Supplementary Tables

Supplementary Table 1. Neuropathological characteristics by primary neuropathological group

	NSNC[a] N = 150[1]	ADNC[b] N = 844[1]	NSNC/ADNC[c] N = 549[1]	p-value[2]	q-value[3]
Hippocampal Sclerosis				0.3	0.4
None	132 (90%)	702 (85%)	465 (87%)		
Yes	15 (10%)	122 (15%)	72 (13%)		
Braak Stages				<0.001	<0.001
Stage 0-II	103 (69%)[b,c]	0 (0%)[a,c]	0 (0%)[a,b]		
Stage III-IV	43 (29%)[b,c]	362 (43%)[a,c]	179 (33%)[a,b]		
Stage V-VI	4 (2.7%)[b,c]	482 (57%)[a,c]	370 (67%)[a,b]		
Cerad Scores				0.002	0.003
No-Sparse	0 (0%)[c]	0 (0%)[c]	0 (0%)[a,b]		
Moderate	12 (63%)[c]	273 (40%)[c]	149 (33%)[a,b]		
Frequent	7 (37%)[c]	404 (60%)[c]	309 (67%)[a,b]		
Thal phase				<0.001	<0.001
Phase 0-1	77 (51%)	9 (1.1%)	3 (0.5%)		
Phase 2-3	47 (31%)	209 (25%)	107 (19%)		
Phase 4-5	26 (17%)	626 (74%)	439 (80%)		
NSNC					
No NSNC	0 (0%)[b,c]	841 (100%)[a,c]	0 (0%)[a,b]		
Amygdala predominant	10 (6.7%)[b,c]	0 (0%)[a,c]	157 (29%)[a,b]		
Brainstem predominant	39 (26%)[b,c]	0 (0%)[a,c]	64 (12%)[a,b]		
Limbic (transitional)	47 (31%)[b,c]	0 (0%)[a,c]	133 (24%)[a,b]		
Olfactory bulb	6 (4.0%)[b,c]	0 (0%)[a,c]	29 (5.3%)[a,b]		
Neocortical (diffuse)	48 (32%)[b,c]	0 (0%)[a,c]	166 (30%)[a,b]		
Vascular Pathology				0.5	0.5
No	2 (1.3%)	7 (0.8%)	3 (0.5%)		
One or more vascular pathology	147 (99%)	836 (99%)	546 (99%)		
Cerebral Amyloid Angiopathy				<0.001	<0.001
None	97 (65%)[b,c]	225 (27%)[a]	117 (21%)[a]		
Mild	33 (22%)[b,c]	322 (38%)[a]	205 (37%)[a]		

	NSNC[a] N = 150[1]	ADNC[b] N = 844[1]	NSNC/ADNC[c] N = 549[1]	p-value[2]	q-value[3]
Moderate	14 (9.3%)[b,c]	184 (22%)[a]	139 (25%)[a]		
LATE Stage				<0.001	<0.001
No LATE	79 (71%)[b,c]	332 (60%)[a,c]	176 (44%)[a,b]		
Stage 1	7 (6.3%)[b,c]	49 (8.9%)[a,c]	56 (14%)[a,b]		
Stage 2	23 (21%)[b,c]	126 (23%)[a,c]	129 (32%)[a,b]		
Stage 3	2 (1.8%)[b,c]	42 (7.7%)[a,c]	37 (9.3%)[a,b]		
PART					
No PART	59 (39%)	844 (100%)	549 (100%)		
Possible PART	55 (37%)	0 (0%)	0 (0%)		
Definite PART	36 (24%)	0 (0%)	0 (0%)		

[1] Values are n (%) among participants with available data.

[2] Pearson's Chi-squared test; Fisher's exact test; NA

[3] False discovery rate correction for multiple testing

Superscript letters indicate significant pairwise differences after FDR correction: [a] differs from NSNC; [b] differs from ADNC; [c] differs from NSNC/ADNC.

Footnote: Values are n/N (%) among participants with available data. Overall between-group comparisons were performed only for neuropathological features not used to define the primary neuropathological groups, using Pearson's χ^2 or Fisher's exact test, as appropriate. Overall p values were adjusted across variables using the Benjamini–Hochberg false discovery rate procedure. When the overall comparison was significant, pairwise comparisons were performed and the corresponding p values were adjusted for multiple testing. Superscript letters indicate significant FDR-adjusted pairwise differences ($q<0.05$): [a] versus NSNC; [b] versus ADNC; and [c] versus NSNC/ADNC. No inferential comparisons were performed for neuropathological variables used to define ADNC or NSNC status.

Abbreviations: ADNC, Alzheimer's disease neuropathologic change; CAA, cerebral amyloid angiopathy; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; FDR, false discovery rate; LATE-NC, limbic-predominant age-related TDP-43 encephalopathy neuropathologic change; NSNC, neuronal α-synuclein neuropathologic change; PART, primary age-related tauopathy.

Supplementary Table 2. First-visit demographic and clinical characteristics by neuropathological group and cognitive status

	NSNC		ADNC		NSNC/ADNC	
	Not MCI N = 931	**MCI N = 571**	**Not MCI N = 4851**	**MCI N = 3591**	**Not MCI N = 2531**	**MCI N = 2961**
Age	78 (7)[b3]	76 (8)[b3]	80 (7)[ab3]	76 (8)[ab3]	78 (7)[ab3]	74 (8)[ab3]
Sex (Female)	48 (52%)[b1]	19 (33%)	319 (66%)[ab1]	165 (46%)[a]	145 (57%)[ab1]	111 (38%)[a]
Education	17 (3)[b1]	16 (3)	16 (3)[b1]	16 (3)	16 (3)[b1]	16 (3)
APOE ε4 carrier status	11 (13%)[b1b2]	11 (21%)[b1b2]	177 (38%)[ab1b2]	179 (54%)[ab1b2]	109 (44%)[ab1b2]	169 (62%)[ab1b2]
MMSE	29 (1)[a]	28 (2)[a]	29 (1)[a]	27 (3)[a]	29 (1)[a]	27 (3)[a]
CDR Sum of Boxes	0.17 (0.48)[a]	1.55 (1.18)[a]	0.19 (0.48)[a]	1.58 (1.16)[a]	0.17 (0.46)[a]	1.68 (1.23)[a]
NPS+	18 (19%)[a]	29 (51%)[a]	89 (18%)[a]	154 (43%)[a]	36 (14%)[a]	134 (45%)[a]
MOTOR+	27 (31%)[ab1b2]	26 (57%)[ab1b2]	70 (16%)[b1b2]	61 (20%)[b1b2]	38 (16%)[b1b2]	54 (21%)[b1b2]
Number of visits	7 (3)[a]	6 (3)[a]	7 (3)[a]	5 (3)[a]	8 (3)[a]	5 (2)[a]
Follow-up time (years)	6.9 (3.7)[a]	4.9 (3.0)[a]	6.9 (3.4)[a]	4.7 (3.0)[a]	7.0 (3.4)[a]	4.5 (2.8)[a]
Time from last visit to death (years)	3.16 (2.96)[b3]	3.25 (2.83)	3.22 (2.86)[b3]	3.33 (2.60)	3.76 (3.05)[b3]	3.58 (2.66)
Substantia Nigra Hypopigmentation						
None	38 (42%)[b1b3]	15 (27%)[b1b3]	329 (69%)[ab1b3]	204 (61%)[ab1b3]	130 (53%)[ab1b3]	101 (37%)[ab1b3]
Mild	24 (26%)	16 (29%)	117 (24%)	87 (26%)	69 (28%)	96 (35%)
Moderate	16 (18%)	13 (24%)	26 (5.4%)	36 (11%)	34 (14%)	53 (19%)
Severe	13 (14%)	11 (20%)	6 (1.3%)	5 (1.5%)	14 (5.7%)	25 (9.1%)
Reported use of Antiparkinson agents						
Not reported	79 (85%)[b1b2]	44 (79%)[b1b2]	474 (98%)[b1b2]	348 (97%)[b1b2]	242 (96%)[b1b2]	283 (96%)[b1b2]
Reported	14 (15%)	12 (21%)	10 (2.1%)	9 (2.5%)	10 (4.0%)	11 (3.7%)

[1] Mean (SD); n (%)

[2] Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test

[3] False discovery rate correction for multiple testing

Superscripts indicate FDR-adjusted q < 0.05. [a] Not MCI vs MCI within the same pathological group; [b1] NSNC vs ADNC within the same cognitive stage; [b2] NSNC vs NSNC/ADNC within the same cognitive stage; [b3] ADNC vs NSNC/ADNC within the same cognitive stage; [c] global between-group difference in the overall sample.

Footnotes: Values are mean (SD) or n (%), unless otherwise indicated. Cognitive status was assigned at the first available visit. Not MCI includes participants classified in NACC as cognitively normal or impaired-not-MCI; MCI indicates mild cognitive impairment. Within-group comparisons between Not MCI and MCI used Wilcoxon rank-sum tests for continuous variables and Pearson's χ^2 or Fisher's exact tests for categorical variables, as

appropriate. Between-group comparisons across neuropathological groups used Kruskal–Wallis tests for continuous variables and Pearson's χ^2 or Fisher's exact tests for categorical variables. P values were adjusted for multiple comparisons using the Benjamini–Hochberg false discovery rate procedure. Superscripts indicate FDR-adjusted $q < 0.05$: [a] Not MCI versus MCI within the same neuropathological group; [b1] NSNC versus ADNC within the same cognitive stratum; [b2] NSNC versus NSNC/ADNC within the same cognitive stratum; [b3] ADNC versus NSNC/ADNC within the same cognitive stratum; [c] global between-group difference across neuropathological groups in the overall sample.

Abbreviations: ADNC, Alzheimer's disease neuropathologic change; APOE, apolipoprotein E; CDR-SB, Clinical Dementia Rating Sum of Boxes; FDR, false discovery rate; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; NACC, National Alzheimer's Coordinating Center; NPI, Neuropsychiatric Inventory; NSNC, neuronal α-synuclein neuropathologic change; SD, standard deviation; UPDRS-III, Unified Parkinson's Disease Rating Scale Part III.

Supplementary Table 3. Linear mixed-effects model of longitudinal change in the Cognitive Summary Score (CSS)

	β	SE	95% CI low	95% CI high	t-value	p-value
Intercept	2.822	0.419	2.001	3.643	6.740	<0.001
Age at First Visit	−0.026	0.004	−0.034	−0.017	−5.872	<0.001
Male	−0.309	0.069	−0.444	−0.174	−4.484	<0.001
Education	0.107	0.012	0.084	0.130	9.253	<0.001
Time	−0.170	0.032	−0.232	−0.108	−5.364	<0.001
ADNC	−0.312	0.145	−0.596	−0.028	−2.159	0.031
NSNC/ADNC	−0.113	0.155	−0.416	0.191	−0.729	0.466
MCI at First Visit	−1.626	0.216	−2.050	−1.202	−7.529	<0.001
Time x ADNC	−0.110	0.035	−0.178	−0.042	−3.187	0.001
Time x NSNC/ADNC	−0.172	0.037	−0.244	−0.100	−4.656	<0.001
Time x MCI at First Visit	−0.138	0.054	−0.245	−0.032	−2.542	0.011
ADNC x MCI at First Visit	−0.035	0.233	−0.493	0.423	−0.150	0.880
NSNC/ADNC x MCI at First Visit	−0.155	0.242	−0.629	0.320	−0.640	0.523
Time x ADNC x MCI at First Visit	−0.111	0.059	−0.227	0.004	−1.890	0.059
Time x NSNC/ADNC x MCI at First Visit	−0.128	0.061	−0.248	−0.009	−2.105	0.036

Footnote: Linear mixed-effects model estimating longitudinal change in the Cognitive Summary Score (CSS). Time was modeled continuously as years from the first neuropsychological assessment. The model included fixed effects for time, age at first visit, sex, education, neuropathological group, and cognitive status at first visit, together with all two-way and three-way interactions among time, neuropathological group, and first-visit cognitive status. Participant-specific random intercepts and random slopes for time were included. Reference categories were NSNC, female sex, and no MCI at first visit. The coefficient for time represents the annual change in CSS in the reference group. Neuropathological-group coefficients represent differences from NSNC at the first visit among participants without MCI, whereas interaction terms indicate additional differences relative to their corresponding reference categories. Negative β coefficients for time or time interactions indicate a greater longitudinal decline in CSS.

