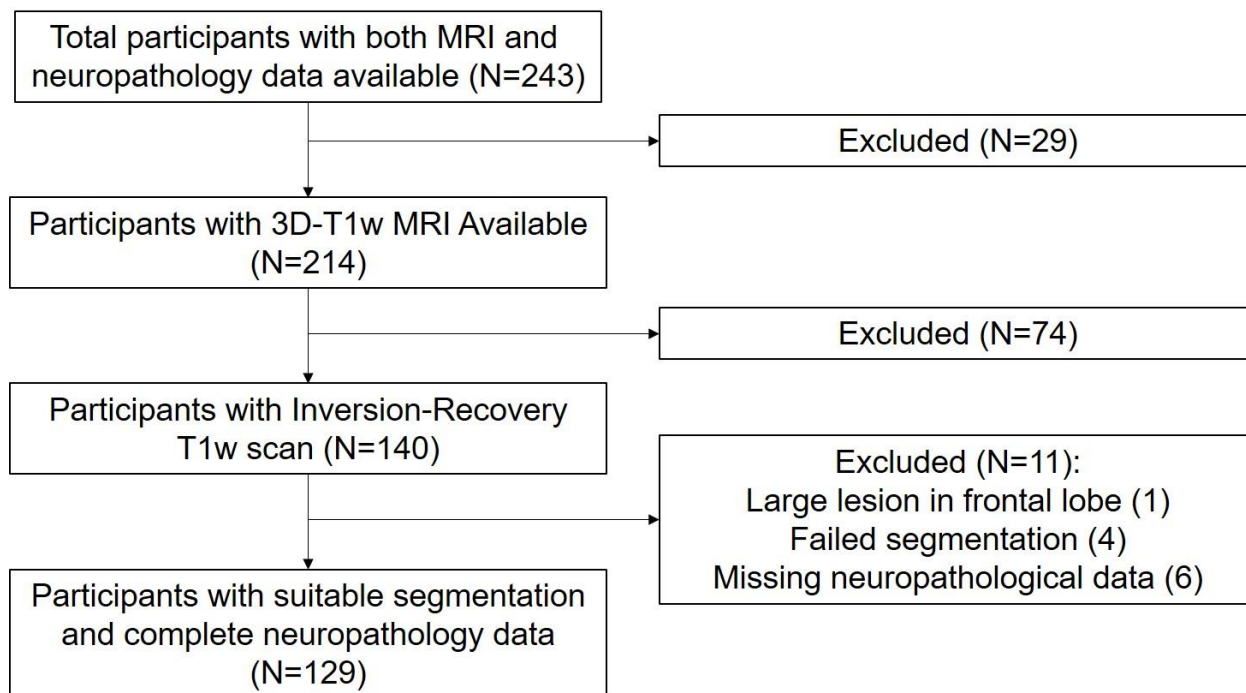


Supplementary Figure 1. Flowchart of inclusion criteria for National Alzheimer's Coordinating Center (NACC) participants.



Supplementary Table 1. Multiple linear regression results for ROI volumes using full severity (CAA and atherosclerosis) or staging (Braak and CERAD) information as continuous variables in the NACC data (N=129).

