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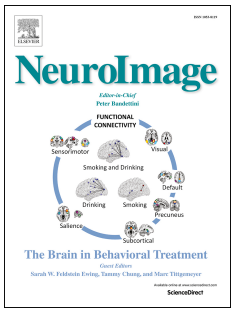

The lifespan Human Connectome Project in aging: An overview

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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 is collecting multimodal MRI and behavioral assessments from 1200+ participants aged 36-100+.
- MRI includes structural (whole brain and high-resolution hippocampal), resting state fMRI, task fMRI, diffusion, and arterial spin labeled perfusion imaging.
- Bio-behavioral assessments 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 brain structure, function, and connectivity.

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Abstract

The original Human Connectome Project yielded a rich data set on structural and functional connectivity in a large sample of healthy young adults using improved methods of data acquisition, analysis, and sharing. More recent efforts are extending this approach to include infants, children, older adults, and brain disorders. This paper introduces and describes the Human Connectome Project in Aging (HCP-A), which is currently recruiting 1200+ healthy adults aged 36 to 100+, with a subset of 600+ participants returning for longitudinal assessment. Four acquisition sites using matched Siemens Prisma 3T MRI scanners with centralized quality control and data analysis are enrolling participants. Data are acquired across multimodal imaging and behavioral domains with a focus on factors known to be altered in advanced aging. MRI acquisitions include structural (whole brain and high resolution hippocampal) plus multiband resting state functional (rfMRI), task fMRI (tfMRI), diffusion MRI (dMRI), 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 resource for examining how brain organization and connectivity changes across typical 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 NIMH Data Archive (NDA). Here we provide the rationale for our study design and sufficient details of the resource for scientists to plan future analyses of these data. A companion paper describes the related Human Connectome Project in Development (HCP-D, Somerville et al, 2018), and the image acquisition protocol common to both studies (Harms et al, in press).

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

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The transition between development and senescence of the human body involves a complex progression of events whereby body organs and systems begin to deteriorate based to a large degree on diverse genetic and lifestyle factors. The most vulnerable systems in turn promote deterioration of other organs and systems with which they interact. Subtle or more profound changes in systemic health often begin in midlife, including attenuation in cardiovascular physiology and hormonal changes, accompanied by lifestyle changes that impact general health. Some cognitive abilities begin to decline in early adulthood (Craik and Bialystok, 2006; Park et al., 2002; Salthouse, 1996)**,** linked to variation in brain health and brain connectivity, with later life status potentially promoted by declines in organ systems and in systemic health throughout the lifespan (Carmelli et al., 1998; Kivipelto et al., 2001; Knopman et al., 2001; Whitmer et al., 2005). Substantial variability exists in brain structure among healthy young individuals, and this variation is compounded by age and age-associated conditions. In later life, there is a dissociation between changes thought to be common and those indicative of aberrant physiological processes such as vascular and neurodegenerative disease. It is therefore important to elucidate how these complex factors that vary across individuals and change within an individual throughout the adult lifespan affect brain structure, function, and connectivity, and contribute to the spectrum of typical to abnormal cognitive aging.

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 freely share these data with the scientific community. In this paper, we describe the rationale, procedures, and protocols used in the HCP-A project, and provide details on the data being generated. We hope this will promote interest among the scientific community in accessing this resource once data sharing commences in early 2019. Somerville et al (Somerville et al.) provide an analogous overview of the companion project -- the Human Connectome Project in Development (HCP-D). A more detailed description of the imaging protocol common to both projects, including data and rationales for changes relative to the original Human Connectome Project ('HCP-YA', 2010-2016), is contained in (Harms et al., 2018). Protocols and operating procedures for the HCP-A were established in close coordination with the HCP-D to enable 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 original Human Connectome Project ('HCP-YA', 2010-2016) focused on healthy young adults and collected behavioral and multimodal imaging data from ~1100 participants. Over 570 publications using HCP-YA data (as of July, 2018) (Glasser et al., 2016; Marcus et al., 2013); (Barch et al., 2013; Fan et al., 2016; Finn et al., 2015; Glasser et al., 2013; Setsompop et al., 2013; Smith et al., 2013; Sotiropoulos et al., 2013; Ugurbil et al., 2013), underscoring the importance of normative imaging data repositories. The HCP-A will inform our understanding of changes in the human brain structure, function, and connectivity during healthy aging, reveal factors associated with a preserved quality of life throughout aging, identify patterns that suggest a departure from a healthy trajectory, and provide a rich resource for future explorations and comparisons with the disease-specific connectome initiatives.

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1. OVERVIEW OF HCP-A

1.1 Outline of the HCP-A Resource:

HCP-A takes advantage of improved MRI sequences and the Siemens Prisma platform to collect high-quality structural, task and resting functional MRI, data, combined with behavioral, psychological, health, and genetic assessment. We chose MRI and behavioral protocols designed to reveal age-related cognitive, behavioral, and brain changes optimized to meet the practical challenges of studying older adults. This included extensive testing of different MRI scan parameters (see Harms et al., In press) 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.

To obtain these data, we are recruiting over 1200 cross-sectional participants with matched protocols across four acquisition sites. The sample excludes major diagnosed disease but otherwise aims for a 'typical' population 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.

The consortium identified three focus areas to enhance in HCP-A. First, women in the pre- and peri-menopausal phase are oversampled and assayed for hormone levels, to enable assessment of how changes during this important life period may influence brain connectivity and cognition. 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). Finally, a large sample of individuals in the 36-44 year age-range, often omitted in aging studies, will be included in HCP-A.

In addition to the cross-sectional sample, HCP-A is collecting longitudinal data from 600+ participants with an emphasis on understudied and scientifically interesting groups. Longitudinal assessments will be carried out at 20-24 months after baseline imaging sessions. All ages (36 - 100+) will be included, but with larger numbers for 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).

The HCP-A resource will include 'minimal preprocessing' of the MRI data as a starting point for researchers to launch their own additional analyses, as well as some targeted additional processing (e.g., optimized for longitudinal analysis). We are making both the data and these analytic tools publicly available for the scientific community. Notably, the analysis techniques will be conducted in harmony with HCP-D study, facilitating studies that cross the lifespan. In combination with the HCP-D and the HCP-YA datasets, we will generate a complementary in-depth imaging, behavioral, and biosample repository of typical brain changes spanning ages 5 through over 100. We briefly summarize these focus areas and describe the motivation and rationale for our study design and methods in the following sections. We also discuss the relationship of HCP-A to various other large-scale imaging projects (see Section 6).

