Overall Specific Aims

The Healthy Aging and Senile Dementia (HASD; AG03991, JC Morris PI) program project grant initially was funded in 1984 and now is in year 30 (last year of the sixth 5-year funding cycle). With this application, we request funding for Years 31-35 to build on the theme of preclinical Alzheimer's disease (AD) that is being explored in the current funding cycle. At the time of our 2008 submission, the concept of preclinical AD and the assumption that imaging and fluid biomarkers reflect its presence were not fully accepted premises. Mounting evidence, **much of which has emanated from HASD**, (see Clinical Core Publication List, which highlights HASD-supported peer-review publications addressing AD biomarkers) supports the notion that the presence of molecular and degeneration biomarkers for AD **[***identify preclinical AD but, other than for autosomal dominant AD,[1] this is not yet indisputable***]**.[2-4] What remains to be determined is whether all older adults with *presumptive* preclinical AD (*defined by biomarkers*) will inevitably progress to symptomatic AD and whether the period of transition from cognitive normality to symptomatic AD can be identified. With this application HASD takes the logical next step from its current focus on characterizing preclinical AD to the evaluation of potential indicators of the transition to symptomatic AD, as shown in Table 1 below. It does so with the following Specific Aims.

1. Maintain the current fully functioning HASD infrastructure as organized into 5 Cores: Core A: Administration; Core B: Clinical; Core C: Biostatistics; Core D: Neuropathology; and Core E: Imaging.
2. Maintain the HASD Clinical Core cohort at N~250, representing older adults ≥65 years who are cognitively normal (CN) or have very mild/mild symptomatic AD, by enrolling 35 new participants (23 CN, 12 symptomatic AD) each year to replace attritional losses.
3. On all Clinical Core participants, at baseline and annually thereafter, obtain clinical and cognitive assessments, and at baseline and every 3 years thereafter obtain sleep variables, cerebrospinal fluid (CSF) assays, imaging studies (MRI, PET amyloid imaging), and blood for DNA extraction **[***and, for those participants who die, obtain brain autopsy consent, all in***]** support of the successful completion of the aims of the 3 HASD Projects (See Table 1).
4. Analyze the associations between all variables, both cross-sectionally and longitudinally
5. Maintain the productive collaboration (see Letter of Support from Drs. Merchant and Mintun) with Eli Lilly and Company and its wholly owned subsidiary, Avid Radiopharmaceuticals, that **[***with the now completed contract will***]** provide HASD with funding for MRI and florbetapir amyloid imaging PET scans (baseline and 3 years thereafter) for the entire HASD Clinical Cohort and the identically assessed ADRC Clinical Cohort (Total Registry N~550).

Table 1. Correspondence of Proposed HASD to its Prior Structure

	Current (1/09-12/13)	Proposed (1/14-12/18)
Core	A: Administration (JC Morris)	A: Administration (JC Morris)
	B: Clinical (JC Morris)	B: Clinical (JC Morris)
	C: Biostatistics (C Xiong)	C: Biostatistics (C Xiong)
	D: Neuropathology (NJ Cairns)	D: Neuropathology (NJ Cairns)
	E: Imaging (M Mintun)	E: Imaging (T Benzinger)
Projects	1. Preclinical AD predicts poststroke dementia (JC Morris)	1. Cognitive and functional indicators of transition to symptomatic AD (JC Morris)
	2. Antecedent biomarkers of AD in CSF and plasma (DM Holtzman)	2. Potential prognostic and theranostic marker for preclinical AD (DM Holtzman)
	3. Markers for DAT: Control, variability, and personality (DA Balota)	3. Identification of genetic variants associated with rate of disease progression (C Cruchaga/ AM Goate)
	4. Sequence variation in genes for biomarker proteins and age at onset of AD (AM Goate)	

Overall Strategy

Glossary of Terms and Abbreviations Used in this Application

HASD: Healthy Aging and Senile Dementia (P01 AG03991)

ADRC: Alzheimer Disease Research Center (P50 AG05681), endowed in 2010 by a gift from Charles F and Joanne Knight (Knight ADRC)

Total Registry (TR): the Clinical Core cohorts of HASD and ADRC are intentionally designed so that they can be combined into a larger uniform cohort (see Administration Core)

ACS: The Adult Children Study (P01 AG026276)

DIAN: The Dominantly Inherited Alzheimer Network (U19 AG032438)

AD: Alzheimer disease, the neurodegenerative brain disorder, regardless of clinical status.

