

Supplementary Online Content

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eMethods. Participants and Study Design, clinical follow-up data, and AD biomarkers.

1. DELCODE (DZNE-Longitudinal Cognitive Impairment and Dementia Study).

1.1. Participants:

The DELCODE study is a longitudinal, observational, memory clinic-based study conducted across nine sites in Germany, seven of which are linked to local university memory centers. Initiated in 2014 under the leadership of Prof. Dr. med. Frank Jessen, inclusion and exclusion criteria are described in Jessen et al., 2018.¹ The current study focuses on controls, first-degree relatives of Alzheimer's disease (AD) patients, and patients with subjective cognitive decline (SCD). Recruitment occurred through local newspaper advertisements and memory center referrals. All participants scored better than 1.5 standard deviations below the age-, sex-, and education-adjusted norms on the CERAD neuropsychological battery (German norms available at www.memoryclinic.ch). SCD patients were additionally defined by subjectively reported cognitive decline, with concerns raised to memory center physicians, in line with criteria from previous studies.^{2,3} Participants in the current study were aged 60-84, had at least 8 years of education, and no significant psychiatric, neurological, or substance abuse history. They also did not take psychoactive or anti-dementia medications. In total, 151 controls, 60 AD-relatives, and 279 SCD patients were included. They were enrolled between May 13, 2014, and August 31, 2018.

1.2. Clinical conversion to incident-MCI:

Consensus diagnoses of incident MCI were determined through a two-step review process, adapted from the Wisconsin Registry for Alzheimer's Prevention study and described in Stark et al, 2023.⁴ In the first step, an algorithmic screening identified participants who were cognitively normal at baseline but showed potential cognitive decline at follow-up. The criteria for this included: (i) normative deficits (e.g., at least two cognitive tests ≥ 1.0 SD below the demographically adjusted mean, or one CERAD-NAB subtest ≥ 1.5 SD below the mean), (ii) individual cut-offs (e.g., CERAD-NAB word list delayed recall or FCSRT free recall ≥ 1.5 SD below the mean, FCSRT total recall ≤ 46 points, or MMSE ≤ 26 points), and (iii) reports from physicians or study partners (e.g., an increase in CDR global score, or FAQ score ≥ 4). In the second step, flagged cases were reviewed by a team of five neuropsychologists who assessed MCI conversion using established diagnostic criteria: (i) cognitive impairment (≥ 1.5 SD below the mean in at least two tests measuring the same ability), (ii) intra-individual cognitive decline (based on longitudinal test scores or participant/study partner reports), (iii) preserved functional abilities, and (iv) absence of dementia.^{5,6} The review committee was blinded to baseline group assignments, biomarkers, imaging data, and genetic information.

1.3. AD biomarkers:

In the current study, amyloid and tau positivity were first assessed using cerebrospinal fluid (CSF) data, and plasma data when CSF was unavailable.

CSF Biomarkers: A subset of participants underwent lumbar puncture for CSF sampling (N=274, sampling rate: 55.9%). Amyloid beta (A β)₄₂, A β ₄₀, and phospho-tau181 (p-tau181) levels were measured using standardized commercial kits: V-PLEX A β Peptide Panel 1 (6E10) Kit (K15200E, Mesoscale Diagnostics LLC, USA) and Innostest Phospho-Tau(181P) (81581; Fujirebio Germany GmbH). Assays were performed centrally, with independent reference samples used for quality control. Cut-offs were derived using Gaussian mixture modeling (R package flexmix, version 2.3-15)⁷ and set at A β _{42/40} ≤ 0.08 and p-tau181 ≥ 73.65 pg/ml.⁸

Plasma A β _{42/40}: Plasma samples (500 μ L EDTA) were processed according to DELCODE standard operating procedures and stored at -80°C . A β _{X-40} and A β _{X-42} levels, along with the A β _{X-42/X-40} ratio, were measured using a semi-automated immunoprecipitation-immunoassay (IP-IA). The plasma A β immunoprecipitation was performed using a CyBio FeliX liquid-handling instrument (Roboscreen, Leipzig, Germany), followed by detection with the Mesoscale Discovery A β V-PLEX immunoassay (6E10). The cut-off for plasma A β _{42/40} was set at ≤ 0.106 , as detailed in Vogelgsang et al., 2024.⁹

Plasma pTau181: Plasma levels of p-tau181 were measured using Simoa assays on Quanterix HD-1 and HD-X instruments (Quanterix, Billerica, MA) with pTau-181 Advantage version 2 kits, following the manufacturer's instructions. Assays were performed by the same operator, with two internal control samples assessed at the start and end of each run to ensure repeatability and monitor inter-assay variability.¹⁰ The plasma p-tau181 cut-off for this study was determined via receiver operating characteristic (ROC) analysis, using CSF p-tau181 classification and the Youden Index to establish the threshold. The cut-off was set at ≥ 1.707 pg/mL, with an area under the curve (AUC) of 0.78 (95% CI: 0.73-0.83), based on 466 DELCODE participants, including MCI and demented patients (unpublished).

2. ADNI (Alzheimer's Disease Neuroimaging Initiative).

In the current study, we utilized data from the ADNIMERGE dataset, extracted on September 21, 2023.