2. POPULATION OF THE HCP-A STUDY

2.1 Sample rationale: focus on "typical" aging

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 in efforts 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. Our goal for HCP-A is to study 'typical' aging (Borghesani et al., 2013; Jack et al., 2002; Jack et al., 1998).

We use 'typical' in relation to our objective of enrolling individuals who exhibit typical health for their age in absence of 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 may confound the interpretation of the data, such as suspected Alzheimer's Disease (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 et al., 2016).

This general approach of examining typical aging will enable analyses of links between common health conditions (health 'modifiers') and connectomics measures. Importantly, participants from different age-bands will not be exactly matched in relation to many factors such as previous environmental experience, number and degree of medical conditions, and sensory deficits that may affect cognitive testing. Also, individuals in the oldest old range might be considered atypical in being 'survivors' to late life. Any interpretation of cross-sectional results should take these factors into account.

2.2. Mid-life through Menopause

The first age band in HCP-A (36-64 years) 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, much less neuroimaging data has been reported for 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. This age band spans the peri-menopausal period in women. As this is a key period of interest for cognitive aging, we have over-recruited women aged 40-59 (280 subjects, 120 longitudinal). While age-related changes in hormone levels occur in both genders, they 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) is 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.

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 other evidence suggests 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. 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. We will stage menopause objectively using validated criteria (Harlow et al., 2012) and obtain multiple hormonal measures for all participants (across age and gender) for comparison (see Section 5.1). Longitudinal assessment will allow us to better characterize how menopausal stage and changing hormone levels affect brain connectivity.

2.3. Older to oldest old:

The second age band is 65-79 years. Ages 65 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.

A major focus for HCP-A is extending recruitment to a third age band comprising the *oldest old* (ages ≥80), a population not typically accessed in large aging cohorts. The definition of oldest old varies, but commonly refers to individuals ≥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'. 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 in imaging studies is limited. Individuals in this cohort who are free of degenerative disease represent models of 'successful' aging. Although the oldest old are currently rare, they are a rapidly growing segment 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 (Jacobsen, 2011).

2.4. Sample demographics and recruitment strategy

Data will be collected from 1200+ cross-sectional participants between the ages of 36 and 100+ using a matched protocol across four acquisition sites (Washington University St. Louis, University of Minnesota, Massachusetts General Hospital and University of California, Los Angeles, with Oxford University contributing to the data analysis efforts). A subset of the participants (600+) will be scanned longitudinally. While data acquisition (including optimization) was planned over four years, additional longitudinal scanning may extend the project by one year.

The recruitment targets for the three age cohorts, Mature (36-64), Old (65-79) and Oldest Old (80 Plus) are shown in Table 1 for age, gender and longitudinal follow-up. 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. Age 36-39 projections are used for ages 36-64, and age specific projections are applied for ages 65 and older. All sites will strive for balance across low, middle and high-income SES brackets. Participants are recruited from multiple sources, including advertisements and flyers, active senior centers, places of worship, public lectures and workshops on aging, and senior living centers. Longitudinal data will be collected in each age band, as detailed below.

Recruitment for the finalized protocol began in the spring of 2017 and has proceeded on a pace adequate to meet our recruitment objectives. As of September 2018, 854 HCP-A subjects have been recruited of the total of 1208 participants targeted for initial sessions by late summer of 2019. While this is slightly ahead of the overall pace needed, we anticipate that the remaining stages of recruitment will be more challenging in order to meet our multiple demographic targets (age bins, sex, race/ethnicity, and SES).

			MATURE						OLD			OLDEST OLD			TOTALS
			36-64		Peri-menopause				65-79			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	Time 1	10	46	70	70	70	70	46	46	46	46	56	56	28	660
	Time 2		**26**	**30**	**30**	**30**	**30**	**30**	**30**	**30**	**30**	**20**	15	10	311
Males	Time 1	10	46	46	46	46	46	46	46	46	46	48	48	28	548
	Time 2		**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 (Time 1=baseline; Time 2= follow-up).

2.5 Longitudinal component

A total of 600+ participants across all age bands will be invited for a 20-month longitudinal follow-up, with a target maximum follow-up window of 24 months permitted. A two-year interval is adequate to detect brain structural changes during aging (Barrick et al., 2010; Jiang et al., 2014) (Donix et al., 2010). Table 1 shows the distribution of cross-sectional and longitudinal participants by age and sex. An ongoing recruitment database guides completion of the planned cohort sizes. We anticipate an attrition rate of ~10% in keeping with our prior experience with longitudinal studies in older adults. To avoid a biased selection of participants for longitudinal follow-up, we will randomly select from among participants having complete baseline data (meaning data acquired regardless of quality) in bins that assure appropriate age and demographic distributions for the longitudinal data. We will not exclude participants at longitudinal follow-up if they have developed age-related disorders which would have excluded them at study entry, except if: 1) they can no longer be scanned safely (for example, had a pacemaker implant), or 2) no longer have the capacity to consent (see section 2.6.3).

2.6 Screening and Exclusionary criteria

2.6.1. Initial Screening

A phone screen is performed for all potential participants to rule out major exclusionary health conditions. 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.

In individuals 60 years and older, we also exclude those with impaired cognitive abilities using a cognitive screener, the Telephone Interview for Cognitive Status modified (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. For subjects over 80 for whom there are no normative data on TICS-M, we require participants to pass critical orientation items, and screen for capacity to consent those passing critical items but achieving scores lower than 30.

2.6.2 Inclusion and Exclusion Assessment

After consent, we administer the Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005). 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 their baseline visit; this information is captured in Redcap, so that users can investigate or avoid specific medication confounds.

Conditions are 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, which allow inclusion of individuals who may have low scores for other reasons beside mild cognitive impairment or dementia.

Table 2: **Overview of inclusion and exclusion criteria for older adults.** Tiered cutoff scores by age for the TICS-M, the MoCA and presence of macular degeneration. See Supplementary Table 2 for a complete list of inclusion/exclusion criteria.

Exclusion Criteria for Older Adults						
	Age Bin	**36-59**	**60-79**	**80**	**81-89**	**90+**
	Criteria					
Phone Screening	**TICS-M**	**--**	**29**	**If less than 30, screened for capacity**		
	Macular Degeneration	**Diagnosis excludes**			**Record and Enroll**	
	Hearing	**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	**MoCA Score**	**19**	**19**	**17**	**17**	**16**

We use a liberal threshold for participant inclusion to reflect the general population, which may lead to including individuals with mild to moderate cognitive deficits. In the oldest old, our exclusions are more tolerant for auditory or visual deficits. 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 caveat that auditory or visual deficits may impact task performance (Gussekloo et al., 2005).