Preclinical AD: the brain disorder prior to its clinical expression (i.e., persons with preclinical AD are cognitively normal (**CN**) as assessed by current methods and here are operationalized as CDR 0)

Symptomatic AD: the clinically expressed stage of AD. Symptoms range from subtle (prodromal or very mild AD; mild cognitive impairment [**MCI**]) to mild, moderate, and severe AD dementia. Symptomatic AD is operationalized in HASD as CDR>0 with a clinical diagnosis of AD.

ADAD: Autosomal dominant AD

LOAD: Late onset AD

Aβ: Amyloid-beta, a peptide produced by cleavage of the amyloid precursor protein (APP)

APOE: apolipoprotein E; the ε4 allele confers increased susceptibility for AD

CDR: Clinical Dementia Rating

CDR-SumBox (CDR-SB): A more quantitative representation of global cognitive/functional ability, with a range from 0 (no impairment) to 18 (maximal impairment)

CTT: Continuous Tapping Test

CWIT: Color Word Interference Test

CSF: Cerebrospinal fluid, obtained by lumbar puncture (**LP**) for assays of central nervous system proteins

MRI: Magnetic resonance imaging, in this application all performed at 3 Tesla

Rs-fcMRI: Resting state functional connectivity MRI

NACC: National Alzheimer's Coordinating Center (U01AG016976)

PET: Positron emission tomography

PIB: Pittsburgh Compound B, [^{11}C] amyloid tracer

Florbetapir: [^{18}F] amyloid tracer, also known as AV45 and Amyvid ®

UDS: Uniform Dataset, the standard clinical and cognitive assessment protocol used by all NIA-funded Alzheimer Disease Centers (**ADCs)**

MAP: Memory and Aging Project, established at Washington University in 1979 as the clinical research office and staff for all clinical and psychometric assessments in research participants

NIH/NIA: National Institutes of Health/National Institute on Aging,

CL/PL: Core Leader/Project Leader

[Note: We define "**biomarker-positive**" or "**biomarker-negative**" based on values from the 3 molecular markers to be obtained in HASD: cortical Aβ uptake with Florbetapir, levels of CSF $A\beta_{42}$, and levels of CSF tau/$ptau_{181}$. We have used both absolute measures and ratios of the CSF biomarkers to discriminate individuals with symptomatic AD and to compare these values with other biomarkers (e.g., amyloid imaging; hippocampal volume). We also use these values in CN individuals to predict progression to symptomatic AD. The CSF values are assayed with the Innotest ELISA, which yields consistent and reproducible results. If the results remain consistent, we can continue to use cutoffs that have been useful for us thus far to correlate with amyloid imaging and predict progression to symptomatic AD. Examples of these cutoffs are CSF $A\beta_{42}$ <500pg/ml, CSF tau >440pg/ml, and CSF tau/$A\beta_{42}$ ratio of >0.94. However, all these values and cutoffs may be adjusted as we obtain and analyze the new data proposed in this application. For purposes of this application, an abnormal value on any one biomarker will be considered as "biomarker-positive".]

A. Significance

1. The Summary Statement (released 8/22/08) for the last renewal application noted few perceived weakness: 1) concern that Project 1, addressing post-stroke dementia, would not meet recruitment goals; 2) caution about equating amyloid-positivity using PIB with preclinical AD; and 3) uncertainty as to how the Neuropathology Core supported the Projects. These concerns have been carefully considered. **[***In this renewal application, 3 new Projects are proposed and are all supported by the Neuropathology Core. Whether*

a "biomarker-positive" CN person equates to preclinical AD remains the central question to be addressed by HASD and its 3 Projects in this application.]