2.1. Participants:

ADNI is an ongoing, longitudinal, multicenter study conducted in 63 sites across the USA and Canada. The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimer's disease (AD). Further details can be found in Weiner et al,¹¹ and inclusion and exclusion criteria have been described at <http://adni.loni.usc.edu/>. Briefly, participants included in the current study were all aged between 56-90 years, had at least 8 years of education, and had no clinically significant psychiatric (including alcohol or drug abuse) or neurologic disease. All cognitively unimpaired (CU) participants had MMSE¹² scores of 24 or greater (total possible range: 0-30) and Clinical Dementia Rating (CDR) of 0.0 (total possible range 0-3, with higher scores indicating worse functioning)¹³, are not depressed, did not have mild cognitive impairment or dementia, have preserved activities of daily living (FAQ \leq 9), and had scores on delayed recall of one paragraph from Wechsler Memory Scale Logical Memory II within the norm according to their level of education (\geq 9 for 16 or more years of education, \geq 5 for 8-15 years of education, \geq 3 for 0-7 years of education). Part of those participants (N=145 [51.8%]) had a significant subjective cognitive decline, defined by the presence of a significant subjective memory concern reported by subject, informant, or clinician, CCI score \geq 16 (based on first 12 questions).¹⁴

Clinical Conversion to Incident MCI: To determine the presence of a clinical conversion during the follow-up period, we used an algorithm based on the "DX" (diagnosis) column from the ADNIMERGE dataset. Individuals diagnosed with mild cognitive impairment (MCI) at any point during follow-up were considered converters to incident MCI from the time of diagnosis. However, individuals with reversible MCI, defined as those who had an inconsistent MCI diagnosis, followed by a return to normal cognition in subsequent assessments (with at least three total assessments), were considered stable and not counted as converters.

2.2. AD biomarkers:

Ab-PET biomarkers: The ADNI FreeSurfer 5.3 pipeline yields a global standard uptake value ratio (SUVR) measure representing a non-weighted average of radiotracer retention in four FreeSurfer-defined regions (frontal, anterior/posterior cingulate, lateral parietal, and lateral temporal cortices) normalized to whole cerebellum. To directly convert [18F]-Florbetapir- and [18F]-Florbetaben-PET data to centiloid values, equations describe in ADNI guidelines were used (see details [here](#)). Centiloids were calculated as follows:

- [18F]-Florbetapir-PET: $CL=(196.9 \times SUVR)-196.03$. The amyloid positivity threshold was set at 22.529, corresponding to 1.11 SUVR (see also [UCBERKELEY AV45 Methods 11.15.2021.pdf](#)).^{15,16}
- [18F]-Florbetaben-PET: $CL=(159.08 \times SUVR)-151.65$. The amyloid positivity threshold was set at 20.1564, corresponding to 1.08 SUVR (see also [UCBerkeley FBB Methods 11.15.2021.pdf](#)).¹⁷

Tau-PET biomarker: The processing of [18F]-Flortaucipir PET images is summarized as follows (please see [here](#) for details). Each PET scan is co-registered to the closest available bias-corrected T1-weighted MRI in native space, using FreeSurfer (v7.1.1) for anatomical accuracy. This registration allows the calculation of the mean flortaucipir uptake within predefined regions of interest (ROIs). For the current study, tau positivity is defined based on the standardized uptake value ratio (SUVR) in the entorhinal cortex (corresponding to Braak stage 1). A positivity threshold of $SUVR \geq 1.2$ was used, as established in a previously published paper.¹⁸

CSF ptau181: Data were extracted from the "PTAU" variable in the ADNIMERGE dataset, that use Roche Elecsys immunoassays. A positivity threshold of ≥ 24.3 pg/mL was used, as established in a previously published paper,¹⁹ which reported an area under the curve (AUC) of 0.79 ± 0.03 .

