectively using validated criteria (Harlow et al., 2012) and obtain multiple hormonal measures for participants of all ages and genders, including serum estradiol (E2), testosterone, Luteinizing hormone (LH), and Follicle Stimulating Hormone (FSH), in addition to relevant cognitive, sleep, mood and HT factors. E2 and FSH will particularly help define the menopausal stage of an individual in conjunction with the STRAW-10 working group. Due to variable hormone levels across the menstrual cycle, especially for peri-menopausal women, blood samples for women 45-55 years old will be collected 2 to 6 days after the start of their cycle. Longitudinal assessment will allow us to better characterize how the brain changes during the menopause transition and how these changes may relate to cognition. In particular, the slope of change in hormone levels E2 and FSH will be used in prediction models of connectivity and cognitive changes. Menstrual history and menopause status and history are collected through two questionnaires: Menstrual Questionnaire and Menopause screener.

5.2.4 Genetic testing: Variation in the *APOE-4* allele confers a high risk for development of AD (Liu et al., 2013). The presence of at least one allele increases the risk of developing AD four-fold and the presence of two alleles increases the risk twelve-fold (Liu et al., 2013). Recently, additional genetic variations with smaller effect sizes have also been shown to confer risk for AD (Harold et al., 2009; Lambert et al., 2013).

The HCP-A acquires blood or saliva samples for genotyping. Samples are collected and banked for future analysis at RUCDR (<http://www.rucdr.org>). Blood is acquired into RUCDR custom kits and shipped to RUCDR within three days of collection. Since drawing blood can be anxiety provoking, participants may opt out of the blood draw, though it is highly encouraged. If blood is not obtained, a saliva sample is collected for genotyping. An additional 5 ml of whole blood collected in EDTA tubes will be stored at -80 degrees C and batch shipped to Washington University Hope Center for DNA purification and processing. Following typical purity and DNA size checks, samples will be assayed for 8 SNP regions that are associated with common

variants of neurodegenerative conditions (especially AD), including ApoE, CLU, PICALM, CR1, BIN1, CD2AP, EPHA1 and ABCA7. These SNPs were chosen as genome wide analyses have shown replicable associations with variants of neurodegenerative conditions, particularly AD (Naj et al., 2017). Budgetary constraints preclude more comprehensive genotyping including markers for admixture but bloodlines are maintained in RUCDR for future analysis should funding become available.

## **6. SUPPLEMENTS AND RELATED R01**

HCP-A investigators have applied for or received several supplements and linked R01 grants that enhance the value of the data. Most notably, a critique provided in the summary statement for this proposal (1 U01 AG052564-01) expressed concern that the originally proposed sample size for the longitudinal study was low and did not the 60-79 year age group for longitudinal study, given the high risk for age related illnesses including stroke, MCI and dementia in this age-range. In addition, nearly all people in this age-range develop subcortical white matter lesions that are likely to interfere with connectivity. An administrative supplement solved the gap in the enrollment plan for longitudinal scanning, increased the overall number of longitudinal scans, and enabled extension of the interval between the first and second scan to 20-24 months. All scans, including those originally proposed and those accommodated via the administrative supplement, are represented in the enrollment plan of Table 1. We hope to extend the HCP-A by an additional year (via the no cost extension mechanism) to accommodate additional longitudinal scans. Other supplements funded or in progress will 1) collect data on dysexecutive function in AD and related dementias, 2) increase the representation of bilingual ethnic minorities, and 3) create the infrastructure for obtaining brain donations to link advanced brain connectivity measures *in vivo* to confirmed post mortem evidence of AD neurodegenerative pathology. One R01 was funded that adds a spectroscopy scan for one site. These additional studies are described in detail in Supplementary Data.

## **7. DATA SHARING**

All HCP-A imaging, biological, and behavioral data will be shared publicly via a cloud-based data sharing environment managed by the NIMH Data Archive (NDA). The Connectome Coordination Facility (CCF) at Washington University, built on the original HCP-YA informatics infrastructure (Hodge et al., 2016; Marcus et al., 2013; Marcus et al., 2011) will play an important intermediate role, providing central quality control (QC) and image processing services for all lifespan and disease-focused HCP projects. The publicly released data will include the ‘raw’ (unprocessed) structural, fMRI, dMRI, and ASL data, and minimally preprocessed data which adopt the “HCP-style” processing approach (Glasser et al., 2013) with

modifications and extensions appropriate for HCP-A (Harms et al., 2018), carried out largely in the Freesurfer (Fischl, 2012), FSL (Jenkinson et al., 2012), and Connectome Workbench (Marcus et al., 2011) platforms.