Table 2. Partial list of variables to be collected in this HASD proposal.	
Clinical Core	Annual unless otherwise noted • CDR, CDR-SB, MMSE, [*neuropsychiatric measures (State Trait Anxiety Inventory, Neuropsychiatric Inventory, Geriatric Depression Scale)*], HgbA1C (baseline and every 3y thereafter), BMI, APOE genotyping (baseline only) • ***Psychometric measures***[†] • ***Attentional control (Stroop Color Word Interference Task (CWIT), Continuous Tapping Test (CTT))***
Neuropathology Core	At time of autopsy • Standard neuropathologic assessment, in accordance with each of 4 sets of criteria (NIA-AA, NIA-Reagan, CERAD, Khachaturian) • **Aβ and tau burden assessed with an Area Fraction Fractionator probe, estimates of synaptic loss, and *neuronal count estimates based on dissector probe***
Imaging Core	Baseline and every 3y thereafter • ***Structural 3T MRI: volumetric (whole brain & regional volumes & thickness),*** diffusion tensor imaging (DTI), FLAIR (for WM disease), GET2* (for microhemorrhages), ARIA and white matter disease scoring. • ***Physiologic 3T MRI: rs-fcMRI*** • ***PET amyloid imaging:^{18}F florbetapir***
Proj. 1	Primary data from Clinical and Imaging Cores; processed and analyzed in Project 1 • ***Stroop Color Word Interference Test (CWIT), Continuous Tapping Test (CTT) (annual)*** • ***Functional connectivity and resting state network maps (baseline and every 3y thereafter)***
Proj. 2	Baseline and every 3y thereafter • ***Quantitative measures of sleep: total sleep time, sleep onset, sleep efficiency (% time sleeping when in bed), time in each sleep stage,* [*and delta power during NREM sleep*]** • [*Sleep questionnaire (to assess sleep disorders)*] • ***CSF levels of $A\beta_{42}$, tau, $ptau_{181}$, VILIP-1, YKL-40***
Proj. 4	• ***Genotype data (common and rare SNPs)*** from expanded TR (to include individuals who no longer are active but contributed DNA and had biomarker data) and newly enrolled HASD participants • Genotype data from ADNI

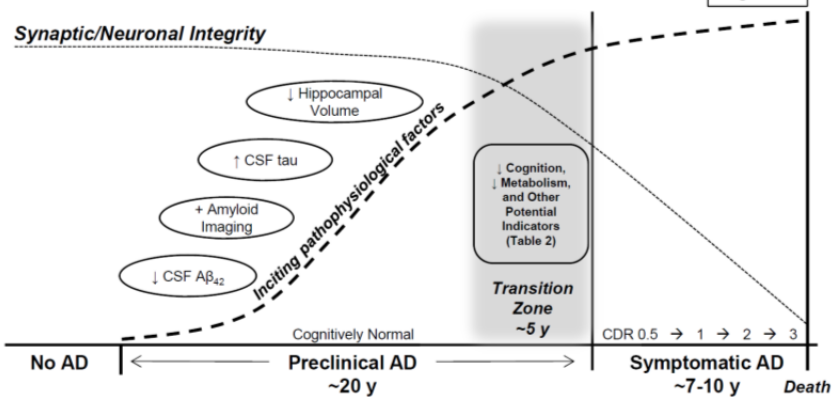
[†] HASD psychometrics measures include: Logical Memory, Associate Learning, Digit Span, Letter-Number Sequencing, and Mental Control from the Wechsler Memory Scale; Digit-Symbol Coding, Block Design, and Information from the Wechsler Adult Intelligence Scale; Trailmaking Test Part A & B; Category Fluency; Word Fluency; Boston Naming Test; Slosson Oral Reading Test-Revised; Free & Cued Selective Reminding Test; Mini-Mental State Examination; Handedness; and the Reading Span, Simon Task, and Consonant-Vowel Odd-Even Switching Task from the Executive, Linguistic, Spatial, and MEMory Abilities (ELSMEM) battery. For detailed descriptions of these measures, see the Psychometric Codebook in the Clinical Core Appendices.