Abbreviations: ADNC, Alzheimer's Disease Neuropathologic Change; β, beta coefficient; CI, confidence interval; CSS, Cognitive Summary Score; MCI, mild cognitive impairment; NSNC, neuronal α-synuclein neuropathologic change; NSNC/ADNC, neuronal α-synuclein neuropathologic change with concomitant Alzheimer's Disease Neuropathologic Change; SE, standard error.

Supplementary Table 4. Linear mixed-effects model of longitudinal change in the FAQ Scores

	β	SE	95% CI low	95% CI high	t-value	p-value
Intercept	4.006	1.577	0.911	7.101	2.540	0.011
Age at First Visit	−0.041	0.017	−0.073	−0.008	−2.466	0.014
Male	0.078	0.257	−0.425	0.582	0.305	0.761
Education	−0.072	0.043	−0.156	0.013	−1.659	0.097
Time	0.706	0.180	0.353	1.060	3.924	<0.001
ADNC	0.013	0.516	−0.998	1.025	0.026	0.979
NSNC/ADNC	−0.646	0.552	−1.729	0.436	−1.171	0.242
MCI at First Visit	3.060	0.831	1.430	4.690	3.684	<0.001
Time x ADNC	0.288	0.196	−0.097	0.674	1.469	0.142
Time x NSNC/ADNC	0.520	0.210	0.107	0.933	2.471	0.014
Time x MCI at First Visit	0.834	0.330	0.186	1.481	2.526	0.012
ADNC x MCI at First Visit	1.026	0.895	−0.731	2.783	1.146	0.252
NSNC/ADNC x MCI at First Visit	1.989	0.931	0.163	3.816	2.137	0.033
Time x ADNC x MCI at First Visit	0.973	0.356	0.275	1.670	2.735	0.006
Time x NSNC/ADNC x MCI at First Visit	1.053	0.369	0.329	1.778	2.852	0.004

Footnote: Linear mixed-effects model estimating longitudinal change in the FAQ Score. Time was modeled continuously as years from the first neuropsychological assessment. The model included fixed effects for time, age at first visit, sex, education, neuropathological group, and cognitive status at first visit, together with all two-way and three-way interactions among time, neuropathological group, and first-visit cognitive status. Participant-specific random intercepts and random slopes for time were included. Reference categories were NSNC, female sex, and no MCI at first visit. The coefficient for time represents the annual change in FAQ Score in the reference group. Neuropathological-group coefficients represent differences from NSNC at the first visit among participants without MCI, whereas interaction terms indicate additional differences relative to their corresponding reference categories. Positive β coefficients for time or time interactions indicate a greater longitudinal increase in FAQ scores and therefore greater functional worsening

Abbreviations: FAQ, Functional Activities Questionnaire; ADNC, Alzheimer's Disease Neuropathologic Change; β, beta coefficient; CI, confidence interval; MCI, mild cognitive impairment; NSD, neuronal α-synuclein disease; NSNC, neuronal α-synuclein neuropathologic change; NSNC/ADNC, neuronal α-synuclein neuropathologic change with concomitant Alzheimer's Disease Neuropathologic Change; SE, standard error.

Supplementary Table 5. Linear mixed-effects model of longitudinal change in the UPDRS-III Scores

	β	SE	95% CI low	95% CI high	t-value	p-value
Intercept	−4.787	2.813	−10.305	0.730	−1.702	0.089
Age at First Visit	0.152	0.029	0.094	0.210	5.156	<0.001
Male	1.038	0.463	0.130	1.946	2.242	0.025
Education	−0.013	0.077	−0.165	0.139	−0.170	0.865
Time	1.544	0.246	1.061	2.026	6.280	<0.001
ADNC	−4.373	0.972	−6.281	−2.466	−4.498	<0.001
NSNC/ADNC	−4.651	1.037	−6.685	−2.616	−4.485	<0.001
MCI at First Visit	4.607	1.514	1.637	7.577	3.043	0.002
Time x ADNC	−0.675	0.267	−1.199	−0.150	−2.525	0.012
Time x NSNC/ADNC	−0.435	0.286	−0.997	0.126	−1.522	0.129
Time x MCI at First Visit	−0.121	0.436	−0.977	0.735	−0.278	0.781
ADNC x MCI at First Visit	−3.634	1.630	−6.832	−0.436	−2.229	0.026
NSNC/ADNC x MCI at First Visit	−2.503	1.684	−5.806	0.801	−1.486	0.137
Time x ADNC x MCI at First Visit	0.456	0.473	−0.473	1.384	0.964	0.336
Time x NSNC/ADNC x MCI at First Visit	0.475	0.489	−0.485	1.435	0.972	0.332

Footnote: Linear mixed-effects model estimating longitudinal change in the UPDRS-III Score. Time was modeled continuously as years from the first neuropsychological assessment. The model included fixed effects for time, age at first visit, sex, education, neuropathological group, and cognitive status at first visit, together with all two-way and three-way interactions among time, neuropathological group, and first-visit cognitive status. Participant-specific random intercepts and random slopes for time were included. Reference categories were NSNC, female sex, and no MCI at first visit. The coefficient for time represents the annual change in UPDRS-III in the reference group. Neuropathological-group coefficients represent differences from NSNC at the first visit among participants without MCI, whereas interaction terms indicate additional differences relative to their corresponding reference categories. Positive β coefficients for time or time interactions indicate a greater longitudinal increase in UPDRS-III scores and, therefore, greater motor worsening relative to the reference category.

Abbreviations: UPDRS-III, Unified Parkinson's Disease Rating Scale Part III (Motor Examination); ADNC, Alzheimer's Disease Neuropathologic Change; β, beta coefficient; CI, confidence interval; MCI, mild cognitive impairment; NSNC, neuronal α-synuclein neuropathologic change; NSNC/ADNC, neuronal α-synuclein neuropathologic change with concomitant Alzheimer's Disease Neuropathologic Change; SE, standard error.

Supplementary Table 6. Linear mixed-effects model of longitudinal change in the NSD related Neuropsychiatric Changes Scores

	β	SE	95% CI low	95% CI high	t-value	p-value
Intercept	3.474	0.502	2.489	4.458	6.923	<0.001
Age at First Visit	−0.032	0.005	−0.042	−0.022	−6.097	<0.001
Male	0.190	0.082	0.030	0.350	2.332	0.020
Education	−0.026	0.014	−0.053	0.001	−1.897	0.058
Time	0.095	0.032	0.031	0.158	2.918	0.004
ADNC	−0.031	0.186	−0.396	0.335	−0.165	0.869
NSNC/ADNC	−0.086	0.199	−0.476	0.305	−0.430	0.667
MCI at First Visit	1.435	0.279	0.888	1.983	5.140	<0.001
Time x ADNC	0.036	0.035	−0.033	0.105	1.020	0.308
Time x NSNC/ADNC	0.055	0.038	−0.019	0.129	1.458	0.145
Time x MCI at First Visit	0.072	0.059	−0.045	0.188	1.211	0.226
ADNC x MCI at First Visit	−0.555	0.302	−1.148	0.037	−1.839	0.066
NSNC/ADNC x MCI at First Visit	−0.338	0.313	−0.952	0.276	−1.081	0.280
Time x ADNC x MCI at First Visit	−0.014	0.064	−0.140	0.113	−0.216	0.829
Time x NSNC/ADNC x MCI at First Visit	0.006	0.067	−0.125	0.137	0.092	0.926

Footnote: Linear mixed-effects model estimating longitudinal change in the NSD related Neuropsychiatric Changes Score. Time was modeled continuously as years from the first neuropsychological assessment. The model included fixed effects for time, age at first visit, sex, education, neuropathological group, and cognitive status at first visit, together with all two-way and three-way interactions among time, neuropathological group, and first-visit cognitive status. Participant-specific random intercepts and random slopes for time were included. Reference categories were NSNC, female sex, and no MCI at first visit. The coefficient for time represents the annual change in NSD related Neuropsychiatric Changes Score in the reference group. Neuropathological-group coefficients represent differences from NSNC at the first visit among participants without MCI, whereas interaction terms indicate additional differences relative to their corresponding reference categories. Positive β coefficients for time or time interactions indicate a greater longitudinal increase in the NSD-related neuropsychiatric changes score.

Abbreviations: ADNC, Alzheimer's Disease Neuropathologic Change; β, beta coefficient; CI, confidence interval; MCI, mild cognitive impairment; NSD, neuronal α-synuclein disease; NSNC, neuronal α-synuclein neuropathologic change; NSNC/ADNC, neuronal α-synuclein neuropathologic change with concomitant Alzheimer's Disease Neuropathologic Change; SE, standard error.

Supplementary Table 7. Linear mixed-effects model of longitudinal change in memory

	β	SE	95% CI low	95% CI high	t-value	p-value
Intercept	0.335	0.180	−0.018	0.688	1.862	0.063
Age at First Visit	0.000	0.002	−0.003	0.004	0.137	0.891
Male	−0.113	0.030	−0.171	−0.055	−3.827	<0.001
Education	0.032	0.005	0.022	0.042	6.405	<0.001
Time	−0.026	0.013	−0.051	−0.001	−2.053	0.040
ADNC	−0.033	0.063	−0.156	0.090	−0.531	0.596
NSNC/ADNC	−0.007	0.067	−0.138	0.124	−0.103	0.918
MCI at First Visit	−0.485	0.094	−0.669	−0.301	−5.175	<0.001
Time x ADNC	−0.065	0.014	−0.092	−0.038	−4.745	<0.001
Time x NSNC/ADNC	−0.084	0.015	−0.113	−0.055	−5.732	<0.001
Time x MCI at First Visit	−0.061	0.022	−0.105	−0.018	−2.771	0.006
ADNC x MCI at First Visit	−0.247	0.101	−0.445	−0.048	−2.434	0.015
NSNC/ADNC x MCI at First Visit	−0.357	0.105	−0.563	−0.151	−3.402	<0.001
Time x ADNC x MCI at First Visit	−0.017	0.024	−0.064	0.030	−0.698	0.485
Time x NSNC/ADNC x MCI at First Visit	−0.017	0.025	−0.065	0.032	−0.677	0.499

Footnote: Linear mixed-effects model estimating longitudinal change in the Memory Score . Time was modeled continuously as years from the first neuropsychological assessment. The model included fixed effects for time, age at first visit, sex, education, neuropathological group, and cognitive status at first visit, together with all two-way and three-way interactions among time, neuropathological group, and first-visit cognitive status. Participant-specific random intercepts and random slopes for time were included. Reference categories were NSNC, female sex, and no MCI at first visit. The coefficient for time represents the annual change in Memory in the reference group. Neuropathological-group coefficients represent differences from NSNC at the first visit among participants without MCI, whereas interaction terms indicate additional differences relative to their corresponding reference categories. Negative β coefficients for time or time interactions indicate a greater longitudinal decline in Memory.

Abbreviations: ADNC, Alzheimer's Disease Neuropathologic Change; β, beta coefficient; CI, confidence interval; MCI, mild cognitive impairment; NSNC, neuronal α-synuclein neuropathologic change; NSNC/ADNC, neuronal α-synuclein neuropathologic change with concomitant Alzheimer's Disease Neuropathologic Change; SE, standard error.