HCP-A data will be distributed with open access to the majority of the data and restricted access to a limited subset of the data deemed sensitive to the study participants' privacy. HCP-A data will be distributed by the CCF and NDA in multiple data releases over the course of the study. We aim to release the first datasets in early 2019 and datasets on all participants by 2022.

## **8. STUDY PROGRESS**

The consortium has optimized and implemented the HCP-A protocol. Optimization of the imaging protocol to accommodate scanning older adults was synergistic with optimization for children, since rapid acquisition and accommodating an increased propensity for motion were key factors for both cohorts (Harms et al., 2018). Data acquisition with the final protocols commenced in February 2017. High-resolution hippocampal structure, and visuomotor and episodic memory task fMRI are unique to the aging imaging protocol, reflecting the specific brain changes that commonly accompany aging. The implemented HCP-A protocol represents the consortium's consensus on the parameters that are most likely to be of maximal interest to research on healthy and suboptimal brain aging. The behavioral protocol has been well tolerated, with completion of behavioral aspects near 100%.

Centralized leadership has trained personnel with ongoing oversight of data quality. Personnel from St. Louis trained staff at each site prior to beginning recruitment (including site visits) and provide regular enrollment audits to guide toward recruitment goals. The established infrastructure has accommodated steady enrollment, monitoring of data integrity, and protocol compliance since the commencement of data acquisition. The leadership has accommodated site-specific constraints while maintaining scientifically robust implementation.

## **9. LIMITATIONS**

In developing a normative database of the aging brain, there are inherent limitations in determining what is "normal" aging. While the HCP-A is recruiting a normative sample without known disease, it is nonetheless likely that some participants will have pre-clinical disease or mild cognitive impairment. It is not feasible to limit enrollment to only cognitively normal participants who are free of any trace of a condition or disease, particularly in the older cohorts, as medical problems become the norm in late-life. We attempted to strike a balance by excluding known neurological and active psychiatric diseases while relaxing the criteria for conditions in the older participants when those problems become very common. For instance,



conditions such as “pre-diabetes” and high blood pressure are relatively common in elderly participants and excluding these conditions would leave us with a “super-normal” sample that would not be representative of the general population of the US. Similarly, as some memory decline is typical in aging, we chose to relax our enrollment cutoffs with older participants. As another example, we did not exclude individuals who may have had depression early in their life, but have not required treatment in the past five years or individuals who may have been diagnosed with attention-deficit hyperactivity disorder earlier in life. The advantage of this approach is that the participants are ultimately more representative of the total population, however, it means they may not be as disease-free as the younger participants in the study. Measuring many of these health variables and including them in the database for future analyses that can choose whether or not to include individuals with various experiences may mitigate these concerns.

We have not used a collateral source so we are somewhat limited in our ability to evaluate if the participants have had a significant change in their behavior. Collection information from a collateral source was not feasible but would have provided a better overall evaluation of the current state of the individual.