2.6.3. Assessing capacity to consent

At both the baseline and follow-up visits, we assess the potential participants' capacity to give informed consent. Particularly in older participants, it is important to determine whether participants who pass the reduced cognitive screening threshold are able to comprehend the nature of the 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). Four principles guide assessment of capacity to consent: Understanding, Appreciation, Reasoning, and Expression of a Choice. These are assessed formally for subjects 80 and older using a brief version of the MacArthur Capacity to Consent Scale (Appelbaum, 2007) which was designed for AD clinical trials. Four key questions are considered 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?" (4) "Must you take part in this study, or is it okay to say 'no'?". Participants who can answer each question correctly are considered competent to participate as research participants. Supplementary Figure 1 shows the decision tree for inclusion and exclusion by age group.

Following phone screening, participants are scheduled for imaging, cognitive testing, and biosample collection (Sections 4, 5). Supplementary Figure 2 describes the study flow and standard sequence of subject activities.

3. BRAIN IMAGING

3.1. Overview of imaging

The HCP-A protocol includes structural scans, task fMRI, resting state fMRI, diffusion, and cerebral blood flow (arterial spin labeling - ASL), collected over two imaging sessions. Each session entails approximately 45 minutes of scanning, performed in a single day or across two days depending on site-specific procedures and constraints. A simulated 'mock scanner' is available for subjects anxious about undergoing MRI, though in practice this is rarely used. The total scanning session length was capped based on preliminary experience with these age ranges. In this paper, we describe the unique aspects of the scanning protocol for HCP-A, the rationale for choosing them, and some preliminary data. Details regarding the many elements of the imaging protocol that are in common with HCP-D are described in (Harms et al., 2018).

3.2 Structural imaging specific to HCP-A: 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. Medial temporal structural changes are the hallmark of memory disorders in aging and 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-minute acquisition and piloted a 2D TSE scan with 0.39x0.39x2 mm^3 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 high resolution is most informative and identification of HC sub-regions is possible (Kirwan et al., 2007; Winterburn et al., 2013; Yushkevich et al., 2010; Zeineh et al., 2000). Coarse slice thickness axis is necessary to maintain sufficient signal-to-noise ratio with a limited scan duration, and is acceptable because the sub-regional architecture of the hippocampus varies less along the long axis of the HC (Zeineh et al., 2000). The decreased resolution along the long axis of the HC (see Supplementary Figure 3) will reduce the accuracy of sub-regional measurements where there is rapid variation along the anterior-posterior direction (e.g., in anterior hippocampus). Sub-regional analyses can also be performed on the standard T1w structural scan obtained with isotropic voxels, but our preliminary data suggested better segmentation results with the TSE sequence. This and other approaches have been used to identify unique alterations in specific HC sub-regionals in aging, genetic risk for AD, MCI and AD (Burggren et al., 2008; Das et al., 2012; Khan et al., 2015; Varma et al., 2016; Yassa et al., 2010).

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-A Preliminary data show excellent parcellation of HC sub-regions (Figure 1). Expected age-related volumetric changes in HC volume are evident in an initial comparison between 10 younger (mean age 38.8) and 10 older (mean age 71.5) participants from automated segmentation of the high resolution hippocampal scans (Figure 2).

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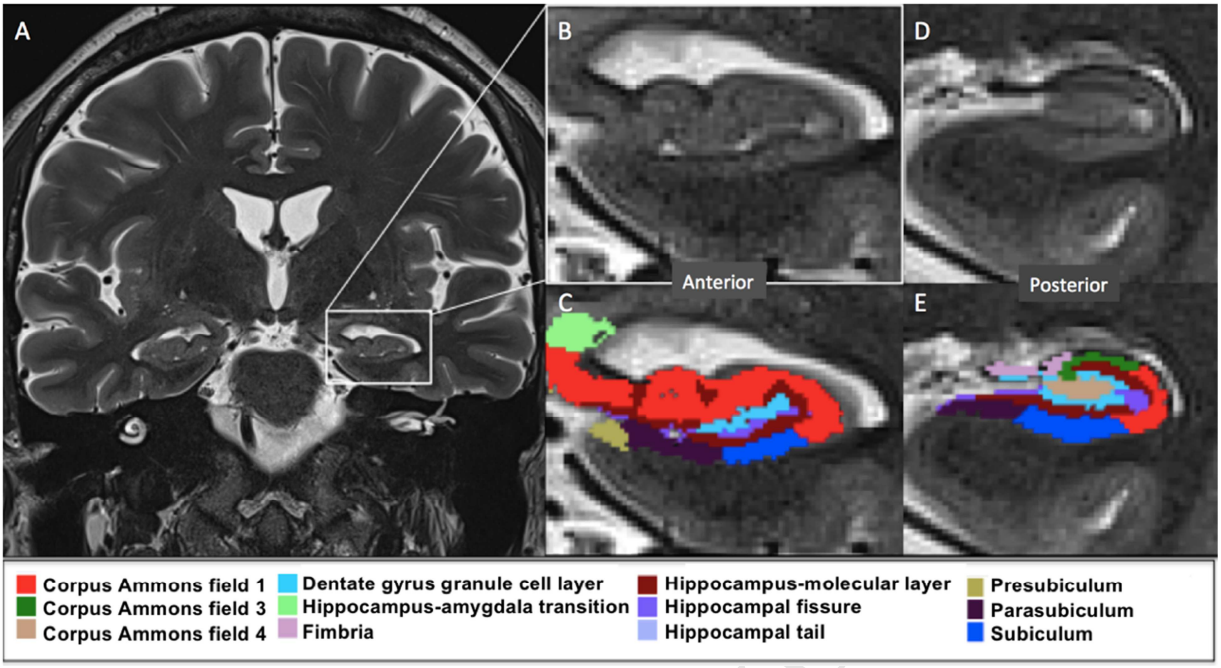


Figure 1. Hippocampal High-resolution coronal TSE scan and hippocampal parcellation. A: Image shows one slice through the anterior HC portion of an older adult; **B**: Magnification of a section around the left HC; **C:** Automated parcellation of hippocampal sub-regions on image B; **D:** Magnification of a more posterior HC section, same subject; **E:** parcellation of posterior slice shown in panel D. The high-resolution 2D TSE acquisition yields extremely high in-plane resolution (0.39mm) in a field of view extending from the anterior margin of the amygdala to just past the most posterior part of the hippocampal tail. FreeSurfer 6.0 was used on the TSE scans to generate the sub-region parcellation with a subset of the labeled regions denoted in the legend including the subfields of the hippocampus proper. Images are in radiological standard (left hemisphere=right side of the brain).