Note: Bolded and italicized items reflect proposed transition indicators (see Figure 1).

This renewal application retains and extends all of the observed strengths from the last submission: 1) the PPG is led by Dr. Morris, who has successfully guided it through 3 funding cycles; 2) the highly collaborative investigative team provides remarkable continuity with Morris, Holtzman, and Goate remaining as Project Leaders; and 3) the proposed research builds on prior accomplishments with highly innovative and novel approaches to characterize how CN older adults transition to symptomatic AD (Table 2). Many hypothetical models have been developed to address this transition period[2-5] because of its great importance to the field, and HASD now proposes well-integrated projects to identify indicators of this transition. Project 1 will employ novel and sensitive cognitive measures, as well as functional connectivity changes in resting state networks, to identify and longitudinally assess the transition. Project 2 translates observations from transgenic mouse models of AD showing that sleep regulates amyloid-beta (Aβ) in brain interstitial fluid to the evaluation of sleep parameters in older adults, with and without preclinical AD as defined by CSF AD biomarker assays conducted by Project 2. Project 3 will use rate of symptomatic AD progression and hippocampal volume loss as endophenotypes to identify common and rare genetic variants that influence the rate of disease progression.

Each PL is highly accomplished and will ensure the successful completion of the aims. They also have a long and extremely productive track record of collaborative research together. Each Project also provides key roles for highly promising early-stage investigators so that their HASD involvement will further their career development. These investigators include Jason Hassenstab, PhD, and Beau Ances, MD, PhD, in Project 1, Brendan Lucey, MD, in Project 2, and Carlos Cruchaga, PhD, in Project 3. The outstanding science proposed in the Projects will be supported by five fully established, highly successful Cores: Core A: Administration, Core B: Clinical, Core C: Biostatistics, Core D: Neuropathology, and Core E: Imaging. Together, the Projects and Cores will generate an extensive and unique set of standard and novel variables in well-characterized, longitudinally studied older adults, both those who are CN, with and without preclinical AD, and those with very mild/mild symptomatic AD. These variables (Table 2) will be examined for their ability to identify the period of transition from cognitive normality to symptomatic AD.

Figure 1



2. We address the critically important questions of whether and when CN older adults with preclinical AD will develop symptomatic AD if they continue to live. Characterizing the transition from cognitive normality to cognitive impairment in older adults with preclinical AD is of great clinical and scientific interest. It also is crucial for the optimization of pioneering "secondary prevention" trials of putative disease-modifying drugs in CN older adults who are AD biomarker-positive, as exemplified by the Anti-Amyloid Treatment of Asymptomatic Alzheimer's (A4) trial sponsored by the Alzheimer's Disease Cooperative Study that is expected to launch in 2013.[6] HASD is ideally suited to examine these questions. It is the progenitor of multidisciplinary longitudinal research in aging and dementia at Washington University. Its original aims remain pertinent to HASD's goals and focus on the clinical, cognitive, and biomedical correlates of AD in comparison with cognitively healthy aging. In pursuing these comparisons, it became apparent in our clinicopathological studies that a proportion of individuals who were cognitively normal at death have neuropathological AD; [7,8]similar findings have been reported by others.[9-17] The concept of preclinical AD represented pathophysiological AD at a stage prior to its clinical expression[18,19]and now is widely accepted. [3]

Neuropathological studies of preclinical AD suggest that is not a benign process as it already is associated with subtle cognitive dysfunction[20] but cannot address whether the cases would have progressed to symptomatic AD. In the 2004-2008 funding cycle, we began to systematically explore *in vivo* biomarkers of AD in the HASD cohort using cognitive, CSF, and MRI modalities. (Although neither proposed in that renewal application nor funded by it, later in 2004 we added amyloid imaging using PET with PIB to our biomarker studies **[***with support from philanthropic funds raised by Dr. Morris.***]**) Selected studies from that funding period demonstrated that, regardless of clinical status, individuals with the highest cortical retention of PIB had the lowest CSF levels of amyloid-beta$_{42}$ (Aβ_{42})[21] and that the ratio of CSF tau to CSF Aβ_{42} may predict progression from CN to symptomatic AD.[22] We also showed that the earliest retention of PIB in preclinical AD occurs in regions associated with the default mode network.[23]