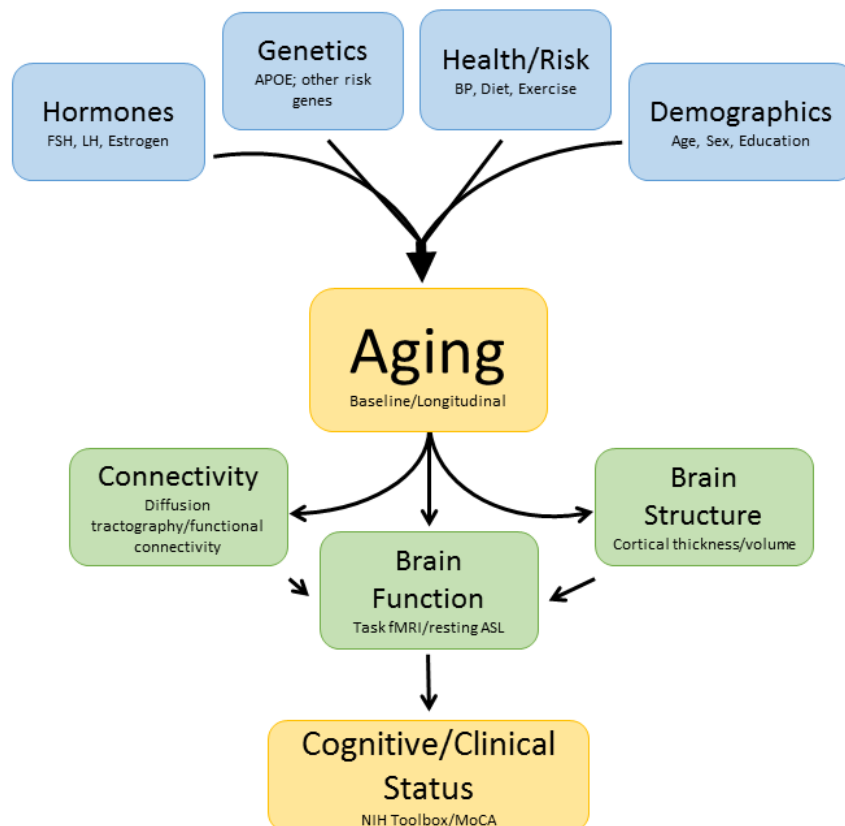
As noted, the Lawton Activities of Daily Living questionnaire reflects a person's own view of their performance, but we do not actively observe participants engaging in real life activities of daily living to independently evaluate their performance. We also did not exclude participants based on current medications. In some instances, patients may be taking blood pressure medications or antidepressants that may affect their functional (task, resting, and ASL) results. This also pertains to caffeine consumption, which is not controlled or restricted.

In order to keep the overall time commitment within 8 hours, it was also not possible to include all of the behavioral assessments that would likely be useful to investigators. This was a particular concern for the oldest participants, who may tire more easily. Thus, the cognitive testing battery is not as extensive as would typically be seen in a clinical evaluation; nevertheless we attempted to cover each of the major domains in cognition and behavior.

## **10. SUMMARY**

Using recently innovated MRI acquisition strategies, the HCP-A is generating an extensive dataset of age-related differences and longitudinal change in brain structure, function, and connectivity across the adult age span, focusing on typical aging. This will serve as a reference dataset for insights to understanding typical and pathological changes in brain circuits and networks. The consortium designed the enrollment plan to focus on aspects of brain aging that are relevant to public health, and the behavioral protocol to focus on cognitive health-

modifying factors. The enrollment plan invests substantially in peri-menopause, yet attends to sex balance, early aging, advanced aging, and the oldest old. This design will contribute data on how rapid hormone changes affect the brain and cognition, effects of hormone replacement therapy, factors contributing to the appearance of white matter lesions and dementia onset, and the “healthy survivor state”, including disease prevention and cognitive reserve. The consortium anticipates that cognitive health-modifying factors will include hormonal status, vascular burden, genetic status, physical fitness, systemic health, sensory acumen, and life history of stress and other environmental factors (Figure 9).



**Figure 9. Summary of the primary components of HCP-A.** The overarching goal of HCP-A is to understand how connectivity changes across the middle-age and older adult age span and the factors that are associated with such changes. To do so, data are being acquired on adults ranging in age from 36 years to 100+ with a subset of individuals examined at multiple time points. A range of biological, physiological, genetic, health and demographic information are being acquired to understand how such factors may contribute to brain aging. Advanced image acquisition and analysis will allow examination of associations between contributing factors and markers of brain aging including structural and functional connectivity measures as well as relationships among contributing factors, brain markers, and cognitive and clinical status. Ultimately, the full sample of data will allow multivariate statistical modeling of the host of interacting factors that contribute to decline as well as preservation in brain connectivity and functional

status linked to aging.

A major objective of the project is to make the collected imaging data and behavioral assessments widely and openly available to the scientific community. The consortium designed the HCP-A protocol to optimize utility of the data being produced to fuel discovery. In particular, this normative database was designed to accelerate discovery of disease-modifying approaches. The administrative supplements and related R01 on AD attest the utility and value of the HCP-A data set.

The HCP-A data will be used by the scientific community to expand understanding of the fundamental organization and operation of the brain and its manifestation in behavior. This project will provide valuable reference data to support research examining the role of aging in brain disorders, ultimately accelerating discoveries and reducing the burden of nervous system disorders.