eTable 1. Baseline participants demographics by cohort subsample

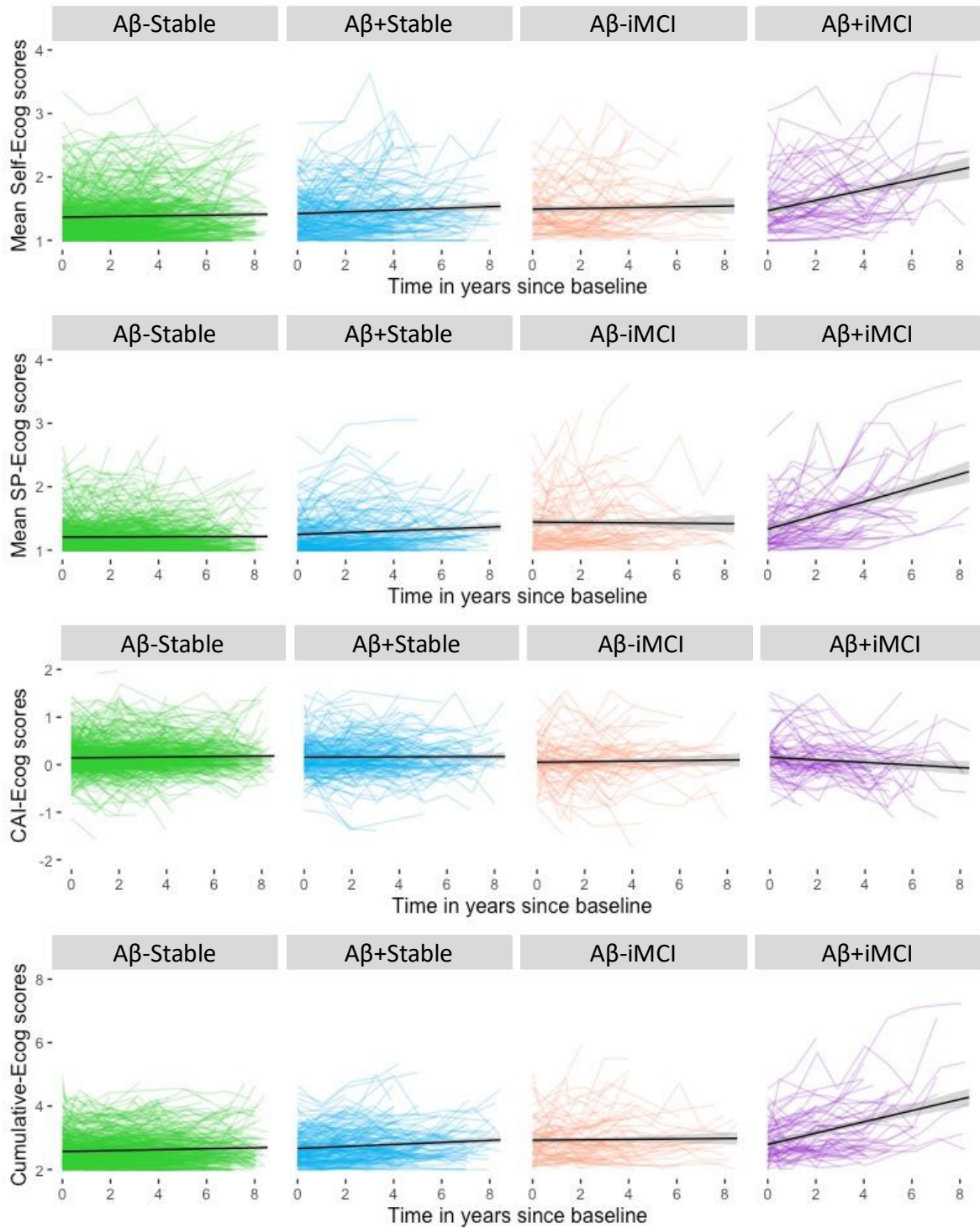
	DELCODE (N=490)					P	ADNI (N=280)					P
	Ab-Stable	Ab+Stable	Ab-iMCI	Ab+iMCI	Overall		Ab-Stable	Ab+Stable	Ab-iMCI	Ab+iMCI	Overall	
No. (%)	290 (59.2%)	104 (21.2%)	53 (10.8%)	43 (8.8%)	490 (100%)		172 (61.4%)	73 (26.1%)	16 (5.7%)	19 (6.8%)	280 (100%)	
FU time, median (IQR), y ^a	5.1 (4.0-6.9)	5.0 (4.0-7.0)	4.2 (3.4-6.0)	5.0 (4.0-6.1)	5.1 (4.0-6.6)	.05	4.4 (3.2-7.7)	4.0 (2.6-5.3)	6.9 (4.2-8.0)	4.0 (2.5-5.4)	4.2 (3.0-7.5)	.02
Age, median (IQR), y ^b	68.0 (64.3-72.4)	72.1 (67.5-76.4)	71.0 (67.3-76.4)	74.4 (69.2-77.5)	69.8 (65.3-74.5)	<.001	69.4 (66.1-74.0)	70.4 (67.4-76.4)	70.8 (66.8-76.1)	75.1 (71.1-81.0)	70.0 (66.7-75.3)	<.001
Female, No. (%) ^c	170 (58.6%)	30 (28.8%)	28 (52.8%)	15 (34.9%)	243 (49.6%)	<.001	97 (56.4%)	49 (67.1%)	7 (43.8%)	9 (47.4%)	162 (57.9%)	.18
Education, median (IQR), y	15 (13-17)	15 (13-18)	13 (12-17)	13 (12-17)	14 (13-17)	.34	17 (16-18)	16 (14-19)	16 (13.8-18.3)	16 (16-20)	16.5 (16-18)	.46
APOEε4 carrier, No. (%) ^d	45 (15.6%)	54 (52.4%)	13 (24.5%)	23 (53.5%)	135 (27.7%)	<.001	40 (24.1%)	40 (56.3%)	3 (18.8%)	10 (55.6%)	93 (34.3%)	<.001
MMSE score, median (IQR) ^e	30 (29-30)	30 (29-30)	29 (28-30)	29 (28.5-30)	30 (29-30)	<.001	29 (29-30)	29 (29-30)	29 (27-30)	29 (28-30)	29 (29-30)	.11
Memory clinic, No. (%) ^f	148 (51.0%)	60 (57.7%)	36 (67.9%)	35 (81.4%)	279 (56.9%)	<.001						
No. (%) with tau status	270 (59.5%)	93 (20.5%)	53 (11.7%)	38 (8.4%)	454 (100%)		157 (61.3%)	71 (27.7%)	12 (4.7%)	16 (6.3%)	256 (100%)	
Tau status T+, No. (%) ^{fg}	18 (6.7%)	18 (19.4%)	7 (13.2%)	15 (39.5%)	58 (12.8%)	<.001	27 (17.2%)	34 (47.9%)	5 (41.7%)	10 (62.5%)	76 (29.7%)	<.001