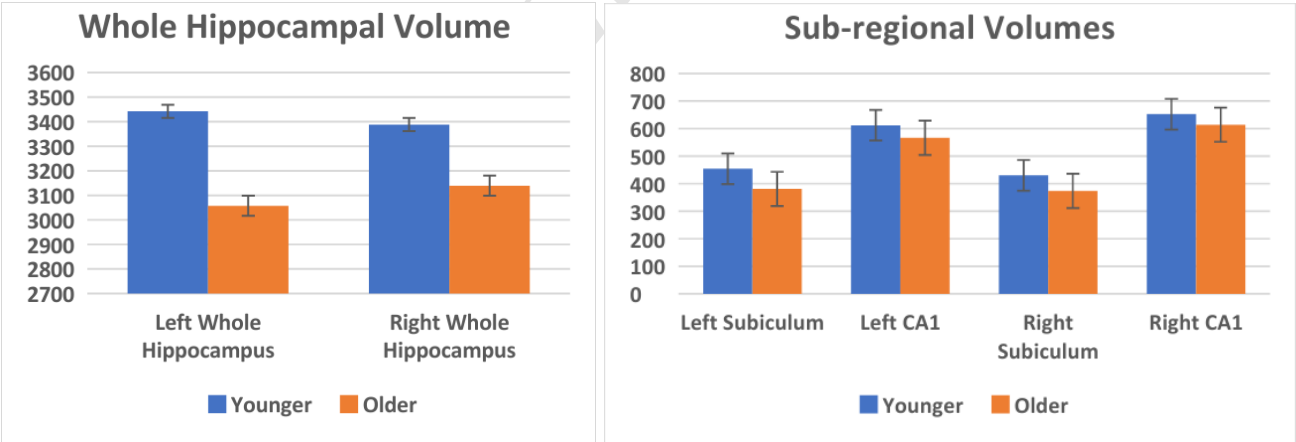


Figure 2: Preliminary volumetric data from the HCP-A high resolution HC scans. Whole and sub-regional volumes in 10 younger (mean age 38.8 years) vs. 10 older participants (mean age 71.5 years) HCP-A participants. Error bars are standard deviations; y-axis values are cubic millimeters.

3.3 Task fMRI specific to HCP-A

3.3.1. Visuomotor task

Visual and sensory-motor responses can be consistently generated through simple stimuli and task paradigms, making them useful for assessing the hemodynamic response in individuals and groups, which is known to be affected in aging (Ances et al., 2009). The

Visuomotor task in HCP-A is a single run of 155 seconds (Figure 3). 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, each 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.

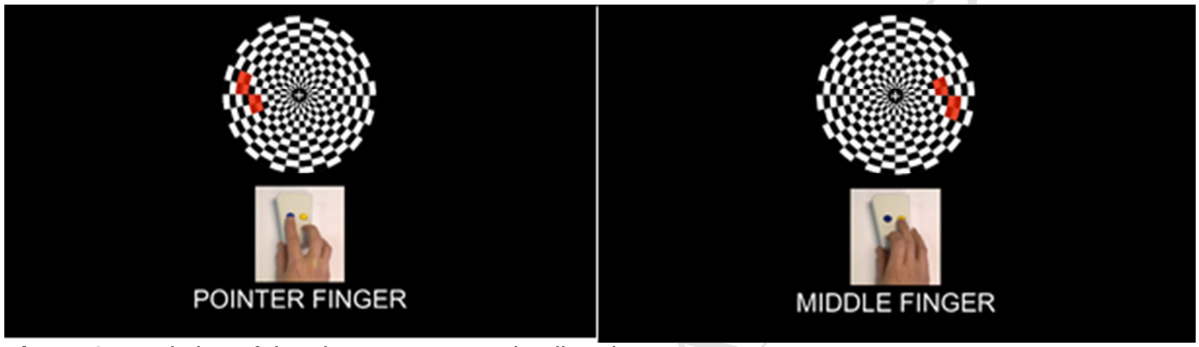


Figure 3: Depiction of the visuomotor test stimuli and response.

3.3.2. Inhibitory Control task (shared task with HCP-D)

HCP-A participants perform a Go/NoGo task that taps into inhibitory control processes. This “CARIT” task (Conditioned Approach Response Inhibition Task) is similar to the Go/NoGo task used in the HCP-D to assess inhibitory control (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. 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).

3.3.3 FaceName 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 for decades (McCarty, 1980) and was later 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 (during encoding blocks) and try to (silently) remember them for later (recall blocks). 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 4). 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 each 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 removal from the magnet at the conclusion of the scan session for retrieval accuracy. This task is always the last task performed during the session, therefore minimizing and standardizing the retrieval interval.

Figure 4: Example of face name stimuli; Encoding (left) and Retrieval (right).

In preliminary analyses, we evaluated the activity evoked by the FaceName task in an initial set of 16 participants in the HCP-A study using the public release HCP Pipelines v3.22. 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) became the effective baseline in contrasts of the memory conditions versus baseline. Preliminary results 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 5).

