

SUPPLEMENTAL MATERIAL

Neuropathological Evaluation

All specimens were grossly examined for macroscopic infarcts [1] and atherosclerosis [2,3]. Atherosclerosis severity was based on visual examination of the Circle of Willis and rated on a scale of 0 to 3 (0: absent; 1: mild; 2: moderate; 3: severe). For these analyses, severity of atherosclerosis was dichotomized into moderate/severe versus absent/mild. Donor brains were fixed in 4% paraformaldehyde (1 hemisphere) for at least two weeks and then sliced into ~1-centimeter coronal slabs; the other hemisphere was frozen upon receipt. Standard brain regions, including hippocampus, entorhinal cortex, midfrontal cortex, middle temporal cortex, inferior parietal cortex, primary occipital cortex, anterior basal ganglia, anterior thalamus, and midbrain, were then dissected, processed and paraffin-embedded, and sectioned at 6 microns and mounted onto charged microscope slides as described previously [4,5].

Immunohistochemical and histochemical analyses followed those outlined by the pathologic dataset recommended by the National Alzheimer's Coordinating Center (NACC) [6]. Alzheimer's disease (AD) pathology was defined using National Institute on Aging (NIA)-Reagan [7,8] and modified Consortium to Establish a Registry for Alzheimer's Disease (CERAD) criteria [2] to estimate neuritic plaque density, and NFT distribution was assessed using Braak staging [9–11]. A diagnosis of pathologic AD required an 'intermediate or high likelihood AD' by NIA-Reagan criteria [12,13].

Amyloid- β was labeled using an N-terminal directed monoclonal antibody [12,14]. Cerebral amyloid angiopathy (CAA) was staged on a scale of zero to four by immunostaining for β -amyloid in the parenchymal vessels of paraffin-embedded sections from the angular gyrus. CAA severity was dichotomized as less than 2 vs. 2 or greater. Lewy bodies were identified on

α -synuclein immunostained sections and Lewy body disease was diagnosed based on consensus guidelines including designations as olfactory, brainstem predominant, limbic (transitional) and neocortical [3,15,16]. Pathological TDP-43 inclusions were stained using monoclonal antibodies to phosphorylated TDP-43 [17] so as not to stain normal nuclear TDP-43 [18]. The distribution of TDP-43 pathology was rated on the following scale: (0: none; 1: mild; amygdala only; 2: moderate; amygdala and limbic (entorhinal or hippocampus); 3: severe; amygdala, limbic, and neocortical) [19,20]. TDP-43 pathology was dichotomized as 2 or 3 vs. 0 or 1. Microinfarcts were identified on H&E-stained sections [1,2]. Severity of arteriolosclerosis was graded on a scale of 0 to 3 (0: absent; 1: mild; 2: moderate; 3: severe) based on concentric hyaline thickening of vessel walls with emphasis placed on evaluation of smaller arterioles, less than ~50 microns. For these analyses, severity of arteriolosclerosis was dichotomized into moderate/severe versus not present/mild.

Supplemental Table 1. Cognitive domains and tests assessed in ROSMAP.

Variable	Description	Comments	Secondary Structure
Memory			
Q1mme	What is the year?		F1
Q2mme	What is the season of the year?		
Q3mme	What is the date?		F1
Q4mme	What is the day of the week?		F1
Q5mme	What is the month?		F1
Q6mme	What state are we in?		F2
Q8mme	What city are we in?		F2
Q7mme	What county are we in?		F2
Q9mme	What room are we in?		F2
Q10amme	What is the address of this place?		F2
Q10bmme	Street Name		F2
atb1	Apple, table, penny (immediate)	3 items collapsed	
story	Logical memory		F3
WordT1	Word list learning Trial 1	10 items collapsed	F4
WordT2	Word list learning Trial 2	“	F4
WordT3	Word list learning Trial 3	“	F4
WordRec	Which one of these words is from that list? (Word list recognition)	10 items collapsed	F6
Recall	Word list recall	10 items collapsed	F6
ebmt	East Boston immediate recall	12 items collapsed	F5
atb2	apple, table, penny (delayed)	3 items collapsed	
ebdr	East Boston delayed recall	12 items collapsed	F5
Delay	Tell me the story again		F3
Language			
Q12amme	Spell WORLD forwards		
Q14mme	[SHOW WRIST WATCH] What is this called?		
Q15mme	[SHOW PENCIL] What is this called?		
Q16mme	Repeat a phrase		
Q17mme	Read the words on this card, then do what it says		
paper	Takes piece of paper		
folds	Folds paper in half		
places	Places paper in lap		
Q19mme	Write any complete sentence		
dnaming	What is the name of this object?		
clothing	all of the things that belong in that category		

animals	all of the things that belong in that category		F1
fruits	all of the things that belong in that category		F1
sink1	Will a board sink in water?		
sink2	Will a stone sink in water?		
hammer1	Is a hammer good for cutting wood?		
hammer2	Can you use a hammer to pound nails?		
flour1	Do two pounds of flour weigh more than one?		
flour2	Is one pound of flour heavier than two?		
boots1	Will water go through a good pair of rubber boots?		
boots2	Will a good pair of rubber boots keep water out?		
Visuospatial			
Q20mme	Please copy the drawing on this piece of paper		
Line1...15	Which two lines point in the same direction...?		
Executive			
AA	Which piece would complete the pattern...	4 A patterns merged	
BB	Which piece would complete the pattern...	8 B patterns merged	
Q12bmme	Spell WORLD backwards		
DigBak	digits backward	combined 12 items	
cts_sdmt	symbol digits modality (oral)		F1
cts_ncrtd	Number comparison		F1
DigFor	digits forward	combined 12 items	

Adapted from *Genetic data and cognitively-defined late-onset Alzheimer's disease subgroups* (Mukherjee et al. 2018) [21].