Regions		Hippocampus				Amygdala				Parahippocampus			
Variables	Semi-Part.	% Var. Exp.	T-stat	P-value	Semi-Part.	% Var. Exp.	T-stat	P-value	Semi-Part.	% Var. Exp.	T-stat	P-value	
<i>Demographic</i>	Dementia Status at MRI	-0.29	8.29	-4.27	<0.001	-0.30	8.94	-4.40	<0.001	-0.27	7.29	-3.79	<0.001
	Age	-0.26	6.86	-3.89	<0.001	-0.25	6.20	-3.66	<0.001	-0.25	6.20	-3.50	<0.001
	Sex	0.03	0.11	0.49	0.6	-0.03	0.07	-0.38	0.7	-0.13	1.74	-1.86	0.07
	Years Education	0.13	1.59	1.87	0.06	0.10	1.06	1.52	0.1	0.05	0.21	0.65	0.5
	Years MRI to Death	0.10	1.04	1.52	0.1	0.09	0.74	1.26	0.2	0.10	0.94	1.37	0.2
	TIV	0.18	3.17	2.64	0.01	0.22	4.67	3.18	0.002	0.13	1.72	1.85	0.07
<i>Pathology</i>	Braak Stage	-0.05	0.25	-0.74	0.5	0.02	0.03	0.23	0.8	-0.11	1.21	-1.55	0.1
	CERAD Plaques	0.02	0.03	0.24	0.8	-0.13	1.77	-1.96	0.053	0.04	0.16	0.57	0.6
	HS	-0.30	8.70	-4.37	<0.001	-0.20	3.84	-2.89	0.005	-0.15	2.10	-2.04	0.044
	Lewy Bodies	-0.04	0.13	-0.53	0.6	-0.15	2.22	-2.19	0.03	-0.09	0.76	-1.23	0.2
	CAA	-0.04	0.15	-0.59	0.6	0.09	0.83	1.34	0.2	0.05	0.29	0.77	0.4
	Atherosclerosis	-0.06	0.41	-0.95	0.3	-0.05	0.21	-0.67	0.5	-0.05	0.29	-0.77	0.4
R^2		0.49				0.48				0.41			

Bold denotes $P < 0.05$. TIV: total intracranial volume. ADNP: Alzheimer's disease neuropathology. HS: Hippocampal Sclerosis. CERAD: Consortium to Establish a Registry for Alzheimer's Disease. CAA: Cerebral amyloid angiopathy. Semi-Part.: semi-partial correlation coefficient. Var. Exp.: unique variance explained.

Supplementary Table 2. Multiple linear regression results for ROI volumes across the various demographic and neuropathological measures, including APOE e4 status, for the NACC data (N=123).

Regions		Hippocampus				Amygdala				Parahippocampus			
Variables	Semi-Part.	% Var. Exp.	T-stat	P-value	Semi-Part.	% Var. Exp.	T-stat	P-value	Semi-Part.	% Var. Exp.	T-stat	P-value	
Demographic	Dementia Status at MRI	-0.29	8.24	-4.22	<0.001	-0.31	9.55	-4.61	<0.001	-0.27	7.29	-3.67	<0.001
	APOE e4	-0.13	1.59	-1.86	0.07	-0.17	3.03	-2.59	0.01	0.01	0.01	0.13	0.9
	Age	-0.30	8.82	-4.37	<0.001	-0.25	6.05	-3.67	<0.001	-0.26	6.55	-3.47	<0.001
	Sex	0.03	0.10	0.47	0.6	-0.05	0.23	-0.72	0.45	-0.12	1.44	-1.62	0.1
	Years Education	0.13	1.72	1.93	0.056	0.13	1.56	1.86	0.07	0.03	0.08	0.38	0.7
	Years MRI to Death	0.11	1.17	1.59	0.1	0.09	0.74	1.28	0.2	0.09	0.81	1.22	0.2
	TIV	0.17	2.96	2.52	0.01	0.18	3.20	2.67	0.009	0.14	2.07	1.95	0.053
Pathology	ADNP	-0.07	0.48	-1.01	0.3	-0.15	2.25	-2.24	0.03	-0.05	0.28	-0.72	0.5
	HS	-0.32	10.30	-4.72	<0.001	-0.19	3.69	-2.86	0.005	-0.16	2.56	-2.17	0.03
	Lewy Bodies	-0.04	0.14	-0.55	0.6	-0.14	2.07	-2.14	0.03	-0.09	0.88	-1.28	0.2
	CAA	0.01	0.01	0.18	0.9	0.18	3.06	2.60	0.01	0.03	0.08	0.39	0.7
	Atherosclerosis	-0.05	0.25	-0.74	0.5	-0.07	0.53	-1.08	0.3	-0.07	0.52	-0.98	0.3
R^2		0.49				0.51				0.40			

Bold denotes $P < 0.05$. TIV: total intracranial volume. ADNP: Alzheimer's disease neuropathology. HS: Hippocampal Sclerosis. CERAD: Consortium to Establish a Registry for Alzheimer's Disease. CAA: Cerebral amyloid angiopathy. Semi-Part.: semi-partial correlation coefficient. Var. Exp.: unique variance explained.