Supplementary Table 8. Linear mixed-effects model of longitudinal change in language

	β	SE	95% CI low	95% CI high	t-value	p-value
Intercept	1.069	0.172	0.732	1.407	6.219	<0.001
Age at First Visit	−0.009	0.002	−0.012	−0.005	−4.913	<0.001
Male	−0.107	0.028	−0.162	−0.051	−3.781	<0.001
Education	0.031	0.005	0.022	0.041	6.592	<0.001
Time	−0.058	0.011	−0.080	−0.036	−5.200	<0.001
ADNC	−0.139	0.060	−0.257	−0.021	−2.310	0.021
NSNC/ADNC	−0.089	0.064	−0.215	0.037	−1.383	0.167
MCI at First Visit	−0.557	0.090	−0.734	−0.381	−6.206	<0.001
Time x ADNC	−0.033	0.012	−0.057	−0.009	−2.704	0.007
Time x NSNC/ADNC	−0.049	0.013	−0.075	−0.024	−3.768	<0.001
Time x MCI at First Visit	−0.037	0.020	−0.076	0.001	−1.901	0.058
ADNC x MCI at First Visit	0.066	0.097	−0.125	0.256	0.676	0.499
NSNC/ADNC x MCI at First Visit	0.111	0.101	−0.086	0.308	1.102	0.271
Time x ADNC x MCI at First Visit	−0.041	0.021	−0.083	0.000	−1.939	0.053
Time x NSNC/ADNC x MCI at First Visit	−0.046	0.022	−0.089	−0.003	−2.077	0.038

Footnote: Linear mixed-effects model estimating longitudinal change in the Language Score. Time was modeled continuously as years from the first neuropsychological assessment. The model included fixed effects for time, age at first visit, sex, education, neuropathological group, and cognitive status at first visit, together with all two-way and three-way interactions among time, neuropathological group, and first-visit cognitive status. Participant-specific random intercepts and random slopes for time were included. Reference categories were NSNC, female sex, and no MCI at first visit. The coefficient for time represents the annual change in Language in the reference group. Neuropathological-group coefficients represent differences from NSNC at the first visit among participants without MCI, whereas interaction terms indicate additional differences relative to their corresponding reference categories. Negative β coefficients for time or time interactions indicate a greater longitudinal decline in Language.

Abbreviations: ADNC, Alzheimer's Disease Neuropathologic Change; β, beta coefficient; CI, confidence interval; MCI, mild cognitive impairment; NSNC, neuronal α-synuclein neuropathologic change; NSNC/ADNC, neuronal α-synuclein neuropathologic change with concomitant Alzheimer's Disease Neuropathologic Change; SE, standard error.

Supplementary Table 9. Linear mixed-effects model of longitudinal change in executive functions

	β	SE	95% CI low	95% CI high	t-value	p-value
Intercept	1.026	0.190	0.653	1.399	5.392	<0.001
Age at First Visit	−0.011	0.002	−0.015	−0.007	−5.498	<0.001
Male	−0.073	0.031	−0.134	−0.011	−2.317	0.021
Education	0.038	0.005	0.027	0.048	7.153	<0.001
Time	−0.084	0.011	−0.106	−0.062	−7.486	<0.001
ADNC	−0.160	0.066	−0.290	−0.030	−2.407	0.016
NSNC/ADNC	−0.037	0.071	−0.176	0.102	−0.517	0.605
MCI at First Visit	−0.598	0.099	−0.792	−0.404	−6.039	<0.001
Time x ADNC	−0.008	0.012	−0.032	0.016	−0.619	0.536
Time x NSNC/ADNC	−0.029	0.013	−0.055	−0.004	−2.232	0.026
Time x MCI at First Visit	−0.021	0.020	−0.060	0.017	−1.078	0.281
ADNC x MCI at First Visit	0.159	0.107	−0.051	0.369	1.488	0.137
NSNC/ADNC x MCI at First Visit	0.121	0.111	−0.096	0.339	1.095	0.274
Time x ADNC x MCI at First Visit	−0.051	0.021	−0.093	−0.009	−2.389	0.017
Time x NSNC/ADNC x MCI at First Visit	−0.073	0.022	−0.116	−0.030	−3.313	<0.001

Footnote: Linear mixed-effects model estimating longitudinal change in the Executive Functions Score. Time was modeled continuously as years from the first neuropsychological assessment. The model included fixed effects for time, age at first visit, sex, education, neuropathological group, and cognitive status at first visit, together with all two-way and three-way interactions among time, neuropathological group, and first-visit cognitive status. Participant-specific random intercepts and random slopes for time were included. Reference categories were NSNC, female sex, and no MCI at first visit. The coefficient for time represents the annual change in Executive Functions in the reference group. Neuropathological-group coefficients represent differences from NSNC at the first visit among participants without MCI, whereas interaction terms indicate additional differences relative to their corresponding reference categories. Negative β coefficients for time or time interactions indicate a greater longitudinal decline in Executive Functions.

Abbreviations: ADNC, Alzheimer's Disease Neuropathologic Change; β, beta coefficient; CI, confidence interval; MCI, mild cognitive impairment; NSNC, neuronal α-synuclein neuropathologic change; NSNC/ADNC, neuronal α-synuclein neuropathologic change with concomitant Alzheimer's Disease Neuropathologic Change; SE, standard error.

Supplementary Table 10. Linear mixed-effects model of longitudinal motor function trajectories according to Lewy-type α-synuclein stage, concomitant ADNC, and baseline cognitive status

Term	β	SE	95% CI low	95% CI high	t	p-value
(Intercept)	−2.133	3.666	−9.326	5.060	−0.582	0.561
Age	0.173	0.032	0.110	0.237	5.361	<0.001
Male	0.886	0.507	−0.108	1.880	1.748	0.081
Education	−0.002	0.085	−0.168	0.165	−0.020	0.984
Time	1.676	0.609	0.480	2.872	2.752	0.006
Brainstem predominant	−7.808	2.741	−13.185	−2.430	−2.849	0.004
Limbic (transitional)	−3.832	2.635	−9.003	1.339	−1.454	0.146
Neocortical (diffuse)	−0.439	1.117	−2.630	1.752	−0.393	0.694
ADNC	−8.862	2.134	−13.049	−4.676	−4.154	<0.001
MCI	2.006	3.061	−3.999	8.012	0.655	0.512
Time x Brainstem predominant	−0.728	0.777	−2.253	0.797	−0.937	0.349
Time x Limbic (transitional)	0.104	0.738	−1.346	1.554	0.141	0.888
Time x Neocortical (diffuse)	0.666	0.316	0.044	1.287	2.104	0.036
Time x ADNC	−0.807	0.599	−1.984	0.370	−1.346	0.179
Brainstem predominant x ADNC	8.852	3.019	2.928	14.775	2.932	0.003
Limbic (transitional) x ADNC	2.711	2.817	−2.817	8.238	0.962	0.336
Time x MCI	−1.661	0.927	−3.482	0.160	−1.791	0.074
Brainstem predominant x MCI	3.034	4.474	−5.745	11.812	0.678	0.498
Limbic (transitional) x MCI	−0.066	4.201	−8.309	8.176	−0.016	0.987
Neocortical (diffuse) x MCI	4.253	1.553	1.207	7.300	2.739	0.006
ADNC x MCI	−0.935	2.986	−6.793	4.923	−0.313	0.754
Time x Brainstem predominant x ADNC	1.055	0.857	−0.627	2.738	1.232	0.219
Time x Limbic (transitional)x ADNC	−0.034	0.784	−1.573	1.505	−0.043	0.965
Time x Brainstem predominant x MCI	1.456	1.339	−1.172	4.085	1.088	0.277
Time x Limbic (transitional) x MCI	1.992	1.222	−0.407	4.390	1.630	0.104
Time x Neocortical (diffuse) x MCI	0.442	0.481	−0.502	1.387	0.919	0.358
Time x ADNC x MCI	1.999	0.908	0.216	3.781	2.201	0.028
Brainstem predominant x ADNC x MCI	−3.738	5.025	−13.597	6.120	−0.744	0.457
Limbic (transitional) x ADNC x MCI	1.551	4.414	−7.110	10.212	0.351	0.725
Time x Brainstem predominant x ADNC x MCI	−1.938	1.525	−4.932	1.057	−1.270	0.204
Time x Limbic (transitional) x ADNC x MCI	−1.786	1.281	−4.301	0.728	−1.395	0.163

Footnote: Fixed-effect estimates were obtained from a linear mixed-effects model including the four-way interaction between time, Lewy-type α-synuclein distribution, concomitant ADNC, and baseline cognitive status.

The model was adjusted for age at baseline, sex, and education and included participant-specific random intercepts and slopes for time. Estimates represent differences in UPDRS-III score or annual rate of change according to the corresponding model term.
Abbreviations: ADNC, Alzheimer's disease neuropathologic change; CI, confidence interval; MCI, mild cognitive impairment; SE, standard error.

Supplementary Table 11. Linear mixed-effects model of longitudinal FAQ trajectories according to Lewy-type α-synuclein stage, concomitant ADNC, and baseline cognitive status

Term	β	SE	95% CI low	95% CI high	t	p-value
(Intercept)	4.364	2.004	0.432	8.296	2.178	0.030
Age	−0.043	0.018	−0.079	−0.008	−2.420	0.016
Male	0.131	0.276	−0.412	0.673	0.473	0.636
Education	−0.079	0.047	−0.170	0.012	−1.703	0.089
Time	0.506	0.441	−0.359	1.372	1.149	0.251
Brainstem predominant	0.105	1.433	−2.707	2.916	0.073	0.942
Limbic (transitional)	0.326	1.388	−2.398	3.049	0.235	0.814
Neocortical (diffuse)	−0.789	0.594	−1.955	0.378	−1.327	0.185
ADNC	−0.042	1.125	−2.251	2.167	−0.037	0.970
MCI	4.393	1.655	1.146	7.640	2.655	0.008
Time x Brainstem predominant	0.160	0.560	−0.939	1.260	0.286	0.775
Time x Limbic (transitional)	0.146	0.531	−0.897	1.189	0.275	0.783
Time x Neocortical (diffuse)	0.513	0.230	0.062	0.964	2.233	0.026
Time x ADNC	0.490	0.434	−0.361	1.341	1.129	0.259
Brainstem predominant x ADNC	−0.015	1.584	−3.124	3.094	−0.009	0.992
Limbic (transitional) x ADNC	−0.898	1.486	−3.815	2.019	−0.604	0.546
Time x MCI	0.700	0.658	−0.592	1.992	1.064	0.288
Brainstem predominant x MCI	−1.231	2.502	−6.141	3.679	−0.492	0.623
Limbic (transitional) x MCI	−3.969	2.266	−8.417	0.478	−1.751	0.080
Neocortical (diffuse) x MCI	0.701	0.861	−0.988	2.390	0.815	0.415
ADNC x MCI	−0.334	1.614	−3.502	2.834	−0.207	0.836
Time x Brainstem predominant x ADNC	−0.155	0.614	−1.361	1.051	−0.253	0.801
Time x Limbic (transitional)x ADNC	−0.277	0.569	−1.393	0.839	−0.487	0.626
Time x Brainstem predominant x MCI	−1.362	1.020	−3.363	0.639	−1.335	0.182
Time x Limbic (transitional) x MCI	0.262	0.893	−1.491	2.016	0.294	0.769
Time x Neocortical (diffuse) x MCI	0.229	0.350	−0.458	0.916	0.653	0.514
Time x ADNC x MCI	1.114	0.645	−0.151	2.379	1.729	0.084
Brainstem predominant x ADNC x MCI	−0.247	2.756	−5.654	5.160	−0.090	0.929
Limbic (transitional) x ADNC x MCI	4.569	2.392	−0.125	9.264	1.910	0.056
Time x Brainstem predominant x ADNC x MCI	2.079	1.138	−0.155	4.313	1.826	0.068
Time x Limbic (transitional) x ADNC x MCI	−0.258	0.939	−2.101	1.585	−0.275	0.783

Footnote: Fixed-effect estimates were obtained from a linear mixed-effects model including the four-way interaction between time, Lewy-type α-synuclein distribution, concomitant ADNC, and baseline cognitive status.