The current funding cycle (2009-2013) has focused on determining the temporal appearance of AD biomarkers antecedent to symptomatic AD. For example, individuals who are CN but who later develop symptomatic AD have poorer neuropsychological performance years before dementia diagnosis when compared with CN persons who do not become symptomatic, and an inflection point denoting a sharp decline in cognitive performance occurs 2-3 years prior to dementia diagnosis.[24] We also found that the prediction of incident symptomatic AD for an individual likely will not depend on molecular biomarkers alone but will incorporate characteristics of the individual (especially those that may relate to cognitive and brain reserve) to enhance the predictive power of AD biomarkers.[25,26]However, the factors that mark the (presumably) irreversible process during which a CN person with preclinical AD transitions to symptomatic AD have not been identified. Consequently, it presently is not possible to provide individual level prediction information regarding the transition from cognitive normality to impairment, nor to answer the question as to whether this transition in a person with preclinical AD is inevitable (assuming the person continues to live). It also is unknown whether an older adult without biomarker evidence of preclinical AD still may develop symptomatic AD.

This model clearly is simplistic. Although the number of studies using stereologic techniques to examine processes that distinguish healthy cognitive aging from AD is small,[27-30]the findings support the following hypothesis: the distinction between preclinical AD and very early symptomatic AD rests on the preservation of neuronal integrity. A corollary hypothesis holds that once neuronal integrity is compromised, the transition from cognitively normality to symptomatic AD has begun. (Figure 1) These hypotheses support a model wherein an inciting event, such as Aβ dysregulation (e.g., overproduction or underclearance of Aβ) initially results in cortical Aβ deposits and over many years the process eventually results in neuronal dysfunction and death to ultimately produce symptomatic AD. Cerebral cortical deposits of Aβ in the form of plaques may be "downstream" of more critical Aβ abnormalities, such as a shift from soluble to insoluble forms (fibrils) and the formation of toxic soluble forms (oligomers), and it may be that these earlier changes signal the transition from healthy aging to AD.[31] In this regard, the burden of synaptotoxic Aβ oligomers correlates with synaptic loss around Aβ plaques.[32] Synaptic dysfunction and loss may be equally or more important in producing symptomatic AD than neuronal death.[33]There are many potential mechanistic factors beyond Aβ that likely contribute to the AD process, including tau dysregulation and neurodegeneration, neuro-inflammation, APOE effects and altered cholesterol metabolism, cerebrovascular lesions, and oxidative stress and bioenergetic insufficiency. Nonetheless, the model provides the framework for exploration of indicators of neuronal dysfunction in individuals with preclinical AD. These indicators may signal that the change from cognitive normality to symptomatic AD is underway.