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**Supplementary Table 1.****Full list of contributors to HCP-A (listed alphabetically within affiliation).**

<b>Name</b>	<b>Role</b>
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Nora Downey	Site Coordinator
Bruce Fischl	Investigator
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Danny Wang	Univ. Southern California	Arterial Spin Labeling Sequences
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**Supplementary Table 2: HCP-A and HCP-D Unique and Overlapping Measures**

Test	HCP-A ONLY	Both HCP-A and HCP-D (ages apply to both studies, in this column)	HCP-D Only
Multi-domain cognitive screening (exclusionary @ intake)	Montreal Cognitive Assessment (MOCA) (22+)		Mini-Mental State Examination (MMSE) (14-21)
Bio Samples	Blood for Comprehensive Metabolic Panel, Hormones, etc. (fasting) (22+)	Rutgers University Cell and DNA Repository (RUCDR) Blood (9+) Saliva (5+) Blood – HbA1c (9+) Urine Drug Screen (12+) Breathalyzer (12+)	Hair (5-21) Salimetrics Saliva for Hormones (5-21)
Mock Scanner training	Optional – used with MR scan naïve participants only		Structured mock scanner training– follows SOP, required for all participants (5-21)
Scan types	High-res Hippocampal (22+) VisMotor Task (22+) FaceName + rec (22+)	Resting State (5+) Diffusion (5+) ASL (5+) Structurals (5+) CARIT (5+)	Guessing (5-21) Emotion (5-21)
Cognitive Testing	Rey Auditory Verbal Learning Test (RAVLT)- short delay (22+) Trail Making (22+)	University of Pennsylvania's Computerized Neuropsychological Testing (UPennCNP) Emotion (8+) Delayed Discounting (8+)	Matrix Reasoning (5-21) E-Prime Delayed Discounting (5-7)
Clinical Interview	Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA) (22+)		Kiddie Schedule for Affective Disorders and Schizophrenia (KSADS) (11-21)

Behavioral Measures (in RedCap)	Boston Assessment of Traumatic Brain Injury-Lifetime Questionnaire (BAT-LQ) (22+) Lawton Activities of Daily Living (60+) Menopause/STRAW-10 Staging (22+) Achenbach Older Adult Self Report (ASR-OA) (60+) Broad Experiences (22+) International Physical Activities Questionnaire (IPAQ) (22+)	Menstrual questionnaire (females 5+) Pittsburgh Sleep Quality Inventory (PSQI) (18+) Edinburgh Handedness Scale (11+) Achenbach Adult Self-Report (ASR) (18-59) Phenotypes and Exposures (PhenX) Medication List (5+) Language Experience and Proficiency Questionnaire (LEAP-Q) (5+) Adverse Life Events Scale (18+) NEO (16+) Caffeine questions (5+) Nicotine questions (12+) Dental work questions (5+)	Phenotypes and Exposures (PhenX) Demographics (5-21) Sleep Scale (5-7) Munich ChronoType Questionnaire (MCTQ) (8-17) Adapted Handedness scale (5-10) National Institute on Drug Abuse questionnaire (NIDA) (12-21) Medication Adherence Report Scale (MARS) (5-21) Farnsworth (5-21) Strengths & Difficulties (5-12) Puberty-Morris Udry/Tanner scales (5-21) PhenX Developmental History (5-17) PhenX Medical History (5-17) Family Psych History (5-21) Family Environment Scale (5-21) Child Behavior CHecklist (CBCL) (5-17) Youth Self-Report (YSR) (11-17) 7-UP Inventory (12-17) Screen Timer (5-21) Sports & Activities (5-17) Social Responsiveness Scale (SRS2) (5-21) General Behavior Inventory (GBI) (5-17) Children's Behavior Questionnaire (CBQ) 5-8) Behavioral inhibition system/ Behavioral activation system (BIS-BAS) (5-21) Urgency, Premeditation, Perseverance, Sensation Seeking, Impulsive Behavior Scale (UPPS) (5-21) Early Adolescent Temperament Questionnaire (EAT-QR) (5-15)
Test	HCP-A ONLY	Both HCP-A and HCP-D (ages apply to both studies, in this column)	HCP-D Only