The model was adjusted for age at baseline, sex, and education and included participant-specific random intercepts and slopes for time. Estimates represent differences in FAQ score or annual rate of change according to the corresponding model term.
Abbreviations: ADNC, Alzheimer's disease neuropathologic change; CI, confidence interval; MCI, mild cognitive impairment; SE, standard error.

Supplementary Table 12. Linear mixed-effects model of longitudinal NSD-enriched neuropsychiatric trajectories according to Lewy-type α-synuclein stage, concomitant ADNC, and baseline cognitive status

Term	β	SE	95% CI low	95% CI high	t	p-value
(Intercept)	3.773	0.666	2.466	5.081	5.662	<0.001
Age	−0.033	0.006	−0.044	−0.021	−5.707	<0.001
Male	0.172	0.089	−0.002	0.347	1.935	0.053
Education	−0.033	0.015	−0.062	−0.004	−2.200	0.028
Time	0.144	0.078	−0.009	0.297	1.850	0.065
Brainstem predominant	0.298	0.524	−0.731	1.326	0.568	0.570
Limbic (transitional)	−0.325	0.501	−1.309	0.659	−0.649	0.517
Neocortical (diffuse)	−0.178	0.213	−0.596	0.241	−0.833	0.405
ADNC	−0.156	0.406	−0.953	0.641	−0.385	0.700
MCI	1.189	0.564	0.083	2.295	2.109	0.035
Time x Brainstem predominant	−0.140	0.101	−0.339	0.059	−1.382	0.167
Time x Limbic (transitional)	−0.063	0.093	−0.247	0.120	−0.676	0.499
Time x Neocortical (diffuse)	0.088	0.042	0.006	0.169	2.113	0.035
Time x ADNC	−0.014	0.077	−0.164	0.137	−0.177	0.859
Brainstem predominant x ADNC	−0.014	0.578	−1.147	1.119	−0.024	0.981
Limbic (transitional) x ADNC	0.097	0.539	−0.960	1.154	0.179	0.858
Time x MCI	−0.078	0.122	−0.317	0.161	−0.638	0.523
Brainstem predominant x MCI	−0.415	0.809	−2.002	1.171	−0.514	0.608
Limbic (transitional) x MCI	0.054	0.787	−1.491	1.599	0.068	0.946
Neocortical (diffuse) x MCI	0.690	0.291	0.120	1.260	2.374	0.018
ADNC x MCI	−0.308	0.550	−1.387	0.771	−0.560	0.576
Time x Brainstem predominant x ADNC	0.124	0.110	−0.092	0.340	1.129	0.260
Time x Limbic (transitional)x ADNC	0.033	0.099	−0.162	0.228	0.332	0.740
Time x Brainstem predominant x MCI	0.196	0.172	−0.142	0.534	1.141	0.254
Time x Limbic (transitional) x MCI	0.256	0.164	−0.065	0.577	1.566	0.118
Time x Neocortical (diffuse) x MCI	0.020	0.065	−0.108	0.148	0.309	0.757
Time x ADNC x MCI	0.136	0.119	−0.098	0.370	1.141	0.254
Brainstem predominant x ADNC x MCI	0.333	0.916	−1.464	2.130	0.364	0.716
Limbic (transitional) x ADNC x MCI	−0.077	0.831	−1.708	1.553	−0.093	0.926
Time x Brainstem predominant x ADNC x MCI	0.004	0.200	−0.389	0.397	0.020	0.984
Time x Limbic (transitional) x ADNC x MCI	−0.207	0.171	−0.543	0.130	−1.205	0.229

Footnote: Fixed-effect estimates were obtained from a linear mixed-effects model including the four-way interaction between time, Lewy-type α-synuclein distribution, concomitant ADNC, and baseline cognitive status.

The model was adjusted for age at baseline, sex, and education and included participant-specific random intercepts and slopes for time. Estimates represent differences in NSD enriched Neuropsychiatric Score or annual rate of change according to the corresponding model term.
Abbreviations: ADNC, Alzheimer's disease neuropathologic change; CI, confidence interval; MCI, mild cognitive impairment; SE, standard error.

Supplementary Table 13. Linear mixed-effects model of longitudinal Cognitive Summary Score (CSS) trajectories according to Lewy-type α-synuclein stage, concomitant ADNC, and baseline cognitive status

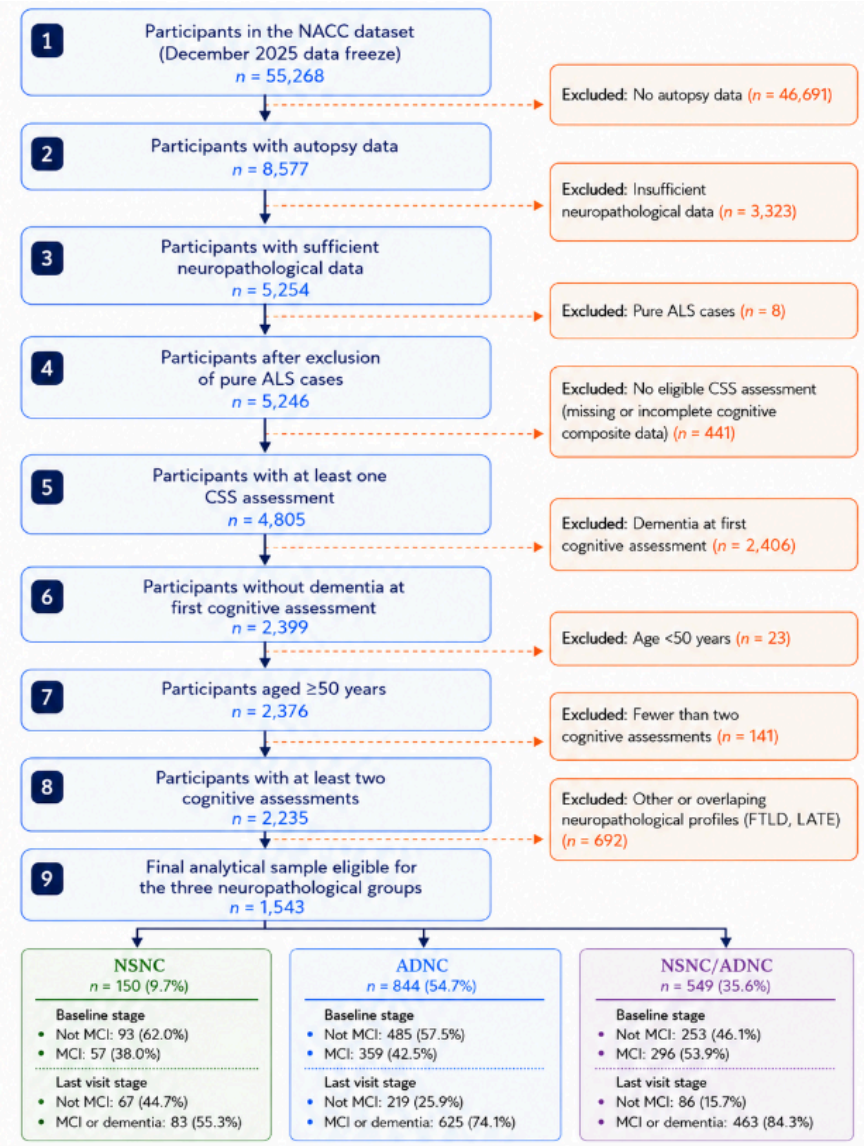
Term	β	SE	95% CI low	95% CI high	t	p-value
(Intercept)	3.128	0.541	2.067	4.188	5.786	<0.001
Age	−0.026	0.005	−0.035	−0.017	−5.487	<0.001
Male	−0.279	0.074	−0.425	−0.133	−3.753	<0.001
Education	0.101	0.013	0.076	0.125	8.038	<0.001
Time	−0.156	0.075	−0.303	−0.009	−2.080	0.038
Brainstem predominant	−0.428	0.404	−1.220	0.365	−1.059	0.290
Limbic (transitional)	−0.290	0.389	−1.052	0.473	−0.746	0.456
Neocortical (diffuse)	−0.001	0.163	−0.321	0.320	−0.005	0.996
ADNC	−0.505	0.315	−1.124	0.113	−1.602	0.109
MCI	−1.971	0.434	−2.821	−1.120	−4.544	<0.001
Time x Brainstem predominant	−0.024	0.097	−0.214	0.165	−0.254	0.800
Time x Limbic (transitional)	0.008	0.091	−0.171	0.186	0.084	0.933
Time x Neocortical (diffuse)	−0.121	0.039	−0.197	−0.045	−3.116	0.002
Time x ADNC	−0.125	0.074	−0.270	0.020	−1.696	0.090
Brainstem predominant x ADNC	0.919	0.446	0.043	1.794	2.059	0.040
Limbic (transitional) x ADNC	0.609	0.418	−0.210	1.428	1.458	0.145
Time x MCI	−0.116	0.109	−0.330	0.098	−1.060	0.289
Brainstem predominant x MCI	0.767	0.620	−0.450	1.983	1.237	0.216
Limbic (transitional) x MCI	0.507	0.601	−0.672	1.687	0.844	0.399
Neocortical (diffuse) x MCI	0.035	0.221	−0.398	0.468	0.158	0.875
ADNC x MCI	0.303	0.423	−0.526	1.133	0.717	0.473
Time x Brainstem predominant x ADNC	0.031	0.106	−0.177	0.240	0.297	0.767
Time x Limbic (transitional)x ADNC	−0.005	0.097	−0.196	0.186	−0.051	0.959
Time x Brainstem predominant x MCI	0.123	0.156	−0.184	0.430	0.788	0.431
Time x Limbic (transitional) x MCI	−0.026	0.148	−0.316	0.265	−0.174	0.862
Time x Neocortical (diffuse) x MCI	0.014	0.057	−0.097	0.125	0.253	0.800
Time x ADNC x MCI	−0.134	0.107	−0.344	0.075	−1.256	0.209
Brainstem predominant x ADNC x MCI	−0.752	0.699	−2.123	0.620	−1.075	0.283
Limbic (transitional) x ADNC x MCI	−0.910	0.635	−2.156	0.337	−1.432	0.153
Time x Brainstem predominant x ADNC x MCI	−0.196	0.178	−0.545	0.153	−1.103	0.270
Time x Limbic (transitional) x ADNC x MCI	0.034	0.156	−0.272	0.339	0.217	0.828

Footnote: Fixed-effect estimates were obtained from a linear mixed-effects model including the four-way interaction between time, Lewy-type α-synuclein distribution, concomitant ADNC, and baseline cognitive status.

The model was adjusted for age at baseline, sex, and education and included participant-specific random intercepts and slopes for time. Estimates represent differences in CSS or annual rate of change according to the corresponding model term.
Abbreviations: ADNC, Alzheimer's disease neuropathologic change; CI, confidence interval; MCI, mild cognitive impairment; SE, standard error.