B. Innovation

We propose in this application to study novel presumptive indicators of neuronal dysfunction in CN older adults, with and without preclinical AD, and follow those individuals for cognitive outcomes. These proposed aims each are highly innovative and, to our knowledge, are not being pursued in an integrated manner elsewhere. In Project 1, we will evaluate sensitive measures of attentional control that have been characterized in current Project 3 of HASD as well as functional connectivity changes in resting state networks, hypothesizing that compromised neuronal integrity will manifest as cognitive impairment and as network disruption. In Project 2, sleep abnormalities will be assessed as an indicator of brain injury in preclinical AD and correlated with CSF markers of neurodegeneration ($A\beta_{42}$, total tau, phospho-tau) to predict transition to symptomatic AD. Project 3 will identify rare and common variants associated with change in cognitive performance, as well as other endophenotypes, and evaluate the functional consequences of these variants. All Projects use the Clinical, Administrative, and Biostatistical Cores; Projects 1 and 3 use the Imaging Core, and all Projects will use the Neuropathology Core for confirmation of diagnostic assignments. **[***Project 3 also uses the Neuropathology Core to provide brain tissue for mRNA expression studies. This Core also will correlate its neuropathologic variables with findings from the Imaging Core (e.g., quantitate post mortem Aβ burden in brain regions that in life were florbetapir-positive) and from Project 1 (e.g., correlate in vivo performance on measures of attentional control with synaptic and neuronal loss in relevant regions, such as dorsal anterior cingulate gyrus) and Project 2 (e.g., correlate sleep quality in vivo with lesions in relevant brain regions, such as locus coeruleus)*.**]** Also, all 3 Projects are linked thematically by their focus on the transition from cognitive normality to symptomatic AD and explore both "face valid" and novel indicators (Table 2).

C. Approach

C.1 Progress Reports (1/1/08-7/31/13)

C.1.1. Project 1: Preclinical AD Predicts Post-stroke Dementia (JC Morris, PL)

[*This was the first HASD Project not to use the Clinical Core for its sample, and***]** recruitment issues severely limited its completion. Over a 34-month recruitment period, less than 6% of all patients (N=3893) admitted to the Barnes-Jewish Hospital (St. Louis, MO) stroke service with an acute ischemic infarct met eligibility criteria (59% of patients were excluded because age was <65 years). Of eligible patients, 30.5% (N=81) consented to participate. The mean age of the sample was 76 +/- 7y, 51.8% were African American, the mean educational level was 12.4 +/- 2.5y, and the mean NIH Stroke Scale score was 5.5 +/- 4. All participants were CN at time of stroke, **[***but those who were cognitively impaired at 1-year follow-up had twice as much amyloid burden, as assessed by retention of PIB at baseline (time of stroke), compared with participants who remained CN. At baseline, 18 of the 79 (22.8%) individuals with amyloid imaging had a mean cortical binding potential for PIB ≥ 0.18, comparable to the CN HASD cohort (~30%)*.**]**

C.1.2. Project 2 Novel Biomarkers to predict Alzheimer's disease (DM Holtzman, PL)

[*We have published 15 papers that primarily derived from the Project with 1 under revision and 1 in preparation. In addition to these 15, we contributed to an additional 27 papers via collaborations*.**]** The aims of this Project were to determine the ability of known CSF biomarkers of AD (CSF Aβ42 and tau) as well as novel

markers (e.g. YKL-40, VILIP-1) to 1) predict progression from CDR 0 to CDR 0.5 and the rate of progression in participants CDR 0.5.; and 2) correlate with imaging and clinical measures. Other aims were to characterize whether a group of plasma proteins could classify AD from controls and to identify new markers with label free proteomics. We were successful in making progress on all Aims.[2,34-40]

[*In collaboration with the Clinical and Imaging Core, we found that all CSF biomarkers and amyloid imaging in CN individuals predict faster time to cognitive impairment, supporting the hypothesis that biomarkers signal underlying AD pathology several years before the appearance of AD symptoms.* [41] *We also found that CSF $A\beta_{42}$ and tau levels delineate stages of presumptive preclinical AD, such that the 5-year progression rate to symptomatic AD for Stage 1 preclinical AD is 11%, for Stage 2 is 26%, and for Stage 3 is 56%. Moreover, individuals with preclinical AD at any stage have an increased risk for death (HR 6.2).***]**[42]

C.1.3. Project 3 Markers for DAT: Control, Variability, and Personality (D Balota, PL)

We explored various experimental tasks of attentional control and measures of participant variability and components of reaction time (RT) distributions as potential markers for AD. We reported that Stroop performance, namely intrusion errors[43] (and the tau parameter from ex-Gaussian analyses)[44] discriminate healthy aging from very mild AD. These two Stroop measures also predict conversion to symptomatic AD in CN controls.[45] Across three selective attention tasks, we found that larger white matter volumes were associated with less slowing in the tail of the RT distribution (i.e., tau parameter).[46] These results suggest that Stroop errors and the tau parameter are particularly sensitive early markers of AD onset.