Toolbox		<p><b>Cognition:</b></p> <p>Flanker (5+)*</p> <p>List Sorting (5+)*</p> <p>Dimensional Card Sort (5+)*</p> <p>Pattern Comparison (5+)*</p> <p>Picture Sequence Memory (5+)*</p> <p>Oral Reading Recognition (5+)</p> <p><b>Motor:</b></p> <p>Grip Strength Test (5+)</p> <p>4-Meter Walk (7+)</p> <p>2-minute walk (5+)*</p> <p><b>Emotion Self-Report:</b></p> <p>Positive Affect (8+)*</p> <p>General Life Satisfaction (8+)*</p> <p>Meaning and Purpose (18+)</p> <p>Emotional Support (8+)*</p> <p>Instrumental Support (18+)</p> <p>Friendship (8+)*</p> <p>Loneliness (8+)*</p> <p>Perceived Rejection (8+)*</p> <p>Perceived Hostility (8+)*</p> <p>Self-Efficacy (8+)*</p> <p>Perceived Stress (13+)*</p> <p>Fear (8+)*</p> <p>Sadness (8+)*</p> <p>Anger-Affect (18+)</p> <p>Anger-Hostility (18+)</p> <p>Anger-Physical Aggression (18+)</p> <p><b>Sensory:</b></p> <p>Pain Intensity (18+)</p> <p>Pain Interference (18+)</p> <p>Visual Acuity (5+)*</p> <p>Words in Noise (6+)</p> <p>*age appropriate Variations</p>	<p>Odor (5-21)*</p> <p>9-hole Pegboard (5-21)</p> <p>Emotion Parent Report (5-12)</p>
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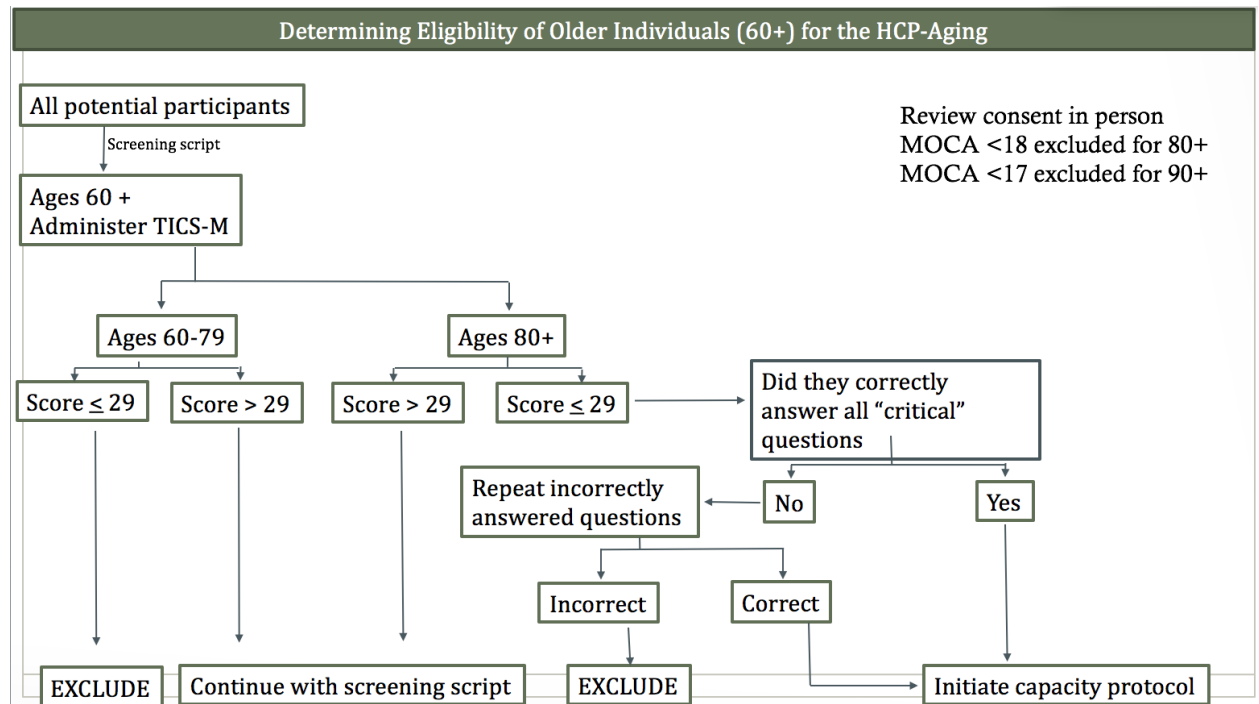
**Supplementary Table 3: Inclusion/ Exclusion Criteria**