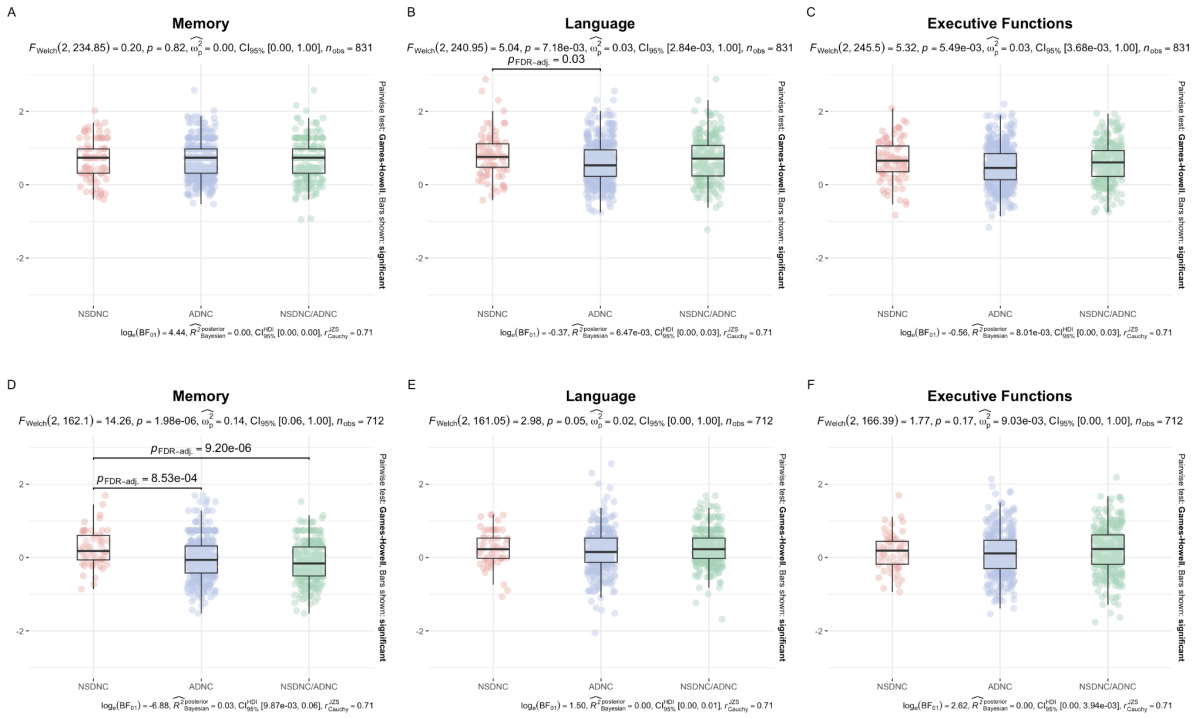
Supplementary Figures

Supplementary Figure 1. Flowchart of sample composition



Footnote: The flowchart summarizes participant selection from the National Alzheimer's Coordinating Center dataset using the December 2025 data freeze. Eligible participants had sufficient neuropathological data, at least one eligible Cognitive Summary Score assessment, no dementia at the first cognitive assessment, were aged ≥50 years, and had at least two cognitive assessments. Baseline stage corresponds to the first eligible cognitive assessment, whereas last-visit stage corresponds to the final available cognitive assessment. Percentages reported for the three neuropathological groups were calculated relative to the final analytical sample; baseline- and last-visit stage percentages were calculated within each neuropathological group.
Abbreviations: ADNC, Alzheimer's disease neuropathologic change; MCI, mild cognitive impairment; Not MCI, no mild cognitive impairment; NSNC, neuronal α-synuclein neuropathologic change.

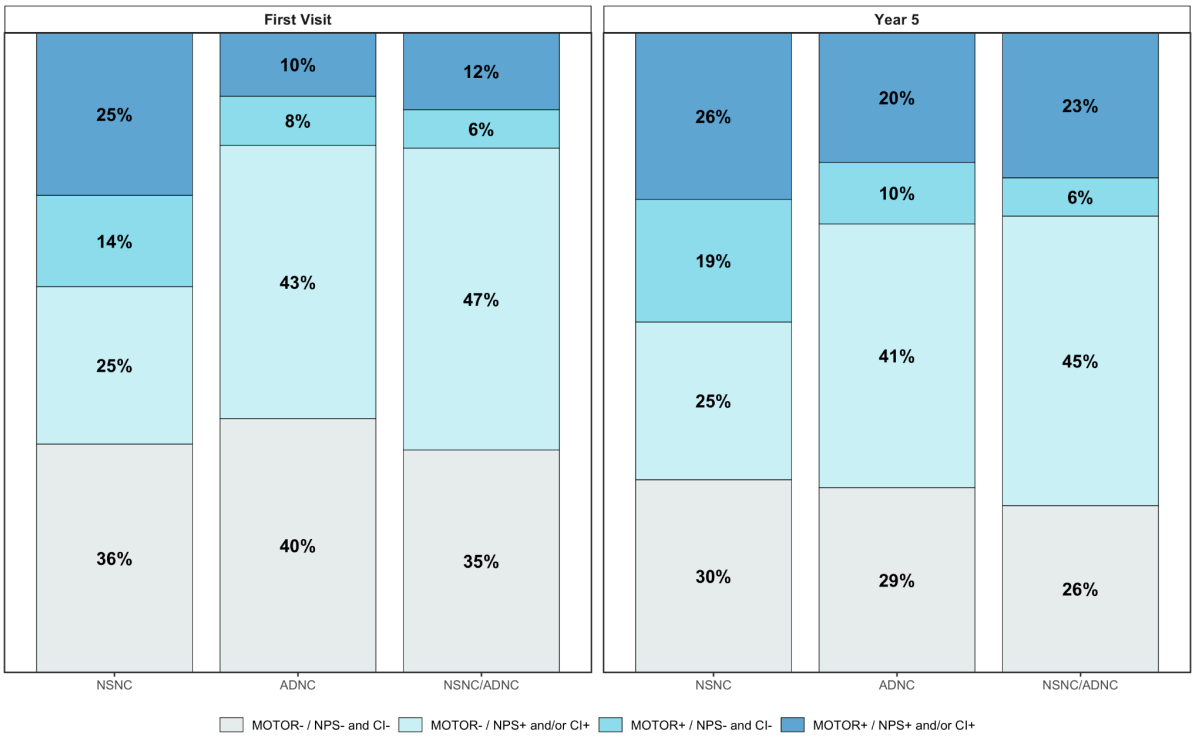
Supplementary Figure 2. First-visit cognitive domain scores by neuropathological group and cognitive status



Footnote: First-visit cognitive domain scores across neuropathological groups stratified by cognitive stage. Panels A–C represent Not MCI individuals and panels D–F MCI individuals. Boxplots indicate the median and interquartile range, with whiskers extending to 1.5× the interquartile range. Group differences were assessed using Welch's ANOVA and Bayesian ANOVA; significant pairwise comparisons were evaluated using Games–Howell post hoc tests.

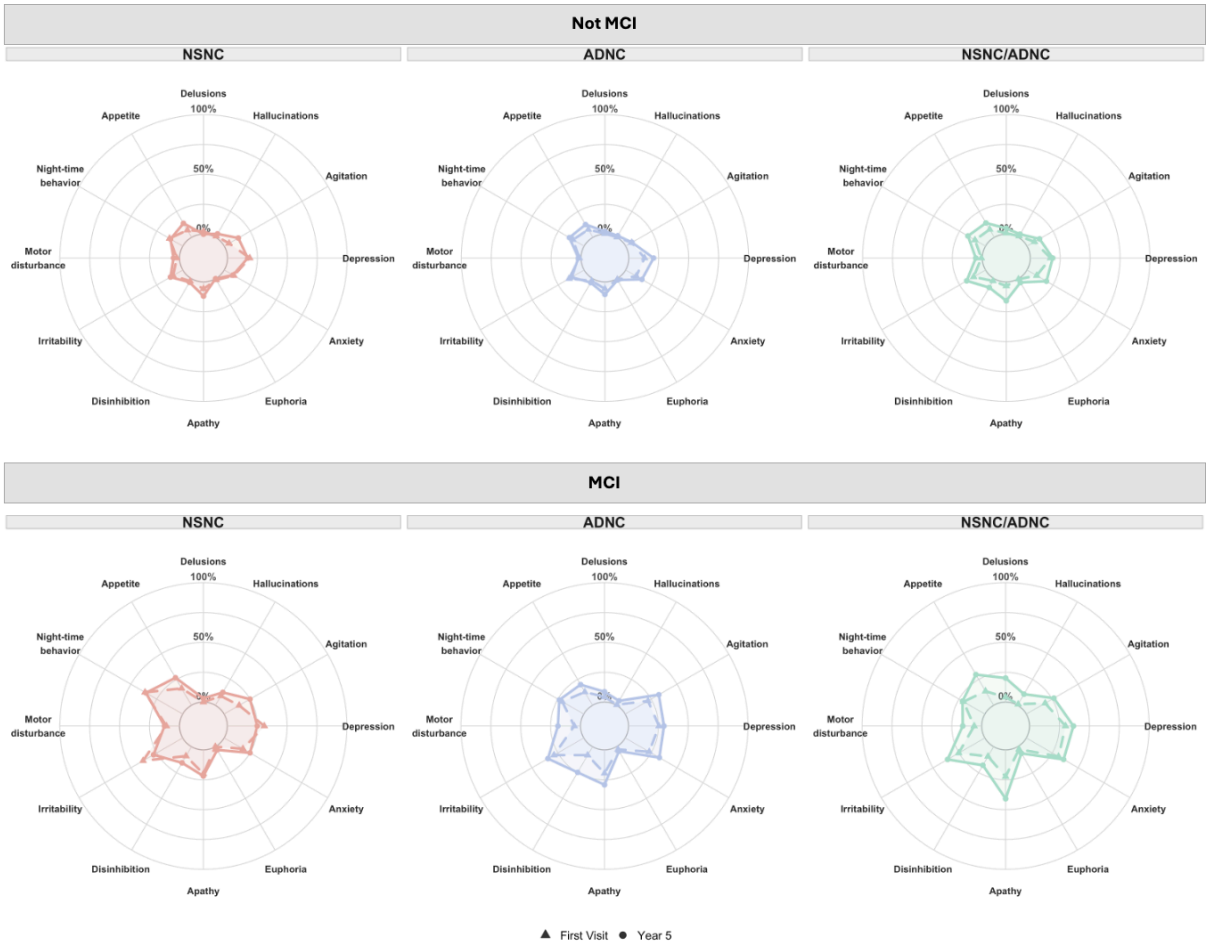
Abbreviations: NSNC, neuronal α-synuclein neuropathologic change; ADNC, Alzheimer's Disease Neuropathologic Change; NSNC/ADNC, neuronal α-synuclein neuropathologic change with concomitant Alzheimer's Disease Neuropathologic Change; MCI, mild cognitive impairment; Not MCI, no mild cognitive impairment.

Supplementary Figure 3. Distribution of combined motor, neuropsychiatric, and cognitive impairment profiles at first visit and Year 5 across neuropathological groups



Footnote: Stacked bars show the percentage of participants in each neuropathological group classified according to the presence or absence of motor symptoms, neuropsychiatric symptoms, and cognitive impairment at first visit and Year 5. Categories were mutually exclusive and were defined as follows: absence of all three features (MOTOR−/NPS−/CI−); neuropsychiatric symptoms and/or cognitive impairment without motor symptoms (MOTOR−/NPS+ and/or CI+); motor symptoms without neuropsychiatric symptoms or cognitive impairment (MOTOR+/NPS−/CI−); and motor symptoms accompanied by neuropsychiatric symptoms and/or cognitive impairment (MOTOR+/NPS+ and/or CI+). Positivity for each feature was determined according to the predefined study criteria. Percentages were calculated within each neuropathological group and assessment time point.
Abbreviations: ADNC, Alzheimer's Disease Neuropathologic Change; CI, cognitive impairment; MOTOR, motor symptoms; NPS, neuropsychiatric symptoms; NSNC, neuronal α-synuclein neuropathologic change; NSNC/ADNC, neuronal α-synuclein neuropathologic change with concomitant Alzheimer's Disease Neuropathologic Change.