Pronounced deficits in a focal prospective memory task suggest that spontaneous retrieval processes serve as an early marker for the disease.[47] We also found that the maintenance of simple repetitive finger tapping performance is a strong discriminator between healthy young and CDR 0.5s.[48] We also explored the modulatory influence of personality on the effect of age on the brain volume of specific neuroanatomical structures.[49] **[***More recently, we found that a larger Stroop effect in errors was associated with decreased rs-fcMRI within the default mode and salience networks that was strongest in persons with reduced CSF $A\beta_{42}$* [50] *and that attentional control performance correlates significantly with AD biomarkers (CSF $A\beta_{42}$, tau, and p-tau; amyloid imaging).***]**[51]Overall, our work has shown that attentional control mechanisms discriminate CN older adults and very early symptomatic AD, are involved in a wide range of cognitive performance including episodic memory and simple repetitive motor tasks, and are related to AD biomarkers. **[***(Note: Current Project 3 (Balota) publications are included in the Overall publication list.)***]**

C.1.4. Project 4: Sequence variation in genes for biomarker proteins and age at onset of AD (AM Goate, PL)
We demonstrated that several variants within *MAPT* influence CSF levels of tau/ptau and that these same variants were associated with variation in the rate of cognitive decline in demented individuals.[52,53] We also observed additive effects on cognitive decline when combined with single nucleotide polymorphisms (SNPs) in other genes that also affect CSF tau levels.[53] We reported rare variants in *TREM2* that are associated with increased risk for LOAD.[54] Analysis of these TREM2 variants in our CSF dataset shows that the rare variant in *TREM2* is also associated with CSF tau ptau levels but that it does not explain the original association suggesting that other variants within genes in this cluster also influence CSF tau and potentially risk for AD. To further examine the functional consequences of variants associated with CSF tau levels we have set up cell culture systems and assays to measure both intracellular and extracellular tau/ptau.[55] This work has demonstrated that tau release from cells is an active process that is altered by variants causing frontotemporal dementia and by different tau isoforms.[55] We are currently developing induced pluripotent stem cells from individuals with different *MAPT* genotypes to study tau release and aggregation in neurons derived from individuals with genetic risk for tauopathy. **[***We performed the largest GWAS study for CSF tau/p-tau levels (n = 1269), demonstrating 3 significant loci that are associated with risk for AD, tangle pathology, and cognitive decline* [56] *and performed whole exome sequencing in large late-onset AD (LOAD) families that identified a rare variant in the phospholipase D family, member 3, gene that has a large effect on risk for AD, comparable to TREM2 or APOE.***]** [57]

C.2. Transitions

C.2.1. Faculty: HASD benefits from remarkably stable leadership as the Leaders of 4 of the 5 Cores and all 3 Projects continue their roles in this application (Table 1).

C.2.2. The Core E: Imaging CL in the previous application, Mark Mintun, MD, left Washington University for an industry position. He was replaced as Imaging CL by his mentee, Tammie Benzinger, MD, PhD, whose research focus is on combined MRI and PET imaging (See Imaging Core). Dr. Benzinger is supported by Marcus Raichle, MD, as Co-CL. Dr. Mintun has been instrumental in supporting the partnership between

HASD and Eli Lilly and Company and its wholly owned subsidiary, Avid Radiopharmaceuticals, to support the costs of baseline and 3-year follow-up MRI and amyloid imaging in ~550 older adults in the TR.

C.2.3. Martha Storandt, PhD, retired from Washington University in 2012 and Jason Hassenstab, PhD, has assumed the leadership of the psychometric aspects of the Clinical Core.

