SUPPLEMENTARY METHODS

Sub-composites for cognition requiring vision and cognition not requiring vision

Because vision can impair performance on cognitive testing and this may have affected the core results, we further separated the 17 tests into two sub-composites based on whether the tests require visual ability or not. Specifically, 9 tests that require vision (Word List Memory, Word List Recall, Word List Recognition, Symbol Digit Modalities Test, Number Comparison, Boston Naming Test, Word Reading, Judgment of Line Orientation, Standard Progressive Matrices) were grouped together into one composite (requires vision), and the remaining 8 tests were grouped into a second composite (does not require vision). These two composites were generated by averaging the z-scores of relevant tests, following the procedure used to create the global cognitive composite.

Neuropathologic assessment and quantification

Brain autopsy procedures follow uniform procedures[1,12,14,17,27,32]. Briefly, brains were removed, weighed, and hemispheres were cut coronally using a Plexiglas jig into 1-cm slabs. One hemisphere was fixed in 4% paraformaldehyde. After gross examination of both hemispheres, 15 brain regions of interest (i.e., midfrontal, superior frontal, inferior orbital frontal, inferior temporal, mid temporal, anterior temporal tip, inferior parietal, anterior cingulate, entorhinal and hippocampal cortices, amygdala, basal ganglia, thalamus, midbrain, occipital cortex) were dissected from the fixed tissue and processed and embedded in paraffin.

Immunohistochemistry is currently done using a Leica-Bond Max autostainer (Leica Microsystems Inc., New Buffalo, IL). 20um paraffin sections were used to localize β-amyloid and neurofibrillary tangles and 6μm paraffin sections were used to localize Lewy bodies and TDP-43. β-amyloid was detected using a monoclonal antibody, 4G8 (1:9000, Covance, Chicago, IL) using proteinase K pretreatment and EDTA based pH 9.0 epitope retrieval solution for heat-induced epitope retrieval (HIER). Neurofibrillary tangles were detected using a phosphorylated anti-Tau antibody, AT-8 (1:2000, Thermoscientific, Rockford, IL) with no pretreatments or epitope retrieval. Lewy bodies were detected using a phosphorylated anti-α-synuclein antibody (clone pSyn#64, 1:20,000, Wako Chem. USA, Richmond, VA) following antigen retrieval by

HIER in citrate buffer (pH 6.0). The Bond™ Polymer Refine Red Detection kit utilizing alkaline phosphatase with a Fast Red chromogen was used for alpha synuclein, and the Bond™ Polymer Refine Detection with DAB as chromogen was used for the other antibodies. For TDP-43 we used Clone 1D3 1:10,000, San Diego, CA; with EDTA based pH 9.0 epitope retrieval solution for the HIER. CAA was identified using one of three antibodies to amyloid beta (10D5 Beta Amyloid, 17–24 (4G8) Covance Madison, 1:9000; Anti-Human Amyloid-Beta 1–16 (10D5) Elan Pharmaceuticals, San Francisco, 1:300; Anti-Human Beta-Amyloid, (6F/3D), DAKO North America, Carpinteria, 1:50).

AD pathology was assessed using both traditional silver stain and separately immunohistochemistry for quantification of markers of B-amyloid and PHFtau tangles. For silver stain, we quantified neuritic plaques, diffuse plaques, and neurofibrillary tangles in 5 regions (hippocampus and entorhinal cortex, midfrontal, midtemporal, and inferior parietal cortex). Regional scores of each pathology were standardized and averaged to yield a continuous composite measure of global AD pathology. For molecularly-specific quantification of B-amyloid and PHFtau tangles, we outlined and sampled 8 cortical regions (superior frontal, midfrontal, hippopcampus and entorhinal cortex, inferior temporal, inferior parietal, anterior cingulate, and occipital cortex) using systematic computerized sampling and then averaged scores across cortical brain regions to create summary measures of B-amyloid and PHFtau tangles for use in analyses. The summary measures reflect the estimated burden of amyloid (% area occupied) and density of tangles (per mm^2) across the brain regions. These measures are highly skewed with many low values; thus, we routinely use a square root transformation as appropriate in statistical analyses[,12,32,36].

Lewy bodies were identified in the substantia nigra, 2 limbic sites (entorhinal cortex, anterior cingulate cortex), and 3 neocortical sites (midfrontal cortex, superior or middle temporal cortex, inferior parietal cortex). We used a modified version of the staging criteria of McKeith et al. to classify Lewy body disease as nigral, limbic, or neocortical. Neocortical disease required Lewy bodies in frontal, temporal, or parietal cortex and was rated as present or absent for analyses[11,12,14,17].

LATE-NC/TDP-43 pathology was assessed in 8 brain regions (amygdala and periamygdalar region when available, hippocampus CA1/subiculum, hippocampal dentate, entorhinal cortex, orbitofrontal, midfrontal, anterior temporal and middle temporal cortices). Immunostaining 6µm sections stain the pathologically phosphorylated TDP-43 proteins in the inclusions (also seen in amyotrophic lateral sclerosis, frontotemporal lobar degeneration but not

the normal nuclear TDP-43). Each region of interest was reviewed for the presence, severity, and location of TDP-43 cytoplasmic inclusions and was rated on a 6-point scale based on the number of inclusions in a 0.25mm^2 area of greatest density within that region. In analyses, we used 4 stages based on the pathological distribution of TDP-43 in older persons: 0 no TDP, stage 1 (TDP-43 pathology localized to the amygdala), stage 2 (extending to limbic structures including hippocampus and/or entorhinal cortex), and stage 3 (extending into the neocortex) [20,32,36].