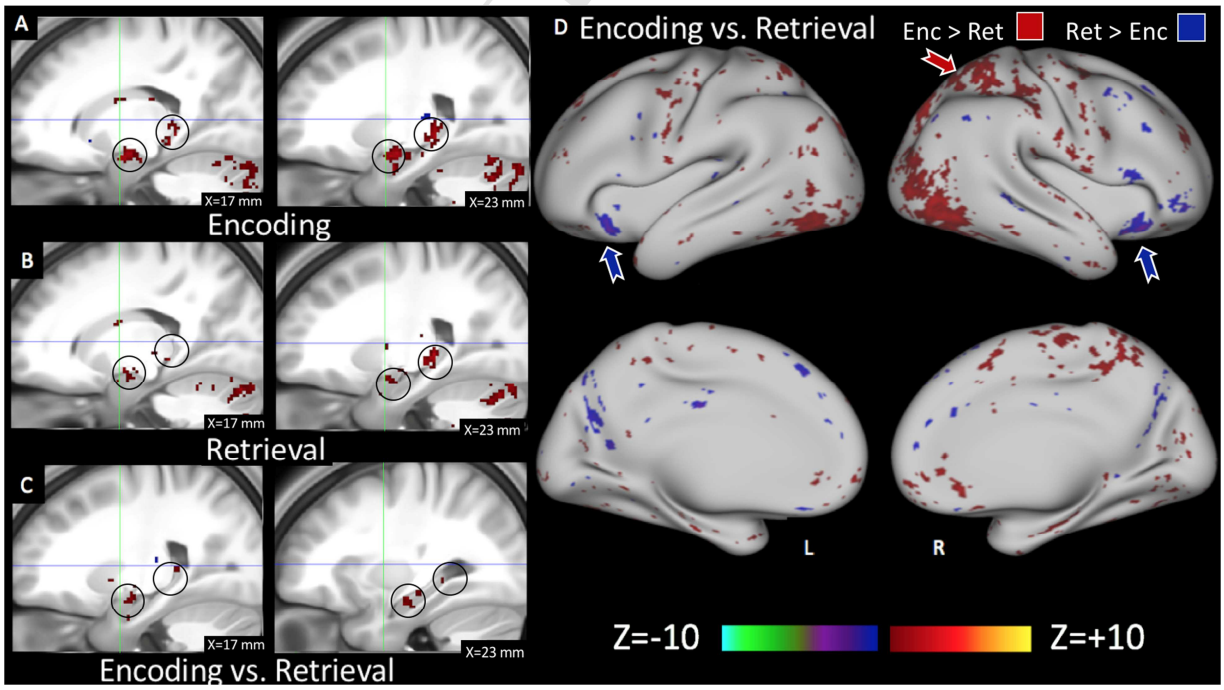


Figure 5: Group activation maps for the Face-Name Association task in an early sample of HCP-A participants (N=16). Participants (mean age 50 years), Z-stat maps, thresholded at Z>2.3

(uncorrected). Analyses were conducted in CIFTI grayordinate space. Panels A-C display only subcortical voxels, and Panel D displays only cortical surface vertices. **A.** Contrast of Encoding > Distractor; **B.** Retrieval > Distractor; **C.** and **D.** Contrasts of Encoding > Retrieval (red) and 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,** circled regions). Fronto-opercular activation is evident for during retrieval vs. encoding (blue-**Panel D**). Sagittal images show the right hemisphere. L = left, R = right.

4. OUTSIDE OF SCANNER MEASURES

4.1 Biological samples and vital signs

HCP-A is collecting information relevant to metabolism, vascular health, hormonal status, stress and other environmental factors, which have known or suspected relationships to brain circuitry during typical aging as well as in dementia and other diseases (Iturria-Medina and Evans, 2015). This information 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).

Shortly after consenting, blood samples for genotyping, metabolic, lipid and hormonal tests are collected from participants, preferably 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. 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 Breath Alcohol Concentration (BrAC) sample is collected (AlcoHAWK breathalyzer test) at the beginning of each study visit day to collect information about alcohol in the system, but is not used to exclude participants.

4.1.1 Glucose metabolism and lipids: To address glucose metabolism and metabolic syndrome, the HCP-A measures 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.

Hormonal assays, HbA1C and metabolic analyses are carried out on blood. Metabolic and lipid assays are 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 provides information on the participant's risk for obesity, diabetes, and other biological markers of vascular risk.

4.1.2. Vascular health/burden factors: Besides genetic risk, HCP-A collects data on potentially modifiable factors such as smoking, physical activity level, body mass index (BMI), blood pressure, and diet, which are linked to cardio/cerebro-vascular risk factors that influence brain aging. 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 structural, functional and cognitive changes (Breteler et al., 1994; Jeerakathil et al., 2004; Longstreth et al., 1996; Reed et al., 2004; van der Flier et al., 2005) (Braskie et al., 2010) (Kennedy and Raz, 2009; Leritz et al., 2010; Salat et al., 2012). The combination of some of these risk measurements- age, smoking history, cholesterol, and blood pressure- enable calculation of the Framingham risk score for men and women, which estimates cardiovascular risk (Marma and Lloyd-Jones, 2009).

4.1.3 Menopause and hormone assessment: 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 most recent Stages of Reproductive Aging Workshop 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 are collected 2 to 6 days after the start of their cycle. Menstrual history and menopause status and history are collected through two questionnaires: Menstrual Questionnaire and Menopause screener (Harlow et al., 2012).

4.1.4 Genetic testing for Alzheimer's risk: Variation in the *APOE-4* allele confers a higher 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). 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 the cell lines are immortalized and are maintained in RUCDR for future analysis should funding become available.

4.2 Assessment of behaviors, abilities, traits, and environments

The cognitive and performance battery includes domains that overlap with those from HCP-D in addition to assessments most relevant for 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; Sections 5.3 and 5.4 discuss domains and tests unique to HCP-A; some questions that were redundant within and between batteries were eliminated.

Table 3: Behavioral Assessment

Domain	Test
Intake Measures	
Cognition	Telephone Interview for Cognitive Status (TICS-M) Montreal Cognitive Assessment (MOCA)
Demographic and Health Questionnaires (non-standardized)	Medication Use Edinburgh Handedness Inventory Dental Work Questionnaires Demographics
NIH Toolbox	
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
Additional Behavioral/Cognitive and Health Measures	
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 NEO-FFI) Achenbach Adults Self-Report (Short version of ASR: 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

4.3 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. For 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 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 reduces the length of the testing battery, a particular concern for older participants, and is justified by evidence 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).

4.4 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. 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 questionnaires and 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 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 reported 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.

4.5 Psychopathology

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. INTENDED USE AND LIMITATIONS

A major objective of HCP-A is to make the collected imaging data and behavioral assessments freely available to the scientific community. 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. We believe the HCP-A dataset will allow scientists to address many outstanding questions and controversies in brain aging. In particular, this normative database was designed to accelerate discovery of disease-modifying approaches; studies of neurologic, psychiatric and lifestyle challenges can use these data to quickly identify deviations from the trajectories of brain changes in typical aging. However, within the dataset itself we can investigate a wealth of important questions about normal aging. A small sample of potential research questions include determining the relationship between changes in structural connectivity and functional connectivity in later life; how rates of brain change predict cognitive outcomes and which affected systems are most relevant these outcomes; the neural correlates of specific cognitive strengths and weaknesses;

what environmental and lifestyle factors protect against brain atrophy; whether there are subgroups with unique focal patterns of structural and functional connectivity that presage different health outcomes. In the realm of women's health, the HCP-A will be able to relate variation in sex hormones to brain structure and function and their combined effects on cognition. Because the study is longitudinal, we can determine which cognitive changes associated with menopause are transitory and how hormone replacement affects both brain and cognition. The limited genetic analyses performed will nonetheless provide important information about single and polygenic risk effects on brain and cognition, and how these risks interact with lifestyle variables. Because cell lines will be stored, future funding may afford the opportunity for more in depth genetic testing. The administrative supplements and related R01 on AD (Supplementary Table 3) will enhance the value of the HCP-A data; to date these supplements will address the effects of bilingualism on brain aging, relate the normative dataset to dysexecutive Alzheimer's disease, and add a more comprehensive imaging series including spectroscopy and amyloid PET to a subset of subjects. More broadly, the HCP-A will help us understand the neural basis of substantial heterogeneity observed in aging and evaluate the myriad factors that may contribute to this heterogeneity.