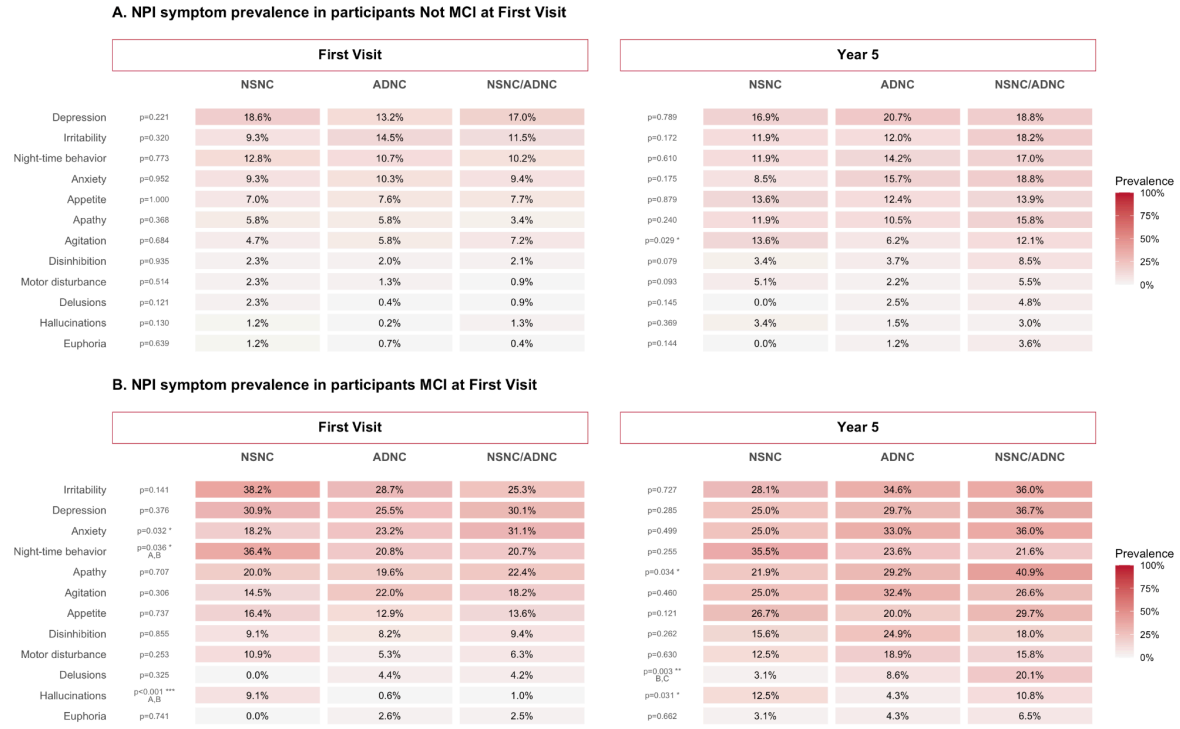
Supplementary Figure 4. Radar plots of neuropsychiatric symptom prevalence by neuropathological group and cognitive status



Footnotes: Prevalence of neuropsychiatric symptoms across NPI domains by neuropathological group and cognitive status. The upper row corresponds to Not Mild Cognitively Impaired (Not MCI) participants and the lower row to Mild Cognitive Impairment (MCI) participants. Dashed lines represent first visit frequencies and solid lines represent frequencies at the five year follow-up.

Abbreviations: ADNC, Alzheimer's disease neuropathologic change; MCI, mild cognitive impairment; Not MCI, no mild cognitive impairment; NPI, Neuropsychiatric Inventory; NSNC, neuronal α-synuclein neuropathologic change.

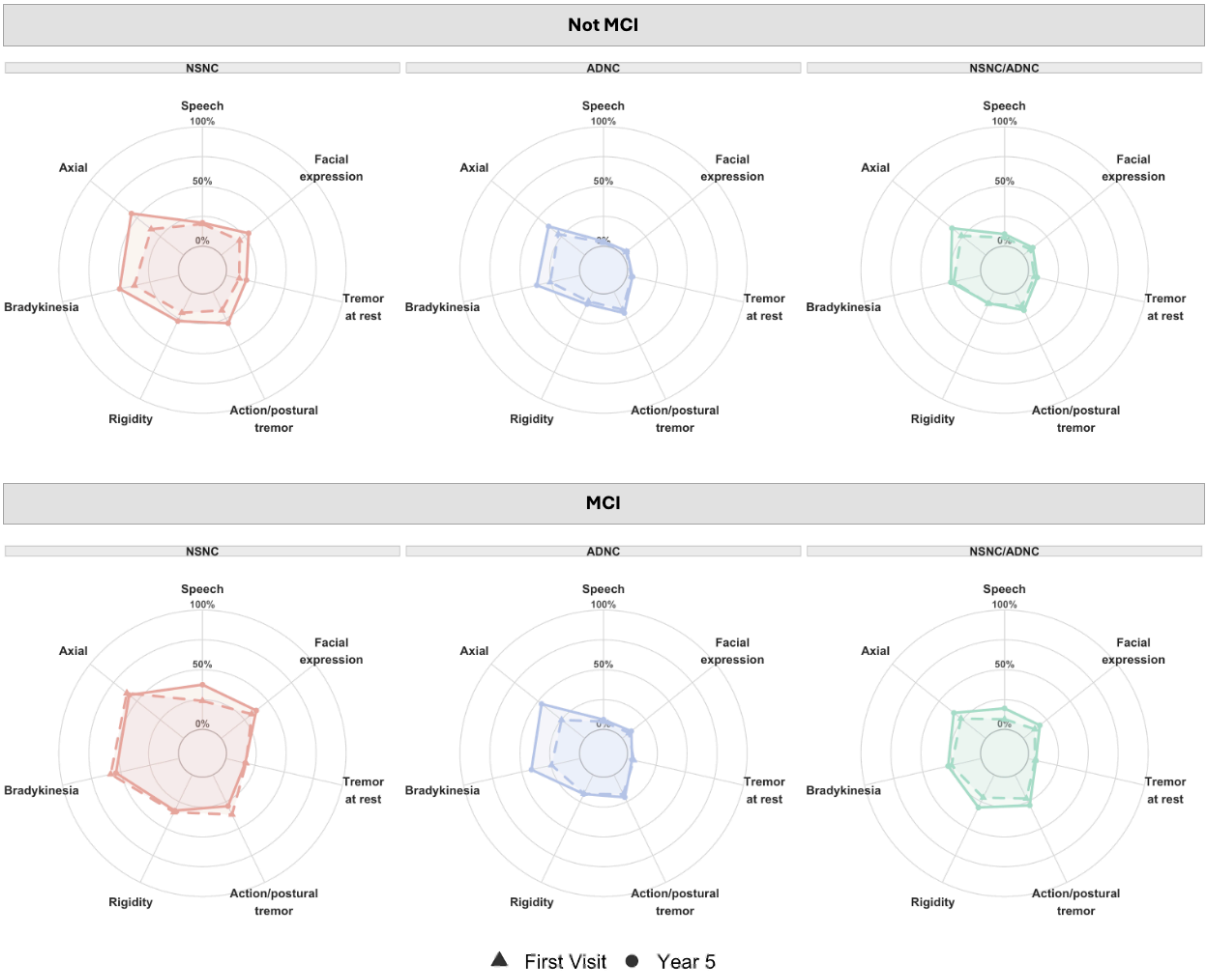
Supplementary Figure 5. Heatmaps of neuropsychiatric symptom prevalence by neuropathological group and cognitive status



Footnote: Heatmaps illustrate the prevalence of neuropsychiatric symptoms assessed using the NPI across pathological groups at first visit and five year follow-up. Analyses are stratified according to cognitive status, including Not MCI (A) and MCI (B) participants. Each cell represents the percentage of participants presenting each symptom, with increasing color intensity indicating higher prevalence. Statistical differences across groups were assessed independently at each timepoint using χ^2. Significant post-hoc pairwise comparisons are indicated below the p-values (A = NSNC vs ADNC, B = NSNC vs NSNC/ADNC, C = ADNC vs NSNC/ADNC).

Abbreviations: ADNC, Alzheimer's disease neuropathologic change; MCI, mild cognitive impairment; Not MCI, no mild cognitive impairment; NPI, Neuropsychiatric Inventory; NSNC, neuronal α-synuclein neuropathologic change.

Supplementary Figure 6. Radar plots of UPDRS-III motor-domain prevalence by neuropathological group and cognitive status



Footnotes: Prevalence of motor signs across diagnostic groups, derived from the UPDRS-III domains, according to cognitive status. The upper row corresponds to Not MCI participants and the lower row to MCI participants. Dashed lines represent first visit frequencies and solid lines represent frequencies at the five year follow-up. UPDRS-III domains comprised speech, facial expression, tremor, rigidity, bradykinesia, and axial symptoms. Domains were considered positive when at least one item was abnormal.

Abbreviations: ADNC, Alzheimer's disease neuropathologic change; MCI, mild cognitive impairment; Not MCI, no mild cognitive impairment; NSNC, neuronal α-synuclein neuropathologic change; NSNC/ADNC, neuronal α-synuclein neuropathologic change with concomitant Alzheimer's disease neuropathologic change; UPDRS-III, Unified Parkinson's Disease Rating Scale Part III.

Supplementary Figure 7. Heatmaps of UPDRS-III motor-domain prevalence by neuropathological group and cognitive status

Footnote: Heatmaps illustrate the prevalence of motor symptoms, as measured by the UPDRS-III, across pathological groups at first visit and at five-year follow-up. Analyses are stratified according to cognitive status, including participants without MCI (Not MCI; A) and participants with MCI (B). Each cell represents the percentage of participants presenting each motor feature, with increasing color intensity indicating higher prevalence. UPDRS-III items were grouped into clinically relevant motor domains, including speech, facial expression, rest tremor, action/postural tremor, rigidity, bradykinesia, and axial symptoms. Statistical differences across groups were assessed independently at each timepoint using χ^2. Significant post-hoc pairwise comparisons are indicated below the p-values (A = NSNC vs ADNC, B = NSNC vs NSNC/ADNC, C = ADNC vs NSNC/ADNC).

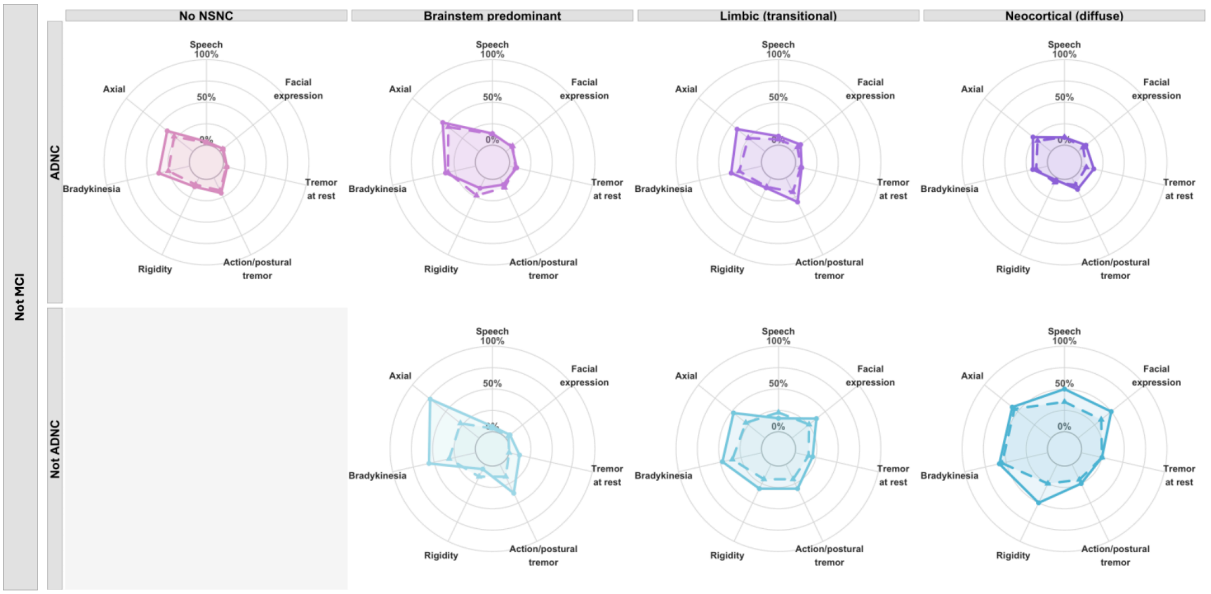
Abbreviations: ADNC, Alzheimer's disease neuropathologic change; MCI, mild cognitive impairment; Not MCI, no mild cognitive impairment; NSNC, neuronal α-synuclein neuropathologic change; NSNC/ADNC, neuronal α-synuclein neuropathologic change with concomitant Alzheimer's disease neuropathologic change; UPDRS-III, Unified Parkinson's Disease Rating Scale Part III.