Large vessel atherosclerosis was assessed via visual inspection of the available Circle of Willis vessels at the base of the brain, including the distal internal carotid arteries, distal vertebral arteries, the basilar, and their proximal branches, including but not limited to the posterior, middle and anterior cerebral arteries, the anterior and posterior communicating arteries, and the anterior inferior and superior cerebellar arteries. Severity was graded based on 3 criteria: the number of vessels involved, the extent of involvement of each artery, and the degree of vessel occlusion, if any. The semi-quantitative rating scale ranged from 0-3 as follows: 0 no visualized atherosclerotic plaques, 1 mild pathology (plaques involving one or a few (e.g., up to 3 vessels), minimal in length (e.g., less than 2mm maximum per vessel) and no significant occlusion, 2 moderate pathology (atherosclerosis in up to half of all visualized major arteries), or up to 50% involvement or occlusion of any single vessel, 3 severe (plaques in more than half of all visualized arteries), and/or more than 75% involvement or occlusion of a single vessel[32,36].

Arteriolosclerosis was evaluated on hematoxylin & eosin (H&E) stained sections of the anterior basal ganglia (i.e., anterior caudate, putamen, globus pallidus, and internal capsule). Severity was graded based on concentric hyaline thickening of vessel walls, with emphasis on smaller arterioles (<50 microns). The semiquantitative rating scale ranged from 0-3 as follows: 0 no arteriolosclerosis; 1 mild arteriolosclerosis (arteriole walls minimally thickened); 2 moderate (arteriole walls increased up to 2×normal thickness), 3 severe (arteriolar wall thickness more than 2-fold greater in size than normal or vessel occluded) [32,36].

CAA was identified in meningeal and parenchymal vessels in four neocortical regions (midfrontal, middle temporal, angular and calcarine cortices). For each region, meningeal and parenchymal vessels were assessed for amyloid deposition and scored from 0 to 4 as follows: 0 no deposition, 1 scattered segmental but no circumferential deposition, 2 circumferential deposition up to 10 vessels, 3 circumferential deposition up to 75% of the region, and 4 circumferential deposition over 75% of the total region. The CAA score for each region was the

maximum of the meningeal and parenchymal CAA scores. Scores were averaged across regions for a continuous measure; for analyses, we classified CAA scores into a 4-level severity rating including none, mild, moderate, and severe using cutoffs determined by the neuropathologist[18,32,36].

Hippocampal sclerosis was examined on 6µm sections of mid hippocampus stained using H&E. We define hippocampal sclerosis as severe neuronal loss and gliosis in CA1 with or without involvement of the subiculum or other regions, and hippocampal sclerosis was rated as present or absent. Microinfarcts are rated separately and TDP is not required[19,32,36].

For gross infarcts, 1cm fixed slabs were reviewed as well as all digital pictures. All suspected infarcts were examined histologically to confirm the presence of an infarct. Infarcts were classified as acute, subacute and chronic; only chronic infarcts were included in analyses[11,12,17].

For microinfarcts, at least 9 brain regions were examined (anterior cingulate, midfrontal, midtemporal, hippocampus, entorhinal, inferior parietal, basal ganglia, thalamus, midbrain). Microinfarcts are rated as present or absent and classified as acute, subacute and chronic, and chronic microinfarcts are included in analyses[11,12,17].

SUPPLEMENTARY RESULTS

Supplementary Table 1. Association of Each Pathologic Index with Rate of Cognitive Decline Separately for Tests that Require Vision and Those that Do Not Require Vision

	Multivariate models			
	Vision Required		Vision not required	
	Estimate (SE)	p-value	Estimate (SE)	p-value
Global AD pathology	-0.018 (0.008)	0.033	-0.021 (0.008)	0.009
B-amyloid	-0.002 (0.003)	0.520	-0.002 (0.003)	0.648

PHFtau tangles	-0.033 (0.003)	<0.001	-0.028 (0.003)	<0.001
Neocortical Lewy bodies	-0.043 (0.008)	<0.001	-0.038 (0.008)	<0.001
TDP-43 (4 stages)	-0.004 (0.003)	0.087	-0.005 (0.002)	0.020
Hippocampal sclerosis	-0.027 (0.009)	0.004	-0.033 (0.009)	<0.001
Gross infarcts, chronic	-0.006 (0.006)	0.348	-0.024 (0.006)	<0.001
Microscopic infarcts, chronic	-0.003 (0.006)	0.603	0.004 (0.006)	0.453
Atherosclerosis	-0.017 (0.004)	<0.001	-0.013 (0.003)	<0.001
Arteriolosclerosis	-0.003 (0.003)	0.340	-0.005 (0.003)	0.093
Cerebral amyloid angiopathy	-0.004 (0.003)	0.213	-0.0004 (0.003)	0.894

AD = Alzheimer’s disease.