In developing a normative database of the aging brain, there are inherent limitations in determining what is "typical" aging. While the HCP-A is recruiting a normative sample without known disease, it is nonetheless likely that some participants will have pre-clinical neurodegenerative diseases or mild cognitive impairment. We aim for a balance by excluding known neurological and active psychiatric disorders 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 arguably result in 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 relaxed our enrollment cutoffs for 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. This approach has the advantage that participants are more representative of the total population, but as a cross-sectional group they may not be as disease-free as the younger participants in HCP-A and HCP-D. Measuring many of these health variables and including them in the database will provide useful flexibility for future analyses that may exclude or include individuals with various experiences.

There are technical challenges in harmonizing data across sites and integrating the HCP-A data with the Young Adult (HCP-YA) and HCP-D datasets; such challenges can limit the inferences we can draw about brain changes across the lifespan. These challenges are discussed in more detail in Harms et al., In press. Additionally, within the older subjects in the cohort, factors including tolerance of the protocol length and head motion may change across age groups, particularly in the oldest old. A resulting caveat to data interpretation is that our oldest subjects may have less data overall, and those who completed the protocol with high quality data may further compound the problem of having a non-representative, "super-normal" sample.

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 brain pathology 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 source 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). 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 limit the visit duration to 8 hours, many potentially informative behavioral assessments were not included. This was a particular concern for the oldest participants, who may tire more easily. While the cognitive testing battery is not as extensive as in some clinical evaluations, it does cover each of the major domains in cognition and behavior.

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.

6. Relation to other imaging projects

There is growing appreciation of the need for "Big Data" repositories with public access for scientists to facilitate discovery of normal and abnormal aging processes. The aging brain has been a focus of several other, large-scale international MRI data acquisition efforts that do not emphasize connectomics to the same degree as HCP-A. These include the Zurich-based "Longitudinal Healthy Aging Brain" (LHAB) project (230 healthy participants 65 years and older with longitudinal imaging) (Zöllig et al, 2011; Muller et al, 2016). The population-based Rotterdam Scan Study now includes over 5000 MRI scans focused on white matter and small vessel disease (Ikram et al., 2011). A similar effort from France, the 3C Study group, collected over 3000 MRI scans on subjects aged 65-79 (The 3C Study Group, 2003). The 1000Brains project is built on a large scale cardiovascular risk study (Caspers et al., 2014). These subjects spanned 45-75 years of age and received extensive health, environmental and laboratory data, and an imaging protocol that included both structural and functional imaging. Among the largest ongoing efforts is the UK Biobank (Miller et al., 2016), which is in the process of imaging 100,000 participants from age 40 to 69 and following them into eventual disease and/ or old age (https://imaging.ukbiobank.ac.uk; http://users.fmrib.ox.ac.uk/~steve/BiobankPiloting). Cross-project comparisons to the UK Biobank will be facilitated by having a protocol harmonization cohort of 20 HCP-A subjects who will additionally undergo the 35-minute Biobank imaging protocol.

Other large-scale imaging databases in aging focus on individuals with age related diseases; among the largest is the Alzheimer's Disease Neuroimaging Initiative (ADNI, www.adni-info,org), which now contains over 1000 participants with Mild Cognitive Impairment (MCI), over 400 with AD, and nearly 500 elderly controls (e.g., Weiner et al., 2017). The Mayo Clinic Study of Aging (Roberts et al., 2008; https://www.mayo.edu/research/centers-programs/alzheimers-disease-research-center/research-activities/mayo-clinic-study-aging) as well as other members of the Alzheimer's Disease Research Consortiums in the USA have a similar focus on dementia, but they are acquiring mainly structural images.

The HCP-A differs from these other projects its focus on connectomics in aging, and incorporates the "HCP-style" brain imaging approach (Glasser et al., Nature Neuroscience, 2016). Unlike other repositories, the HCP-A imaging data includes extensive scanning of multiple MRI modalities (structural, resting state, task fMRI, diffusion and perfusion) in addition to biological, physiological, neuropsychological, and genetic data. HCP-A also differ from other efforts in emphasizing the three focus areas of menopause, oldest old, and and by including a large sample of individuals in the 36-44 year age-range, often omitted in aging studies. Further, the HCP-A dataset was designed for open access with timely data release.

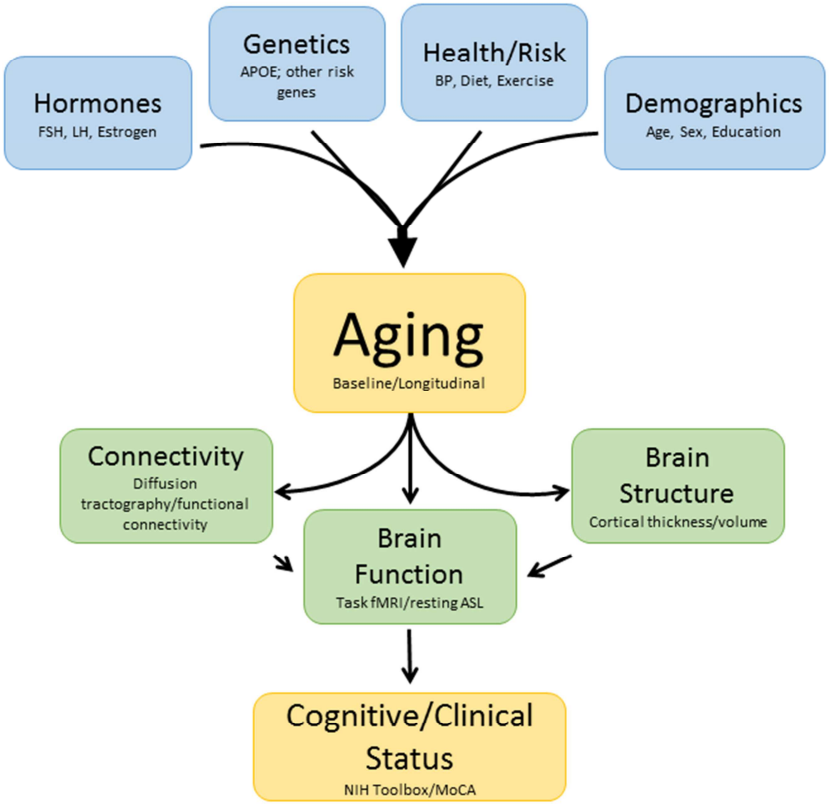
Besides the aforementioned complementarity with the young adult (HCP-YA) and development (HCP-D) projects, the HCP-A project will be synergistic with 14 'Disease Connectome' projects that have been funded to study a range of neurological and psychiatric disorders. The HCP-A shares many MR modalities with these other projects, including

structural, resting state fMRI, and diffusion, with some overlaps in biosample acquisition and cognitive testing domains.