Supplementary Table 3. Semi-partial correlation coefficients for ROI volumes using progressively more homogeneous scan subsets.

Variables	Regions	Hippocampus			Amygdala			Parahippocampus		
		All IR (N=129)	MPRAGE (N=74)	MPRAGE 3T (N=54)	All IR (N=129)	MPRAGE (N=74)	MPRAGE 3T (N=54)	All IR (N=129)	MPRAGE (N=74)	MPRAGE 3T (N=54)
<i>Demographic</i>	Dementia Status at MRI	-0.28	-0.39	-0.35	-0.29	-0.34	-0.30	-0.28	-0.35	-0.29
	Age	-0.27	-0.23	-0.32	-0.24	-0.23	-0.26	-0.25	-0.24	-0.37
	Sex	0.05	-0.02	-0.02	-0.04	-0.02	0.00	-0.12	-0.10	-0.02
	Years Education	0.13	0.17	0.22	0.12	0.09	0.11	0.04	0.09	0.12
	Years MRI to Death	0.11	0.08	0.04	0.09	0.02	-0.02	0.11	-0.01	-0.06
	TIV	0.19	0.12	0.10	0.19	0.28	0.29	0.15	0.18	0.22
<i>Pathology</i>	ADNP	-0.06	-0.01	-0.06	-0.15	-0.05	-0.06	-0.06	0.04	-0.02
	HS	-0.31	-0.37	-0.40	-0.19	-0.23	-0.24	-0.17	-0.25	-0.26
	Lewy Bodies	-0.04	0.03	0.06	-0.17	-0.15	-0.17	-0.09	-0.10	-0.08
	CAA	-0.03	-0.03	0.01	0.12	0.10	0.11	0.05	0.09	0.05
	Atherosclerosis	-0.07	-0.10	0.01	-0.08	-0.07	-0.01	-0.08	-0.10	0.03
R^2	0.47	0.66	0.74	0.48	0.67	0.67	0.41	0.62	0.68	

Bold denotes $P < 0.05$. TIV: total intracranial volume. ADNP: Alzheimer's disease neuropathology. HS: Hippocampal Sclerosis. CAA: Cerebral amyloid angiopathy. IR: inversion recovery. MPRAGE: magnetization-prepared rapid gradient echo.

Supplementary Table 4. Comparison of semi-partial correlation coefficients for hippocampal volumes estimated using different neuroimaging pipelines in NACC data (N=120).

Variables		Hippocampus		
		VBM	FS	ASHS
Demographic	Dementia Status at MRI	-0.28	-0.25	-0.21
	Age	-0.27	-0.23	-0.15
	Sex	0.05	0.05	0.08
	Years Education	0.08	0.09	0.16
	Years MRI to Death	0.12	0.07	0.06
	TIV	0.22	0.30	0.26
Pathology	ADNP	-0.06	-0.07	-0.03
	HS	-0.32	-0.27	-0.29
	Lewy Bodies	-0.05	-0.01	-0.04
	CAA	-0.06	-0.01	-0.02
	Atherosclerosis	-0.06	-0.02	-0.06
R ²	0.45	0.45	0.37	

Bold denotes $P < 0.05$. TIV: total intracranial volume. ADNP: Alzheimer's Disease Neuropathology. HS: Hippocampal Sclerosis. CAA: Cerebral Amyloid Angiopathy. VBM: Voxel-Based Morphometry estimate from Computational Anatomy Toolbox (CAT12). FS: FreeSurfer Hippocampal Subfield Segmentation. ASHS: Automatic Segmentation of Hippocampal Subfields T1w.