<b>HCP-A Inclusion Criteria</b>	
<b>1.</b>	Age 35-100+
<b>2.</b>	Ability to give informed consent
<b>HCP-A Exclusion Criteria</b>	
<b>1.</b>	During the participant's lifetime:
<b>a.</b>	Neurologic disease including multiple sclerosis, cerebral palsy, Parkinson's disease, or Alzheimer's disease
<b>b.</b>	Brain surgery
<b>c.</b>	Major psychiatric disorder, such as bipolar disorder or schizophrenia
<b>d.</b>	Hospitalization for 2 days or more for alcoholism or drug dependence
<b>e.</b>	Head injury causing any of the following:
<b>i.</b>	Loss of consciousness for >30 minutes
<b>ii.</b>	Amnesia for >24 hours
<b>iii.</b>	Change in mental status for >24 hours
<b>iv.</b>	Neuroimaging findings consistent with traumatic brain injury
<b>v.</b>	Persistent (>3 months) post-concussive symptoms following concussion or mild TBI
<b>f.</b>	Two or more non-provoked (e.g. not due to fever) seizures after age 5 years or a diagnosis of epilepsy
<b>g.</b>	Any brain tumor including meningiomas
<b>h.</b>	Any cancer treated with chemotherapy and/or radiation to the head or neck, and/or any stage 4 (metastatic) cancer even if no treated
<b>i.</b>	Hospitalization for brain aneurysm, brain hemorrhage, subdural hematoma or stroke (except TIA is allowed)
<b>j.</b>	Rheumatoid arthritis, HIV or lupus or another condition requiring long-term use of steroids or other immunosuppressant
<b>k.</b>	If 80 years old or younger: Diagnosis of macular degeneration
<b>l.</b>	Known genetic disorder (e.g. sickle cell disease or cystic fibrosis)
<b>2.</b>	Within the last 5 years:
<b>a.</b>	Pharmacologic or surgical treatment by a neurologist, or endocrinologist for a period of 12 months or longer, except for thyroid conditions or for back pain or other condition that is clearly not brain-related.
<b>b.</b>	Severe depression requiring treatment by a psychiatrist for 12 months or longer
<b>3.</b>	Within the last 1 year:

<b>a.</b>	Diagnosis of thyroid problems and/or changing doses of thyroid medication
<b>b.</b>	Heart attack
<b>4.</b>	Current:
<b>a.</b>	Diabetes that has been diagnosed within the past 3 years (diabetes is OK if it is stably controlled per participant report of either HbA1c <7.0 or stable control for at least 3 months)
<b>b.</b>	Hearing loss sufficient to prevent communication via telephone
<b>c.</b>	Vision worse than 20/200
<b>d.</b>	Current pregnancy
<b>e.</b>	Unsafe metal or devices in body
<b>f.</b>	Moderate to severe claustrophobia
<b>g.</b>	Weight greater than 275 and/or BMI >35
<b>h.</b>	Use of prescription medication to prevent migraines (migraines allowed if not taking daily preventive medications)
<b>i.</b>	Migraine less than 72 hours before the first visit or during the visit
<b>j.</b>	Uncontrolled high blood pressure (>170/100) or working with doctor to stabilize blood pressure
<b>k.</b>	Severe lung, living, kidney or heart disease or other major organ failure
<b>l.</b>	Montreal Cognitive Assessment (MoCA) score of 19 or below for participants aged up to 79 years; MoCA score of 17 or below for participants ages 80-89; MoCA score of 16 or below for participants age 90 and above
<b>m.</b>	For participants aged 60 – 79, a score of 29 or below on the TICS-M questionnaire. If participants ages 80 and above score 29 or below on the TICS-M, we give them a secondary screen to determine their eligibility.



Supplementary Figure 1: Screening and Eligibility Flow Chart



### **Supplementary Table 3: HCPA-Supplements and Linked RO1**

#### **1. Dysexecutive AD**

The University of Minnesota PIs responded to NOT-AG-17-008 -- “Administrative supplements to develop research on AD and Alzheimer’s-related dementias (ADRD)” -- and received funds to scan 12 patients with dysexecutive presentation of AD (dAD) with the HCP-A protocol. Data from these patients will be added to the database at the Connectome Coordination Facility. Since therapeutic strategies to cure AD may need to begin before overt clinical symptoms are present, novel network-based biomarkers of early disease-related changes are invaluable. A recently developed rfMRI-based biomarker of cascading network failure (Jones et al., 2016; Wiepert et al., 2017), the network failure quotient (NFQ), may reveal abnormalities sooner than traditional large-scale network based biomarkers of AD. This supplement will take advantage of the HCP-A data quality to achieve the greatest SNR of the NFQ that has been possible thus far. Greater precision to measure abnormal NFQ will ultimately create a larger, more stable difference in the NFQ between patients and controls, and ideally between adults who are at a preclinical stage of AD and those who are not.