7. CONCLUSION

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 enrollment plan emphasizes aspects of brain aging that are relevant to public health, and the behavioral protocol emphasizes 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. We anticipate 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 6).

Figure 6. 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. Ultimately, the full sample of data will allow multivariate statistical modeling of a host of interacting factors that contribute to decline as well as preservation of brain circuitry and functional status linked to aging.



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Supplementary Table 1.
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Supplementary Table 2: Inclusion/ Exclusion Criteria

HCP-A Inclusion Criteria
1. Age 36-100+
2. Ability to give informed consent
HCP-A Exclusion Criteria
1. During the participant's lifetime:
a. Neurologic disease including multiple sclerosis, cerebral palsy, Parkinson's disease, or Alzheimer's disease
b. Brain surgery
c. Major psychiatric disorder, such as bipolar disorder or schizophrenia
d. Hospitalization for 2 days or more for alcoholism or drug dependence
e. Head injury causing any of the following:
i. Loss of consciousness for >30 minutes
ii. Amnesia for >24 hours
iii. Change in mental status for >24 hours
iv. Neuroimaging findings consistent with traumatic brain injury
v. Persistent (>3 months) post-concussive symptoms following concussion or mild TBI
f. Two or more non-provoked (e.g. not due to fever) seizures after age 5 years or a diagnosis of epilepsy
g. Any brain tumor including meningiomas
h. Any cancer treated with chemotherapy and/or radiation to the head or neck, and/or any stage 4 (metastatic) cancer even if no treated
i. Hospitalization for brain aneurysm, brain hemorrhage, subdural hematoma or stroke (except TIA is allowed)
j. Rheumatoid arthritis, HIV or lupus or another condition requiring long-term use of steroids or other immunosuppressant
k. If 80 years old or younger: Diagnosis of macular degeneration
l. Known genetic disorder (e.g. sickle cell disease or cystic fibrosis)
2. Within the last 5 years:
a. 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. Severe depression requiring treatment by a psychiatrist for 12 months or longer

3. Within the last 1 year:
a. Diagnosis of thyroid problems and/or changing doses of thyroid medication
b. Heart attack
4. Current:
a. 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. Hearing loss sufficient to prevent communication via telephone
c. Vision worse than 20/200
d. Current pregnancy
e. Unsafe metal or devices in body
f. Moderate to severe claustrophobia
g. Use of prescription medication to prevent migraines (migraines allowed if not taking daily preventive medications)
h. Migraine less than 72 hours before the first visit or during the visit
i. Uncontrolled high blood pressure (>170/100) or working with doctor to stabilize blood pressure
j. Severe lung, living, kidney or heart disease or other major organ failure
k. 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
l. 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.

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Supplementary Table 4: 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

UCLA has been awarded an administrative diversity supplement (PA – 16-288 – "Research Supplement to Promote Diversity in Health-Related Research") to test the hypothesis that bilingualism contributes to overall cognitive reserve in aging. This study 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

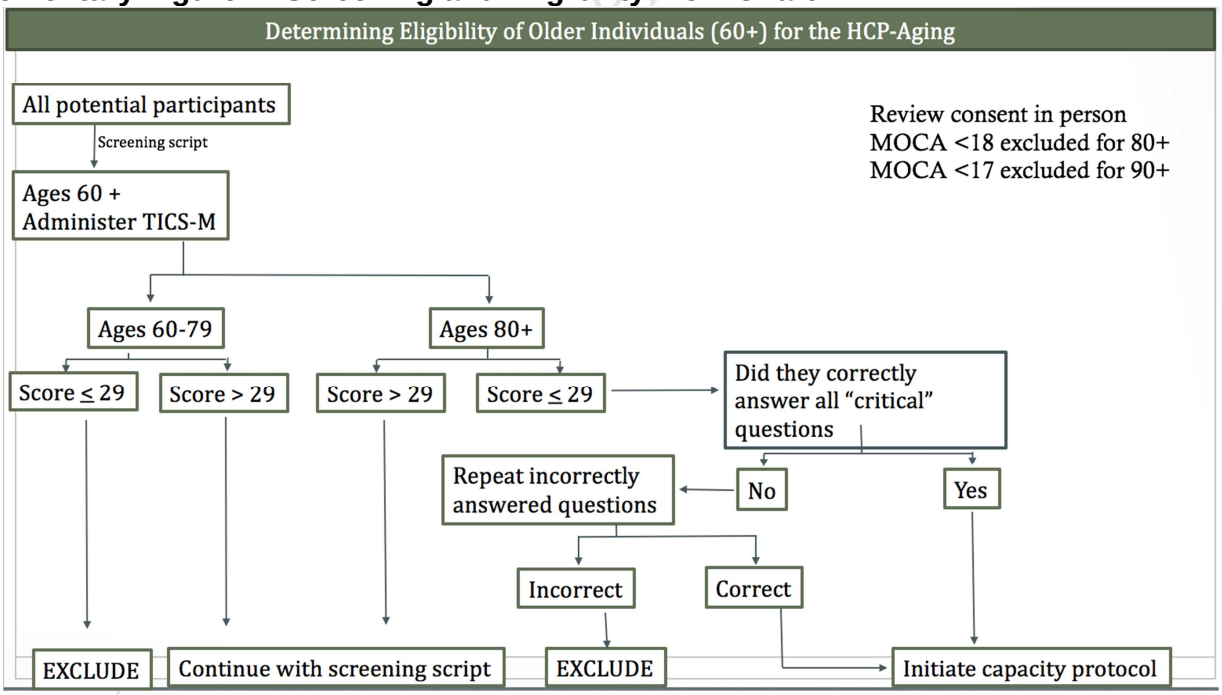
Via PAR-15-357, "Understanding AD in the Context of the Aging Brain", Melissa Terpstra (HCP-A co-PI) and Silvia Mangia (R01 co-PI) at UMinn were awarded R01AG055591, "Linking connectomics to biochemical trajectories of aging: How the human brain ages differentially in key regions of the default mode 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