Supplementary Table 5. Comparison of NACC (N=129) and ADNI (N=49) semi-partial correlation coefficients for ROI volumes across the various demographic and neuropathological measures, with dichotomized Braak stages instead of ADNP included in the model.

Variables	Dichotomized by Braak Stage V/VI		Hippocampus Semi-Part. Corr.		Amygdala Semi-Part. Corr.		Parahippocampus Semi-Part. Corr.	
	NACC	ADNI	NACC	ADNI	NACC	ADNI	NACC	ADNI
Dementia	-0.35	-0.37	-0.33	-0.23	-0.31	-0.36		
Age	-0.37	0.11	-0.32	0.12	-0.34	0.11		
TIV	0.28	0.21	0.37	0.15	0.33	0.05		
Braak V/VI	-0.04	-0.17	-0.08	-0.25	-0.08	-0.27		
HS	-0.28	-0.46	-0.18	-0.26	-0.17	-0.33		
Lewy Bodies	-0.04	-0.26	-0.16	-0.24	-0.07	-0.20		
R ²	0.43	0.43	0.42	0.26	0.38	0.37		

Variables	Dichotomized by Braak Stage III/IV		Hippocampus Semi-Part. Corr.		Amygdala Semi-Part. Corr.		Parahippocampus Semi-Part. Corr.	
	NACC	ADNI	NACC	ADNI	NACC	ADNI	NACC	ADNI
Dementia	-0.35	-0.39	-0.34	-0.26	-0.33	-0.39		
Age	-0.37	0.13	-0.33	0.15	-0.34	0.13		
TIV	0.28	0.22	0.37	0.16	0.33	0.07		
Braak III/IV/V/VI	-0.06	-0.10	-0.07	-0.21	-0.03	-0.20		
HS	-0.28	-0.47	-0.18	-0.28	-0.17	-0.35		
Lewy Bodies	-0.04	-0.27	-0.16	-0.26	-0.06	-0.21		
R ²	0.43	0.41	0.42	0.24	0.38	0.33		

Bold denotes $P < 0.05$. TIV: total intracranial volume. HS: Hippocampal Sclerosis. Semi-Part. Corr.: semi-partial correlation coefficient.

Supplementary Table 6. Comparison of semi-partial correlation coefficients for HS, TDP-43, or both variables in the same model, for ADNI data (N=43).

<i>Variables</i>	<i>Hippocampus Semi-Part. Corr.</i>			<i>Amygdala Semi-Part. Corr.</i>			<i>Parahippocampus Semi-Part. Corr.</i>		
	<i>HS</i>	<i>TDP-43</i>	<i>Both</i>	<i>HS</i>	<i>TDP-43</i>	<i>Both</i>	<i>HS</i>	<i>TDP-43</i>	<i>Both</i>
<i>Dementia</i>	-0.35	-0.27	-0.32	-0.21	-0.16	-0.19	-0.33	-0.28	-0.32
<i>Age</i>	0.08	-0.01	0.07	0.18	0.13	0.17	0.15	0.09	0.15
<i>TIV</i>	0.23	0.19	0.24	0.20	0.18	0.21	0.11	0.07	0.11
<i>ADNP</i>	-0.15	-0.18	-0.17	-0.13	-0.16	-0.15	-0.15	-0.17	-0.16
<i>HS</i>	-0.49		-0.41	-0.29		-0.24	-0.36		-0.31
<i>TDP-43 Hipp.</i>		-0.30	-0.14		-0.20	-0.10		-0.20	-0.08
<i>Lewy Bodies</i>	-0.26	-0.14	-0.26	-0.28	-0.22	-0.28	-0.23	-0.14	-0.23
<i>Adjusted R²</i>	0.33	0.15	0.33	0.12	0.06	0.10	0.21	0.11	0.20

Bold denotes P<0.05. TIV: total intracranial volume. ADNP: Alzheimer's Disease Neuropathology. HS: Hippocampal Sclerosis. Semi-Part. Corr.: semi-partial correlation coefficient. TDP-43: TAR DNA-binding protein 43. Hipp.: Hippocampus.