Supplemental Table 2: Demographic and clinical features of included and excluded neuropathologically-confirmed AD cases in ROSMAP, mean (SD, range) or n (%).

Characteristic	Included n=292 (32.5%)	Excluded n=606 (67.5%)	Total n=898 (100%)	P ^d
Female, n (%)	215 (74%)	409 (67%)	624 (69%)	0.06
Age, mean (SD)				
At first visit	81.3 (5.8) (63.0 - 96.8)	81.4 (7.1) (59.0 - 102.1)	81.4 (6.7) (59.0 - 102.1)	0.75
At first MCI diagnosis (n=651 ^a)	83.3 (5.8) (66.0 - 98.2)	84.2 (6.8) (62.0 - 104.5)	83.9 (6.4) (62.0 - 104.5)	0.08
At first MCI+ diagnosis ^b (n=776)	83.2 (5.9) (63.0 - 98.2)	84.5 (6.8) (62.0 - 104.5)	84.1 (6.4) (62.0 - 104.5)	0.008
At dementia diagnosis (n=510)	85.4 (6.2) (63.0 - 99.4)	87.2 (6.7) (68.6 - 107.2)	86.4 (6.5) (63.0 - 107.2)	0.002
At last visit ^c	88.9 (5.7) (70.6 - 102.6)	88.9 (6.6) (63.0 - 108.1)	88.9 (6.3) (63.0 - 108.1)	0.86
At death	89.9 (5.6) (70.6 - 102.6)	89.7 (6.5) (65.9 - 108.3)	89.8 (6.2) (65.9 - 108.3)	0.59
Race, n (%)				0.33 ^c
White	285 (98%)	582 (96%)	867 (97%)	
Black	6 (2%)	21 (3%)	27 (3%)	
Native American	0 (0%)	2 (0.3%)	2 (< 1%)	
Asian	1 (< 1%)	1 (< 1%)	2 (< 1%)	
Years of education, mean (SD)	16.1 (3.6) (3 - 30)	16.2 (3.7) (3 - 30)	16.2 (3.7) (3 - 30)	0.78
First Clinical Diagnosis				< 0.001
No impairment	133 (46%)	365 (60%)	498 (56%)	
MCI	105 (36%)	176 (29%)	281 (31%)	
AD dementia	50 (17%)	54 (9%)	104 (12%)	
AD w/other dementia	2 (1%)	4 (1%)	6 (1%)	
Non-AD dementia	2 (1%)	5 (1%)	7 (1%)	
Last Clinical Diagnosis				< 0.001
No impairment	27 (10%)	127 (29%)	27 (9%)	
MCI	54 (18%)	160 (26%)	54 (18%)	
AD dementia	186 (64%)	231 (38%)	186 (64%)	
AD w/other dementia	21 (7%)	31 (5%)	21 (8%)	
Non-AD dementia	4 (1%)	9 (1%)	4 (1%)	

≥ 1 <i>APOE</i> ε4 allele	125 (43%)	168 (28%)	293 (33%)	< 0.001
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Abbreviations: MCI: Mild Cognitive Impairment; MMSE: Mini-Mental State Examination; AD: Alzheimer's disease, ROSMAP: Religious Orders Study and Rush Memory and Aging Project

^aParticipants who went from cognitively normal to dementia, skipping MCI, are not included in the mean age of MCI onset

^bMCI+ refers to either MCI or dementia

^cLast visit was first visit for n=53.

^dT-test or Fisher's exact test.

^eWhite versus any other race

Supplemental Table 3. Neurofibrillary tangle counts (per mm²) across regions and AD neuropathological subtypes, median, inter-quartile range, and range

	Limbic Predominant (lpAD)	Hippocampal Sparing (HpSpAD)	Typical (tAD)	Overall
CA1/subiculum hippocampal	74 58-93 47-138	22 13-30 0-44	43 29-62 0-147	47 29.5-69.5 0-147
Inferior temporal gyrus	8 4-14 1-21	27.5 25-37 18-68	18 8-32 1-92	15 7-29.5 1-92
Inferior parietal lobule	2 1-3 0-9	18 10-24 3-48	6 2-14 0-60	4 2-12 0-60
Middle frontal cortex	1 1-3 0-9	9 3-18 1-41	4 1-11 0-65	3 1-9 0-65
Average cortical	1.1 1.0-1.5 0.6-2.6	1.9 1.4-2.7 1.0-3.4	1.4 0.9-2.2 0.3-6.2	1.4 0.9-2.1 0.3-5.3
Ratio of hippocampal to average cortical	6.2 4.4-8.6 3.1-19	0.4 0.2-0.5 0-0.6	1.4 0.9-2.6 0-12	1.7 0.8-3.9 0-19

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