At Bonferroni-adjusted P values (for 6 intergroup comparisons), in DELCODE: ^a Ab-Stable younger than the 3 others groups (all $P_{adj}<0.01$). ^{c,d} Both Ab- groups with higher percentage of female than Ab+ (all $P_{adj}<0.04$) and lower percentage of APOE4 carriers (all $P_{adj}<0.04$), except for Ab-iMCI and Ab+iMCI which did not significantly differ in sex ratio ($P_{adj}=0.72$). Note that only 488 DELCODE participants had available APOE data (1 missing both Stable groups). ^e Both Stable groups with higher MMSE scores than both iMCI groups (all $P_{adj}<0.04$), with no significant differences based on Ab status (both $P_{adj}=1$). ^f Ab+iMCI had a higher percentage of SCD patients compared to Ab-Stable ($P_{adj}=0.002$). ^g Ab+iMCI had a higher percentage of tau-positive individuals compared to the Ab- groups (all $P_{adj}<0.04$), as Ab+Stable compared to Ab-Stable group ($P_{adj}<0.001$). In ADNI: ^a Ab-iMCI with longer follow-up period than Ab+Stable ($P_{adj}=0.02$). ^b Ab+iMCI older than both Stable groups (both $P_{adj}<0.03$). ^d Both Ab- groups with lower percentage of APOE4 carriers compared to both Ab+ groups (between both Stable groups, $P_{adj}<0.001$; only trend level for others, both $P_{adj}<0.08$), except for Ab-iMCI and Ab+iMCI which did not significantly differ ($P_{adj}=0.36$). Note that only 271 ADNI participants had available APOE data (6 missing in Ab-Stable, 2 missing in Ab+Stable and 1 missing in Ab+iMCI). ^g Ab-Stable had a lower percentage of tau-positive individuals compared both Ab+ groups (all $P_{adj}<0.001$). **Abbreviations:** Ab-, participants amyloid-negative at baseline; Ab+, participants amyloid-positive at baseline; ADNI, Alzheimer's Disease Neuroimaging Initiative; FU, Follow-up, iMCI, participants that progressed to incident mild cognitive impairment during the follow-up period; DELCODE, German Center for Neurodegenerative Diseases (DZNE) Longitudinal Cognitive Impairment and Dementia Study; MMSE, mini mental state examination; Stable, participants cognitively stable during the follow-up period; T+, participants tau-positive at baseline.

eTable 2. Participants demographics at the first follow-up (6-18 months after baseline) for the subset with DC1 scores available that did not yet convert to MCI

	Combined Sample (N=353)					P value
	Ab-Stable	Ab+Stable	Ab-iMCI	Ab+iMCI	Overall	
No. (%)	204 (57.8%)	97 (27.5%)	26 (7.4%)	26 (7.4%)	353 (100%)	
DELCODE, No. (%)	123 (60.3%)	54 (55.7%)	20 (76.9%)	18 (69.2%)	215 (60.9%)	
Memory clinic ^a , No. (%)	81 (39.7%)	33 (34.0%)	15 (57.7%)	14 (53.8%)	143 (40.5%)	<0.001
Age ^b , median (IQR), y	69.4 (65.7-73.9)	72.2 (68.2-76.7)	72.5 (70.8-78.6)	76.3 (73.1-80.0)	71.0 (67.1-75.9)	<0.001
Female ^c , No. (%)	10 (53.9%)	38 (39.2%)	9 (34.6%)	11 (42.3%)	168 (47.6%)	0.04
Education ^d , median (IQR), y	16 (13-18)	16 (14-18)	15 (13-17)	14 (12-16)	16 (13-18)	0.01
APOEε4 carrier ^e , No. (%)	37 (18.4%)	53 (56.4%)	6 (23.1%)	14 (53.8%)	110 (31.7%)	<0.001
MMSE score ^f , median (IQR)	30 (29-30)	30 (28-30)	29 (28-30)	29 (27.3-30)	30 (29-30)	0.003
No. (%) with tau status	188 (57.3%)	93 (28.4%)	25 (7.6%)	22 (6.7%)	328 (100%)	
Tau status T+ ^g , No. (%)	19 (10.1%)	36 (38.7%)	7 (28.0%)	9 (40.9%)	71 (21.6%)	<0.001

At Bonferroni-adjusted P values (for 6 intergroup comparisons): ^a iMCI groups have more participants recruited from memory clinics than Stable groups (all $P_{adj}<0.03$). ^{b,g} Ab-Stable younger than the Ab+ groups (all $P_{adj}<0.003$) and with lower percentage of tau-positive participants (all $P_{adj}\leq 0.001$). ^c No significant differences between groups. ^d Ab+Stable more educated than the Ab-iMCI group (all $P_{adj}<0.01$). ^e Only 347 participants (3 missing in Ab-Stable, and 3 missing in Ab+Stable) had available APOE data. Ab-Stable with a lower percentage of APOEε4 carriers than the Ab+ groups (all $P_{adj}<0.001$), and Ab-iMCI than Ab+Stable ($P_{adj}=0.03$). ^f Only 345 participants (2 missing in Ab-Stable, and 6 missing in Ab+Stable) had available MMSE data. Both Stable groups with higher MMSE scores than Ab+iMCI groups (all $P_{adj}<0.02$). **Abbreviations:** Ab-, participants amyloid-negative at baseline; Ab+, participants amyloid-positive at baseline; FU, Follow-up, iMCI, participants that progressed to incident mild cognitive impairment during the follow-up period; MMSE, mini mental state examination; Stable, participants cognitively stable during the follow-up period; T+, participants tau-positive at baseline.



eFigure 1. Spaghetti plot of individual trajectories: SCD reports over time in years since baseline according to amyloid status and future clinical progression.

Abbreviations: Ab-, participants amyloid-negative at baseline; Ab+, participants amyloid-positive at baseline; CAI, Cognitive awareness index; iMCI, participants that progressed to incident mild cognitive impairment during the follow-up period; SP, study partner; Stable, participants cognitively stable during the follow-up period.

eTable 3. Results from Models 1-3, including subgroup slopes and pairwise comparisons with Bonferroni-adjusted p-values using the `ggeffects::hypothesis_test()` function.

eTable 4A. Combined sample.