Supplementary Figure 8. Neuropsychiatric profiles by neuronal α-synuclein distribution and ADNC status

Footnote: Radar plots represent the frequency of neuropsychiatric symptoms (as measured by the NPI) across combinations of ADNC status and NSNC pathology stage. Analyses are shown separately for participants without MCI (Not MCI, top) and participants with MCI (bottom). Dashed and solid lines represent first visit and five year follow-up assessments, respectively.

Abbreviations: ADNC, Alzheimer's disease neuropathologic change; MCI, mild cognitive impairment; NPI, Neuropsychiatric Inventory; Not MCI, no mild cognitive impairment; NSNC, neuronal α-synuclein neuropathologic change; NSNC/ADNC, neuronal α-synuclein neuropathologic change with concomitant Alzheimer's disease neuropathologic change.

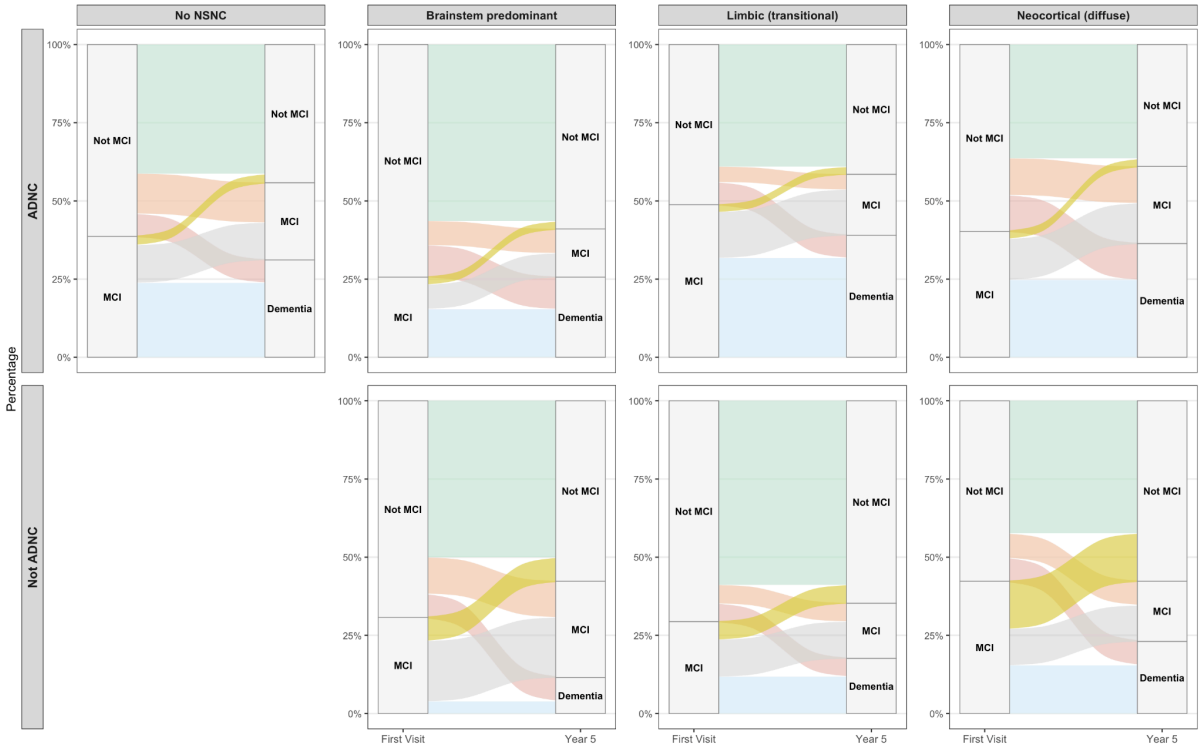
Supplementary Figure 9. Motor profiles by neuronal α-synuclein distribution and ADNC status



Footnote: Radar plots represent the frequency of motor features (as measured by UPDRS-III) across combinations of AD status and neuronal α-synuclein distribution. Analyses are shown separately for cognitively unimpaired (Not MCI, top) and cognitively impaired (CI; bottom) individuals. Dashed and solid lines represent first visit and five year follow-up assessments, respectively. UPDRS-III items were grouped into clinically relevant motor domains including speech, facial expression, rest tremor, action/postural tremor, rigidity, bradykinesia, and axial symptoms.

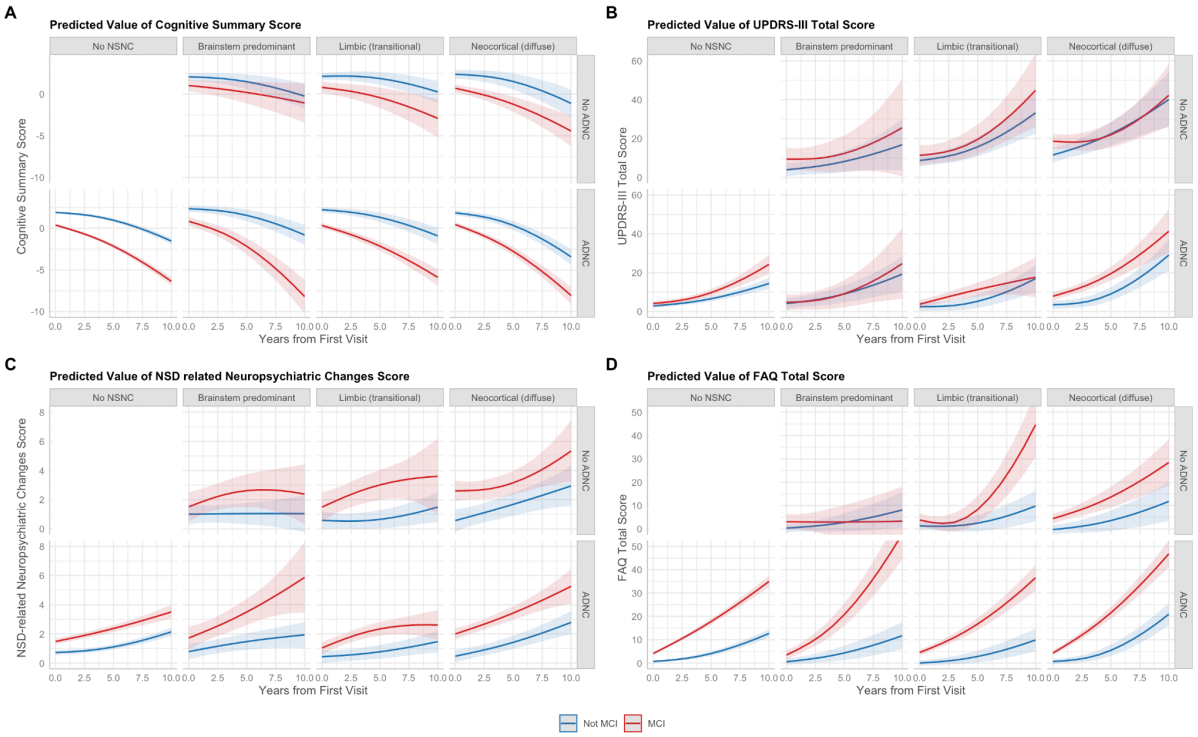
Abbreviations: NSNC, neuronal α-synuclein neuropathologic change; ADNC, Alzheimer's Disease Neuropathologic Change; NSNC/ADNC, neuronal α-synuclein neuropathologic change with concomitant Alzheimer's Disease Neuropathologic Change; Not MCI, Not Mild Cognitive Impairment; MCI, Mild Cognitive Impairment; UPDRS-III, Unified Parkinson Disease Rating Scale Part III.

Supplementary Figure 10. Cognitive-stage transitions by neuronal α-synuclein distribution and ADNC status



Footnote: Alluvial plots show transitions in cognitive stage from first visit to five years after according to neuronal α-synuclein distribution and ADNC status. Percentages are calculated within each neuropathological subgroup. Not MCI includes participants classified as cognitively normal or impaired-not-MCI at first visit.
Abbreviations: ADNC, Alzheimer's disease neuropathologic change; MCI, mild cognitive impairment; Not MCI, no mild cognitive impairment; NSNC, neuronal α-synuclein neuropathologic change.

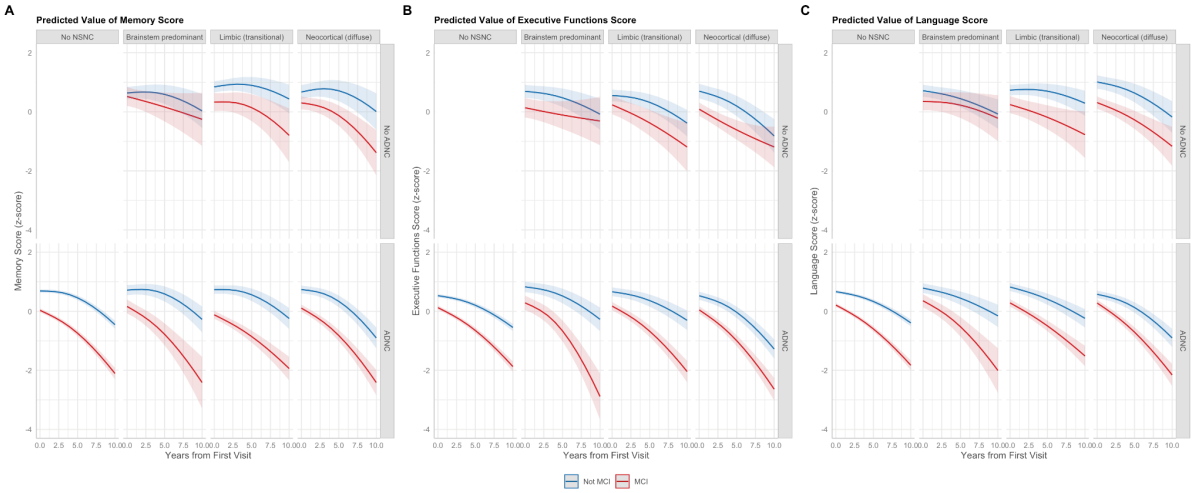
Supplementary Figure 11. Predicted longitudinal trajectories of cognitive, motor, neuropsychiatric, and functional outcomes by neuronal α-synuclein distribution and first-visit cognitive status



Footnote: Predicted longitudinal trajectories of (A) cognitive summary score, (B) UPDRS-III total score, (C) NSD-related neuropsychiatric changes score, and (D) FAQ total score according to neuropathological group and cognitive status at the first visit (Not MCI versus MCI). Estimates were obtained from linear mixed-effects models adjusted for age, sex, and education. Shaded bands represent 95% confidence intervals.

Abbreviations: ADNC, Alzheimer's disease neuropathologic change; FAQ, Functional Activities Questionnaire; MCI, mild cognitive impairment; Not MCI, no mild cognitive impairment at the first visit; NSD, neuronal synuclein disease; NSNC, neuronal α-synuclein neuropathologic change; NSNC/ADNC, neuronal α-synuclein neuropathologic change with concomitant Alzheimer's disease neuropathologic change; UPDRS-III, Unified Parkinson's Disease Rating Scale Part III.