#### **2. Bilingualism**

The UCLA PIs submitted a proposal to test the hypothesis that bilingualism contributes to overall cognitive reserve in aging. An administrative supplement will use the HCP-A protocol to characterize bilingualism as a sociocultural mechanism accounting for age-related differences in structural and functional connectivity. It will scan and measure neurocognitive correlates among healthy adults and older adults that are ethnically Latino (the largest and fastest growing ethnic minority group in the US). Bilingualism has been claimed to subserve cognitive reserve in healthy aging (Bak et al., 2014), especially if high proficiency levels are attained (Gollan et al., 2011). Additionally, neuroimaging studies have also found that life-long bilingualism is positively associated with greater white matter integrity (Gold et al., 2013; Luk et al., 2011; Olsen et al., 2015) and grey matter density (Abutalebi et al., 2015; Abutalebi et al., 2014; Mechelli et al., 2004) in frontal, temporal and parietal structures, which could potentially underlie the bilingual advantages seen in executive functioning (i.e., inhibition, attentional control, and cognitive flexibility). However, at present, it remains unclear whether bilingualism is in fact a neuroprotective factor in healthy aging due to research methodological inconsistencies across studies. This supplement aims to uncover whether bilingualism differentially impacts structural and functional connectivity with its associated neurocognitive correlates across the adult lifespan.

#### **3. Spectroscopy R01**

Via PAR-15-357, “Understanding AD in the Context of the Aging Brain”, Melissa Terpstra (HCP-A co-PI) and Silvia Mangia (R01 co-PI) at UMinn were awarded R01AG055591, “Linking connectomics to biochemical trajectories of aging: How the human brain ages differentially in key regions of the default mode network”. This R01 will complement the HCP-A by adding clinical characterization of cognitive status for HCP-A participants, which will be available at <https://www.lib.umn.edu/datamanagement/drum>. Participants recruited from the University of Minnesota will be invited to return for clinical assessment, amyloid PET, and MR spectroscopy (MRS) of one of the most relevant networks for aging and AD, the default mode network (DMN). Ninety HCP-A participants are expected to enroll and pass cognitive health criteria. To achieve the sample size needed to test the aims of the R01, another 116 participants will be recruited *de novo*, i.e., in addition to the HCP-A. Half of the *de novo* participants are expected to pass cognitive health criteria and proceed to MRS and PET. The ultimate goal is to gain knowledge about the order and nature of metabolic mechanisms that underlie the shift from healthy human brain aging to the pathological processes that are associated with AD, and to relate the timing of changes in metabolism to age-associated alterations in connectivity, structure and microstructure. Because oxidative stress occurs at a very early stage of cellular dysfunction in AD, employing MRS that is sensitive to antioxidant status may facilitate development of an early stage biomarker for AD (Emir et al., 2011; Marjanska et al., 2017).

#### **4. Coordination of Brain Donation**

The MGH PIs responded to NOT-AG-17-008 -- “Administrative supplements to develop research on AD and Alzheimer’s-related dementias (ADRD)” -- and received funds to develop the infrastructure to obtain brain donations from willing HCP-A participants for future neuropathologic assessment and histological assessment and validation of HCP *in vivo* imaging results. This is particularly pertinent to the oldest old and centenarian populations that are a focus of this project. The primary goal of HCP-A is to describe changes in brain structure and function resulting from ‘typical’ aging. However, given limited normative assessment of individuals in the oldest old age-range and particularly in older adults aged 90 and above, it is challenging to determine whether altered connectivity measures may be linked to AD pathology, which is known to be prevalent in older adults even in the absence of obvious cognitive symptoms. This supplement supports the development of the basic infrastructure to coordinate the request for brain donation and could ultimately allow us to directly link specific *in vivo* brain imaging markers to post mortem evidence of AD pathology. To our knowledge, this supplement could therefore contribute to the first linking of advanced brain connectivity measures *in vivo* to confirmed post mortem evidence of AD neurodegenerative pathology.