	SP-Ecog			Self-Ecog			Cum-Ecog			CAI-Ecog		
Model 1 - Fixed Effect^a	Est.	SE	P	Est.	SE	P	Est.	SE	P	Est.	SE	P
(Intercept)	1.18	0.02	<0.001	1.21	0.03	<0.001	2.38	0.04	<0.001	0.02	0.03	0.43
Time	0.01	0.004	0.006	0.02	0.005	<0.001	0.03	0.007	<0.001	0.006	0.005	0.22
iMCI [iMCI]	0.13	0.03	<0.001	0.08	0.03	0.012	0.21	0.04	<0.001	-0.05	0.03	0.18
Time:iMCI [iMCI]	0.04	0.006	<0.001	0.02	0.006	<0.001	0.06	0.009	<0.001	-0.01	0.006	0.02
Slopes	Est.	95% CI	P _{adj}	Est.	95% CI	P _{adj}	Est.	95% CI	P _{adj}	Est.	95% CI	P _{adj}
Stable	0.01	0.003, 0.02	0.02	0.02	0.006, 0.02	0.002	0.03	0.01, 0.04	<0.001	0.006	-0.003, 0.01	0.41
iMCI	0.05	0.04, 0.07	<0.001	0.04	0.02, 0.05	<0.001	0.09	0.07, 0.11	<0.001	-0.008	-0.02, 0.006	0.48
Model 2 - Fixed Effect^b	Est.	SE	P	Est.	SE	P	Est.	SE	P	Est.	SE	P
(Intercept)	1.19	0.03	<0.001	1.23	0.03	<0.001	2.41	0.05	<0.001	0.03	0.04	0.45
Time	0.007	0.006	0.25	0.01	0.006	0.04	0.02	0.009	0.03	0.007	0.006	0.26
Amyloid status [Ab+]	0.009	0.02	0.67	0.04	0.03	0.17	0.04	0.04	0.26	0.02	0.03	0.49
Time:Amyloid status [Ab+]	0.03	0.005	<0.001	0.02	0.005	<0.001	0.04	0.007	<0.001	-0.006	0.005	0.21
Slopes	Est.	95% CI	P _{adj}	Est.	95% CI	P _{adj}	Est.	95% CI	P _{adj}	Est.	95% CI	P _{adj}
Ab-	0.006	-0.005, 0.02	0.62	0.01	-0.0000, 0.02	0.10	0.02	0.001, 0.04	0.07	0.007	-0.005, 0.02	0.49
Ab+	0.03	0.02, 0.05	<0.001	0.03	0.02, 0.05	<0.001	0.06	0.04, 0.08	<0.001	0.0007	-0.01, 0.01	1.00
Model 3 - Fixed Effect^b	Est.	SE	P	Est.	SE	P	Est.	SE	P	Est.	SE	P
(Intercept)	1.17	0.03	<0.001	1.22	0.03	<0.001	2.38	0.05	<0.001	0.04	0.04	0.31
Time	0.005	0.006	0.33	0.01	0.006	0.07	0.02	0.009	0.05	0.007	0.006	0.29
iMCI [iMCI]	0.17	0.03	<0.001	0.07	0.04	0.09	0.24	0.06	<0.001	-0.08	0.04	0.06
Amyloid status [Ab+]	0.01	0.02	0.53	0.03	0.03	0.34	0.03	0.04	0.38	0.009	0.03	0.74
Time:iMCI [iMCI]	0.01	0.007	0.07	0.01	0.008	0.13	0.02	0.01	0.05	0.0001	0.008	0.99
Time:Amyloid status [Ab+]	0.01	0.005	0.02	0.02	0.006	0.006	0.03	0.008	<0.001	0.001	0.005	0.83
iMCI:Amyloid status [Ab+iMCI]	-0.09	0.05	0.08	0.006	0.06	0.93	-0.08	0.09	0.38	0.08	0.07	0.25
Time:iMCI:Amyloid status [Ab+iMCI]	0.06	0.01	<0.001	0.02	0.01	0.19	0.07	0.02	<0.001	-0.03	0.01	0.009
Slopes	Est.	95% CI	P _{adj}	Est.	95% CI	P _{adj}	Est.	95% CI	P _{adj}	Est.Est.	95% CI	P _{adj}
Ab-Stable	0.005	-0.006, 0.02	1.00	0.01	-0.001, 0.02	0.32	0.02	-0.0007, 0.03	0.24	0.007	-0.005, 0.02	1.00
Ab+Stable	0.02	0.005, 0.03	0.03	0.03	0.01, 0.04	0.001	0.04	0.02, 0.06	<0.001	0.008	-0.006, 0.02	1.00
Ab-iMCI	0.02	0.002, 0.04	0.13	0.02	0.004, 0.04	0.06	0.04	0.01, 0.06	0.01	0.007	-0.01, 0.03	1.00
Ab+iMCI	0.09	0.07, 0.11	<0.001	0.05	0.03, 0.07	<0.001	0.13	0.11, 0.16	<0.001	-0.02	-0.04, -0.004	0.07
Pairwise comparisons	Est.	95% CI	P _{adj}	Slope	95% CI	P _{adj}	Slope	95% CI	P _{adj}	Slope	95% CI	P _{adj}
Ab-Stable / Ab+Stable	-0.01	-0.02, -0.002	0.09	-0.02	-0.03, -0.004	0.04	-0.03	-0.04, -0.01	0.005	-0.001	-0.01, 0.01	1.00
Ab-Stable / Ab-iMCI	-0.01	-0.03, 0.001	0.40	-0.01	-0.03, 0.004	0.80	-0.02	-0.04, -0.0003	0.28	-0.0001	-0.02, 0.02	1.00
Ab-Stable / Ab+iMCI	-0.08	-0.10, -0.07	<0.001	-0.04	-0.06, -0.03	<0.001	-0.12	-0.14, -0.09	<0.001	0.03	0.01, 0.05	0.003
Ab+Stable / Ab-iMCI	-0.0007	-0.02, 0.02	1.00	0.003	-0.01, 0.02	1.00	0.003	-0.02, 0.03	1.00	0.001	-0.02, 0.02	1.00
Ab+Stable / Ab+iMCI	-0.07	-0.09, -0.05	<0.001	-0.03	-0.05, -0.009	0.02	-0.09	-0.12, -0.07	<0.001	0.03	0.01, 0.05	0.004
Ab-iMCI / Ab+iMCI	-0.07	-0.09, -0.05	<0.001	-0.03	-0.05, -0.01	0.02	-0.10	-0.13, -0.07	<0.001	0.03	0.009, 0.05	0.03