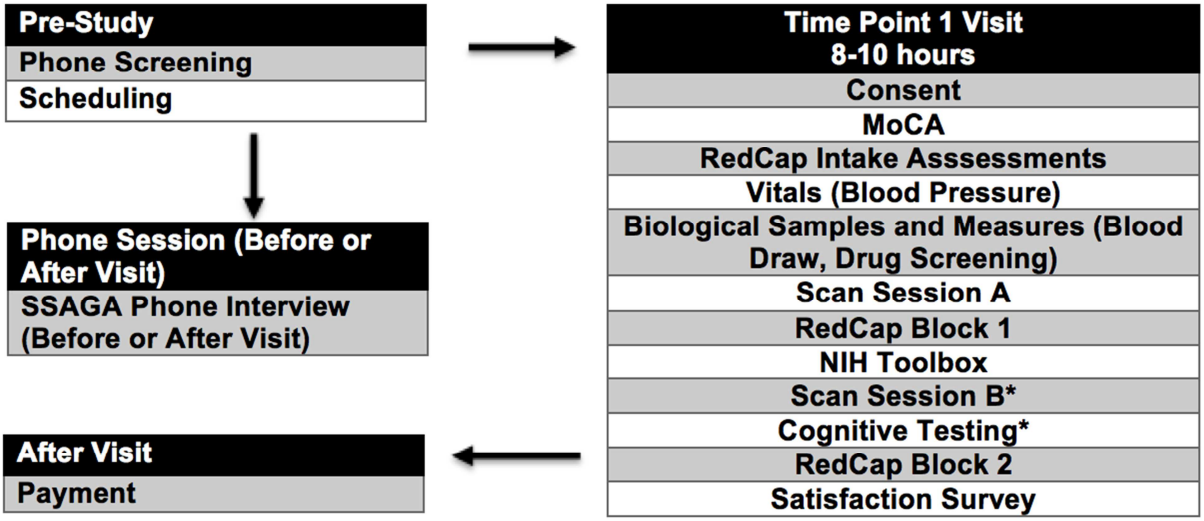
The MGH PIs responded to NOT-AG-17-008 -- "Administrative supplements to develop research on AD and Alzheimer's-related dementias (ADRD)" -- and received funds to develop the infrastructure to obtain brain donations from willing HCP-A participants for future neuropathologic assessment and histological 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.

Supplementary Figure 1: Screening and Eligibility Flow Chart



Supplementary 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.



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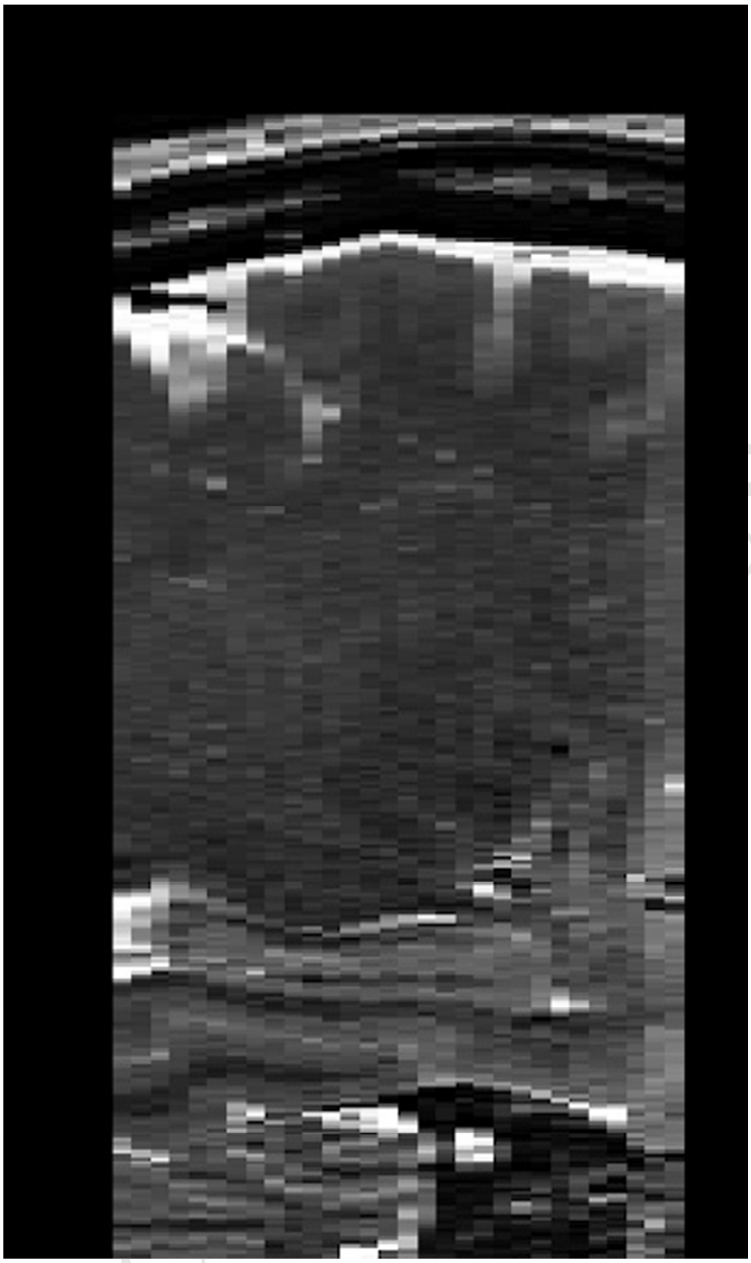
Supplementary Figure 3: Sagittal Reconstruction of the Hippocampal TSE Sequence



The sagittal reconstruction of the Hippocampal TSE sequence shows the anisotropic voxels; while resolution is high within plane (Figure 5), the 2-mm slice thickness creates blurring in the slice plane.

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Age Cohorts			MATURE						OLD			OLDEST OLD			TOTALS
			36-64		Peri-Menopause				65-79			80+			
		<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	Time 1	10	46	70	70	70	70	46	46	46	46	56	56	28	660
	Time 2		26	30	30	30	30	30	30	30	30	20	15	10	311
Males	Time 1	10	46	46	46	46	46	46	46	46	46	48	48	28	548
	Time 2		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**
Total Subjects		**20**	**92**	**116**	**116**	**116**	**116**	**116**	**92**	**92**	**92**	**104**	**104**	**56**	**1208**

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

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