C.2.4. Current Project 1 ends with this cycle and in this application an entirely new Project 1 (Morris, PL) is proposed. Current Project 3 ends with this cycle; David Balota, PhD, current Project 3 PL, will provide expertise with the novel attentional measures for new Project 1, **[***in which he has an investigative role*.**]**

C.2.5. Krista Moulder, PhD, joined HASD in January, 2010. After working with current HASD Executive Director Virginia Buckles, PhD, for 3 years, Dr. Moulder now is fully prepared to serve as HASD Executive Director in this application. Dr. Buckles and Moulder both have scientific backgrounds, are highly organized and efficient, and effectively complement Dr. Morris, thus enabling Morris to maintain successful scientific and administrative leadership of HASD and the other multicomponent grants that foster AD research at Washington University. (See grant interaction chart in Appendix.) The other factor ensuring successful leadership is that HASD, ACS, and DIAN all are studies of antecedent AD biomarkers, albeit in different research populations and with unique scientific goals. The synergistic focus on antecedent biomarkers allows HASD, as the progenitor study, to "anchor" the other grants that in turn benefit from common infrastructure and methodology.

C.3. Productivity: HASD has been productive in the current budget cycle with 246 publications authored by HASD faculty and/or using HASD resources. Publications relating directly to HASD aims number 128 and publications using HASD resources (data, tissue, scans, etc.) total 118, including those resulting from the publically available OASIS data set. Only a few are highlighted here due to space:

1. Three HASD PLs (Holtzman, Morris, Goate) contributed a highly cited review article on AD (**[***119***]** citations since 2011).[58]
2. Morris and colleagues were the first to report that preclinical AD, as detected by PIB imaging in CN older adults, is associated with progression to symptomatic AD.[59]
3. Fagan (in the Holtzman laboratory) and colleagues determined that CSF measures of preclinical AD reflect a toxic process because reduced CSF $A\beta_{42}$ is associated with whole brain atrophy.[60]
4. Morris and colleagues found that reduced CSF $A\beta_{42}$ is the first detectable biomarker abnormality in preclinical AD, and that the frequency of preclinical AD in CN individuals increases as a function of age and *APOE4* status.[35] This article has **[***178***]** citations since 2010.
5. Brier (in the Ances laboratory) reported loss of intra- and internetwork correlations in the default mode and other resting state networks as symptomatic AD progressed in severity.[61]
6. Roe (in the Morris research group) demonstrated that abnormal amyloid imaging and CSF biomarkers in CN older adults are associated with faster time to incident cognitive impairment.[41]
7. Vos, working with Fagan and other HASD investigators, demonstrated that CSF biomarker profiles delineate stages of preclinical AD that in turn are associated with progressively faster rates to incident symptomatic AD.[42]

C.4.Coherence and Interrelationships

The multidisciplinary HASD team is well-integrated and highly collaborative. Virtually every HASD publication appropriately is co-authored by multiple investigators. Dr. Morris has interacted productively with Dr. Grant (Biostatistics Core) for 30 years, Ms. Coats (Clinical Core) for 27 years, Dr. Goate (Project 4) for 21 years, and Dr. Holtzman (Project 2) for 19 years. Morris has co-authored papers with every investigator in this application except Dr. Lucey, who just joined Washington University in 2012.

The Administration and Biostatistics Cores interact regularly with all HASD Projects and Cores and were directly involved in the preparation of each component of this application. The Aims of each Project are organized around the central theme, to characterize the transition from CN to symptomatic AD. Each Project pursues Project-specific approaches but also will combine all data from multiple modalities across HASD. Interactions with other major funded AD research programs at Washington University are shown in (See grant interaction chart in Appendix).

The HASD is highly regarded at Washington University and receives outstanding institutional support, including additional new space and renovated current space in 2012-2013 to expand our square footage by 50%. Letters of Support for this application are provided by the Dean of the School of Medicine and the Chancellor of Washington University. Additionally, a subset of HASD Clinical Core participants now will be studied as part of the Lifespan Pilot supplement of the Human Connectome Project (HCP; U54MH091657) because they are so well-characterized and offer the opportunity to correlate their HASD-derived imaging and biomarker data with HCP findings (see Letter of Support from Dr. Van Essen).

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