eTable 5B. DELCODE cohort.

	SP-Ecog			Self-Ecog			Cum-Ecog			CAI-Ecog		
	Est.	SE	P	Est.	SE	P	Est.	SE	P	Est.	SE	P
Model 1 - Fixed Effect^a												
(Intercept)	1.20	0.02	<0.001	1.22	0.03	<0.001	2.41	0.04	<0.001	0.01	0.03	0.71
Time	0.01	0.004	0.001	0.02	0.005	0.001	0.03	0.007	<0.001	0.005	0.005	0.37
iMCI [iMCI]	0.11	0.03	<0.001	0.05	0.04	0.16	0.17	0.05	<0.001	-0.05	0.04	0.26
Time:iMCI [iMCI]	0.04	0.006	<0.001	0.03	0.007	<0.001	0.07	0.01	<0.001	-0.01	0.008	0.12
Slopes	Est.	95% CI	P _{adj}	Est.	95% CI	P _{adj}	Est.	95% CI	P _{adj}	Est.	95% CI	P _{adj}
Stable	0.01	0.005, 0.02	0.003	0.02	0.006, 0.02	0.002	0.03	0.02, 0.05	<0.001	0.005	-0.006, 0.01	0.75
iMCI	0.05	0.04, 0.07	<0.001	0.04	0.03, 0.06	<0.001	0.10	0.08, 0.12	<0.001	-0.008	-0.02, 0.009	0.73
Model 2 - Fixed Effect^b												
(Intercept)	1.22	0.03	<0.001	1.24	0.03	<0.001	2.45	0.04	<0.001	0.02	0.04	0.65
Time	0.01	0.005	0.05	0.01	0.006	0.02	0.03	0.009	0.003	0.007	0.006	0.23
Amyloid status [Ab+]	-0.01	0.03	0.62	0.009	0.03	0.78	-0.008	0.04	0.85	0.02	0.04	0.66
Time:Amyloid status [Ab+]	0.03	0.005	<0.001	0.02	0.006	0.004	0.05	0.01	<0.001	-0.02	0.007	0.009
Slopes	Est.	95% CI	P _{adj}	Est.	95% CI	P _{adj}	Est.	95% CI	P _{adj}	Est.	95% CI	P _{adj}
Ab-	0.01	0.0003, 0.02	0.11	0.01	0.002, 0.02	0.046	0.03	0.008, 0.04	0.009	0.007	-0.005, 0.02	0.47
Ab+	0.04	0.03, 0.05	<0.001	0.03	0.02, 0.04	<0.001	0.08	0.06, 0.10	<0.001	-0.01	-0.02, 0.004	0.33
Model 3 - Fixed Effect^b												
(Intercept)	1.20	0.03	<0.001	1.24	0.03	<0.001	2.42	0.04	<0.001	0.02	0.04	0.54
Time	0.01	0.005	0.04	0.01	0.006	0.05	0.03	0.008	0.004	0.006	0.006	0.31
iMCI [iMCI]	0.12	0.04	0.002	0.04	0.05	0.37	0.18	0.06	0.005	-0.06	0.06	0.32
Amyloid status [Ab+]	-0.03	0.03	0.45	0.0000	0.04	1.00	-0.02	0.05	0.66	0.02	0.04	0.58
Time:iMCI [iMCI]	0.007	0.008	0.38	0.02	0.009	0.06	0.02	0.01	0.10	0.005	0.01	0.60
Time:Amyloid status [Ab+]	0.01	0.006	0.011	0.01	0.007	0.15	0.02	0.01	0.03	-0.009	0.007	0.24
iMCI:Amyloid status [Ab+iMCI]	-0.02	0.06	0.77	0.02	0.07	0.82	-0.03	0.10	0.80	-0.0000	0.09	1.00
Time:iMCI:Amyloid status [Ab+iMCI]	0.07	0.01	<0.001	0.02	0.01	0.11	0.10	0.02	<0.001	-0.04	0.02	0.02
Slopes	Est.	95% CI	P _{adj}	Est.	95% CI	P _{adj}	Est.	95% CI	P _{adj}	Est.	95% CI	P _{adj}
Ab-Stable	0.01	0.0004, 0.02	0.16	0.01	-0.0000, 0.02	0.20	0.02	0.007, 0.04	0.02	0.006	-0.006, 0.02	1.00
Ab+Stable	0.02	0.01, 0.04	<0.001	0.02	0.007, 0.03	0.01	0.05	0.03, 0.07	<0.001	-0.002	-0.02, 0.01	1.00
Ab-iMCI	0.02	0.0004, 0.03	0.18	0.03	0.009, 0.05	0.02	0.05	0.02, 0.07	0.006	0.01	-0.01, 0.03	1.00
Ab+iMCI	0.10	0.08, 0.12	<0.001	0.06	0.04, 0.08	<0.001	0.17	0.14, 0.20	<0.001	-0.03	-0.06, -0.01	0.02
Pairwise comparisons	Est.	95% CI	P _{adj}	Slope	95% CI	P _{adj}	Slope	95% CI	P _{adj}	Slope	95% CI	P _{adj}
Ab-Stable / Ab+Stable	-0.01	-0.03, -0.003	0.07	-0.01	-0.02, 0.003	0.88	-0.02	-0.04, -0.003	0.16	0.009	-0.006, 0.02	1.00
Ab-Stable / Ab-iMCI	-0.007	-0.02, 0.008	1.00	-0.02	-0.03, 0.001	0.39	-0.02	-0.05, 0.004	0.61	-0.005	-0.03, 0.01	1.00
Ab-Stable / Ab+iMCI	-0.09	-0.11, -0.07	<0.001	-0.05	-0.07, -0.03	<0.001	-0.14	-0.17, -0.11	<0.001	0.04	0.02, 0.06	0.003
Ab+Stable / Ab-iMCI	0.008	-0.009, 0.02	1.00	-0.007	-0.03, 0.01	1.00	-0.0000	-0.03, 0.03	1.00	-0.01	-0.04, 0.008	1.00
Ab+Stable / Ab+iMCI	-0.08	-0.09, -0.06	<0.001	-0.04	-0.06, -0.02	0.001	-0.12	-0.15, -0.09	<0.001	0.03	0.007, 0.05	0.07
Ab-iMCI / Ab+iMCI	-0.08	-0.10, -0.06	<0.001	-0.03	-0.06, -0.008	0.06	-0.12	-0.16, -0.08	<0.001	0.04	0.02, 0.07	0.009