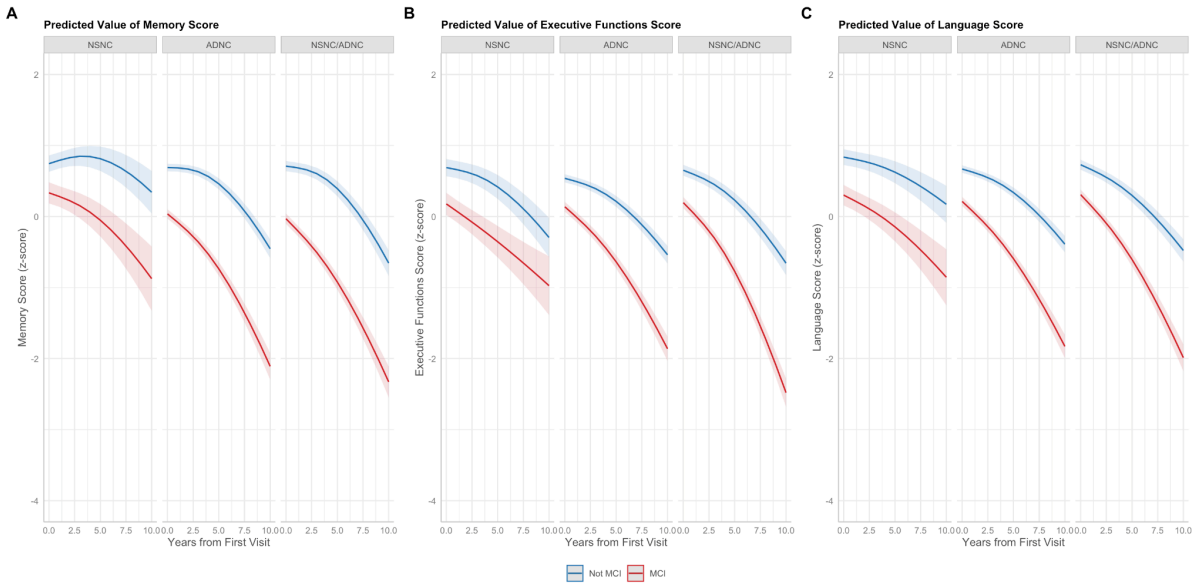
Supplementary Figure 12. Domain-specific cognitive trajectories by neuronal α-synuclein distribution, ADNC status, and first-visit cognitive status



Footnote: Predicted trajectories of (A) memory score, (B) executive functions score, and (C) language score according to neuronal α-synuclein distribution, ADNC status, and cognitive status at the first visit (Not MCI versus MCI). Estimates were derived from linear mixed-effects models adjusted for age at first visit, sex, and education. Shaded bands represent 95% confidence intervals.

Abbreviations: ADNC, Alzheimer's disease neuropathologic change; MCI, mild cognitive impairment; Not MCI, no mild cognitive impairment at the first visit; NSNC, neuronal α-synuclein neuropathologic change.

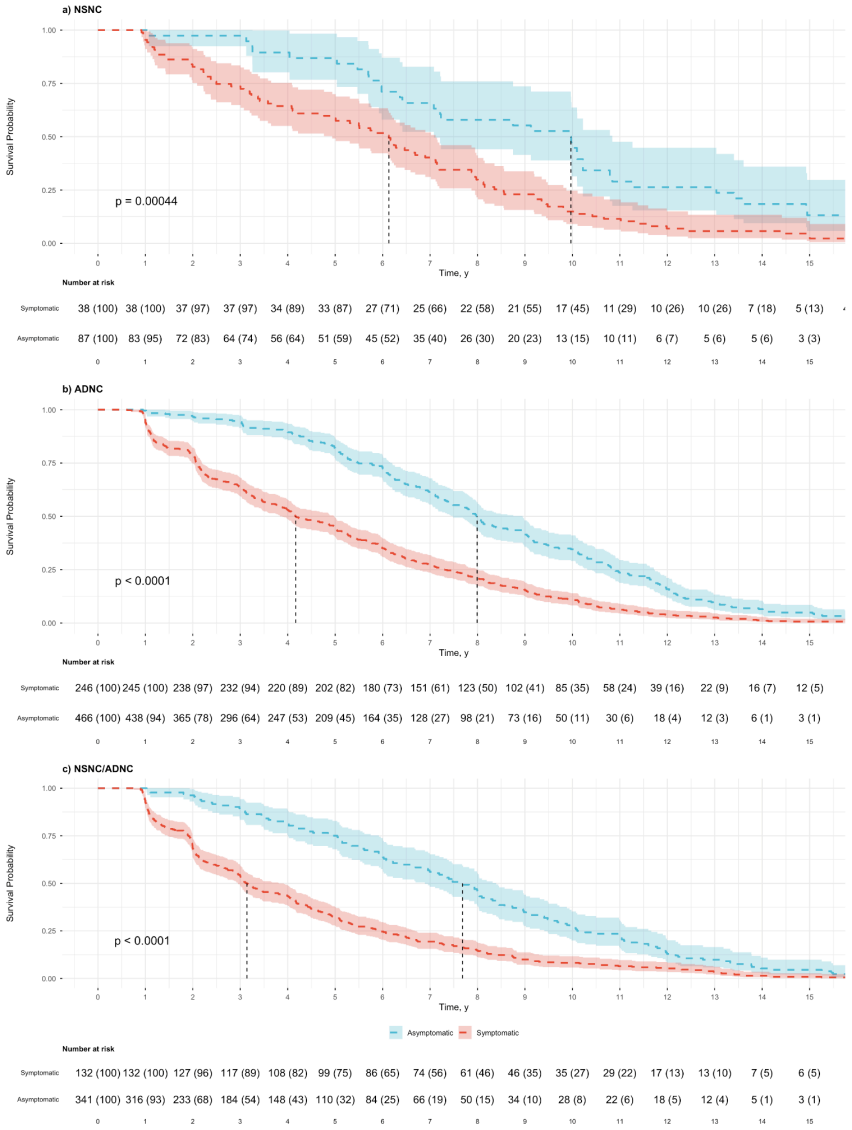
Supplementary Figure 13. Adjusted longitudinal cognitive trajectories by neuropathological group and first-visit cognitive status



Footnotes: Predicted trajectories were derived from linear mixed-effects models adjusted for age at first visit, sex, education, neuropathological group, first-visit cognitive status, and the corresponding interactions with time. Time was modeled as years from the first neuropsychological assessment. Blue curves represent participants without MCI at first visit, and red curves represent participants with MCI at first visit; shaded areas indicate 95% confidence intervals. Panels show the predicted changes in memory, executive function, language, and the Cognitive Summary Score across the NSNC, ADNC, and NSNC/ADNC groups. Lower values indicate worse cognitive performance or greater decline.

Abbreviations: ADNC, Alzheimer's disease neuropathologic change; CSS, Cognitive Summary Score; MCI, mild cognitive impairment; Not MCI, no mild cognitive impairment; NSNC, neuronal α-synuclein neuropathologic change.

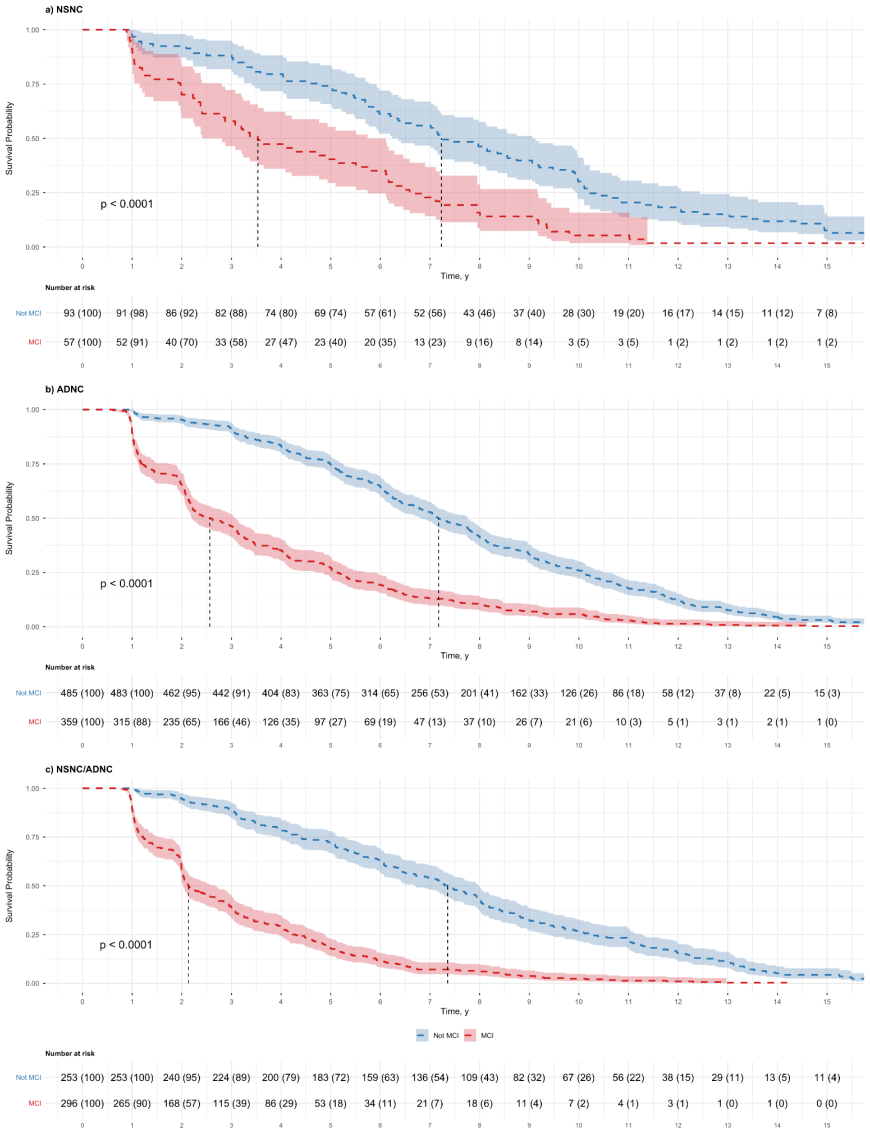
Supplementary Figure 14. Dementia-free survival by first-visit symptomatic status



Footnote: Kaplan–Meier curves show dementia-free survival according to first-visit symptomatic status within each neuropathological group. Symptomatic status was defined by the presence of MCI, NPI positivity, or UPDRS-III motor positivity at first visit. Time was calculated from first visit to the first visit at which the NACC-defined dementia stage was documented or last available clinical assessment. Shaded areas represent 95% confidence intervals. P values were derived from log-rank tests. Vertical dashed lines indicate median dementia-free survival when reached.

Abbreviations: ADNC, Alzheimer's disease neuropathologic change; MCI, mild cognitive impairment; NPI, Neuropsychiatric Inventory; NSNC, neuronal α-synuclein neuropathologic change; UPDRS-III, Unified Parkinson's Disease Rating Scale Part III.

Supplementary Figure 15. Dementia-free survival by neuropathological group and first-visit cognitive status



Footnotes: Kaplan–Meier curves show dementia-free survival according to first-visit cognitive status within each neuropathological group. Blue curves represent participants without MCI at first visit and red curves represent participants with MCI at first visit; shaded areas indicate 95% confidence intervals. Time was calculated from first visit to the first visit at which the NACC-defined dementia stage was documented or last available clinical assessment. P values were derived from log-rank tests. Vertical dashed lines indicate median dementia-free survival when reached.

Abbreviations: ADNC, Alzheimer's disease neuropathologic change; MCI, mild cognitive impairment; Not MCI, no mild cognitive impairment; NSNC, neuronal α-synuclein neuropathologic change.