eTable 3C. ADNI cohort

	SP-Ecog			Self-Ecog			Cum-Ecog			CAI-Ecog		
	Est.	SE	P	Est.	SE	P	Est.	SE	P	Est.	SE	P
Model 1 - Fixed Effect^a												
(Intercept)	1.20	0.03	< 0.001	1.39	0.04	< 0.001	2.65	0.05	< 0.001	0.18	0.03	< 0.001
Time	0.01	0.009	0.11	0.02	0.007	0.003	0.04	0.008	< 0.001	0.0004	0.005	0.94
iMCI [iMCI]	0.17	0.05	< 0.001	0.14	0.06	0.03	0.31	0.08	< 0.001	-0.05	0.06	0.40
Time:iMCI [iMCI]	0.06	0.02	< 0.001	0.007	0.01	0.57	0.04	0.01	0.02	-0.02	0.01	0.08
Slopes	Est.	95% CI	P _{adj}	Est.	95% CI	P _{adj}	Est.	95% CI	P _{adj}	Est.	95% CI	P _{adj}
Stable	0.02	-0.001, 0.03	0.15	0.02	0.007, 0.03	0.005	0.04	0.02, 0.05	< 0.001	-0.0007	-0.01, 0.01	1.00
iMCI	0.07	0.04, 0.10	< 0.001	0.03	0.004, 0.05	0.05	0.07	0.04, 0.10	< 0.001	-0.02	-0.04, 0.0008	0.12
Model 2 - Fixed Effect^b												
(Intercept)	1.22	0.03	< 0.001	1.40	0.04	< 0.001	2.69	0.05	< 0.001	0.17	0.03	< 0.001
Time	0.02	0.009	0.08	0.01	0.007	0.03	0.03	0.008	< 0.001	-0.005	0.006	0.38
Amyloid status [Ab+]	0.03	0.03	0.34	0.07	0.05	0.12	0.09	0.06	0.13	0.04	0.04	0.37
Time:Amyloid status [Ab+]	0.02	0.01	0.11	0.03	0.009	0.004	0.03	0.01	0.001	0.01	0.008	0.15
Slopes	Est.	95% CI	P _{adj}	Est.	95% CI	P _{adj}	Est.	95% CI	P _{adj}	Est.	95% CI	P _{adj}
Ab-	0.02	-0.002, 0.03	0.16	0.01	0.001, 0.03	0.06	0.03	0.02, 0.05	< 0.001	-0.005	-0.02, 0.005	0.67
Ab+	0.03	0.01, 0.06	0.01	0.04	0.02, 0.06	< 0.001	0.06	0.04, 0.09	< 0.001	0.006	-0.010, 0.02	0.93
Model 3 - Fixed Effect^b												
(Intercept)	1.19	0.03	< 0.001	1.38	0.04	< 0.001	2.64	0.05	< 0.001	0.19	0.03	< 0.001
Time	0.007	0.009	0.46	0.01	0.007	0.05	0.03	0.008	0.001	-0.002	0.006	0.72
iMCI [iMCI]	0.30	0.07	< 0.001	0.14	0.09	0.13	0.40	0.12	< 0.001	-0.19	0.08	0.014
Amyloid status [Ab+]	0.05	0.04	0.14	0.06	0.05	0.23	0.09	0.06	0.15	-0.0001	0.04	1.00
Time:iMCI [iMCI]	0.05	0.02	0.011	-0.0008	0.02	0.96	0.02	0.02	0.24	-0.01	0.01	0.26
Time:Amyloid status [Ab+]	0.01	0.01	0.33	0.03	0.01	0.014	0.03	0.01	0.013	0.01	0.008	0.08
iMCI:Amyloid status [Ab+iMCI]	-0.26	0.09	0.005	-0.01	0.13	0.93	-0.20	0.16	0.21	0.28	0.11	0.010
Time:iMCI:Amyloid status [Ab+iMCI]	0.009	0.03	0.78	0.007	0.02	0.76	0.02	0.03	0.55	-0.01	0.02	0.51
Slopes	Est.	95% CI	P _{adj}	Est.	95% CI	P _{adj}	Est.	95% CI	P _{adj}	Est.	95% CI	P _{adj}
Ab-Stable	0.008	-0.01, 0.03	1.00	0.01	0.0007, 0.03	0.16	0.03	0.01, 0.04	0.002	-0.003	-0.01, 0.008	1.00
Ab+Stable	0.02	-0.006, 0.05	0.52	0.04	0.02, 0.06	< 0.001	0.06	0.03, 0.08	< 0.001	0.01	-0.005, 0.03	0.64
Ab-iMCI	0.06	0.02, 0.10	0.01	0.01	-0.02, 0.04	1.00	0.05	0.01, 0.08	0.02	-0.02	-0.04, 0.007	0.64
Ab+iMCI	0.08	0.04, 0.13	0.001	0.05	0.01, 0.08	0.03	0.10	0.06, 0.14	< 0.001	-0.02	-0.04, 0.01	1.00
Pairwise comparisons	Est.	95% CI	P _{adj}	Slope	95% CI	P _{adj}	Slope	95% CI	P _{adj}	Slope	95% CI	P _{adj}
Ab-Stable / Ab+Stable	-0.01	-0.04, 0.01	1.00	-0.03	-0.05, -0.005	0.08	-0.03	-0.05, -0.006	0.07	-0.01	-0.03, 0.001	0.44
Ab-Stable / Ab-iMCI	-0.05	-0.09, -0.01	0.06	0.0008	-0.03, 0.03	1.00	-0.02	-0.06, 0.01	1.00	0.01	-0.01, 0.04	1.00
Ab-Stable / Ab+iMCI	-0.07	-0.12, -0.03	0.006	-0.03	-0.07, 0.002	0.38	-0.07	-0.11, -0.03	0.006	0.01	-0.02, 0.04	1.00
Ab+Stable / Ab-iMCI	-0.04	-0.08, 0.003	0.41	0.03	-0.007, 0.06	0.72	0.008	-0.03, 0.05	1.00	0.03	0.002, 0.06	0.21
Ab+Stable / Ab+iMCI	-0.06	-0.11, -0.01	0.06	-0.007	-0.04, 0.03	1.00	-0.04	-0.08, 0.004	0.47	0.03	-0.003, 0.06	0.48
Ab-iMCI / Ab+iMCI	-0.02	-0.08, 0.03	1.00	-0.03	-0.07, 0.010	0.78	-0.05	-0.10, 0.005	0.45	-0.002	-0.04, 0.03	1.00

To reduce the number of lines, those referring to covariates are not presented above. ^a Adjusted for age, sex, years of education, cohort (only for combined analyses), setting (only for DELCODE), and their interaction with time. ^b Adjusted in addition for amyloid modality (PET, CSF, plasma).

eTable 6. Detailed results from Model 1 according to amyloid status subgroups.

	Model 1	SP-Ecog			Self-Ecog			Cum-Ecog			CAI-Ecog		
Combined sample	Ab- participants - Fixed Effect	Est.	SE	P	Est.	SE	P	Est.	SE	P	Est.	SE	P
	(Intercept)	1.19	0.02	<0.001	1.22	0.03	<0.001	2.40	0.04	<0.001	0.01	0.03	0.67
	Time	0.007	0.005	0.11	0.01	0.005	0.02	0.02	0.007	0.004	0.006	0.005	0.20
	iMCI [iMCI]	0.17	0.03	<0.001	0.07	0.04	0.09	0.24	0.05	<0.001	-0.09	0.04	0.03
	Time:iMCI [iMCI]	0.01	0.007	0.04	0.01	0.007	0.06	0.02	0.01	0.02	0.0008	0.007	0.90
	Ab+ participants - Fixed Effect	Est.	SE	P	Est.	SE	P	Est.	SE	P	Est.	SE	P
	(Intercept)	1.15	0.04	<0.001	1.22	0.05	<0.001	2.35	0.07	<0.001	0.06	0.06	0.32
	Time	0.02	0.009	0.03	0.02	0.01	0.04	0.04	0.01	0.003	0.005	0.01	0.61
iMCI [iMCI]	0.07	0.04	0.09	0.09	0.05	0.08	0.17	0.07	0.02	0.02	0.06	0.77	
Time:iMCI [iMCI]	0.07	0.01	<0.001	0.02	0.01	0.08	0.08	0.02	<0.001	-0.03	0.01	0.003	
DELCODE	Ab- participants - Fixed Effect	Est.	SE	P	Est.	SE	P	Est.	SE	P	Est.	SE	P
	(Intercept)	1.22	0.03	<0.001	1.22	0.03	<0.001	2.42	0.04	<0.001	-0.009	0.04	0.82
	Time	0.006	0.004	0.13	0.01	0.005	0.009	0.02	0.007	0.002	0.009	0.006	0.11
	iMCI [iMCI]	0.12	0.04	0.001	0.04	0.04	0.32	0.19	0.06	0.002	-0.06	0.05	0.30
	Time:iMCI [iMCI]	0.008	0.007	0.23	0.02	0.008	0.02	0.02	0.01	0.04	0.005	0.01	0.58
	Ab+ participants - Fixed Effect	Est.	SE	P	Est.	SE	P	Est.	SE	P	Est.	SE	P
	(Intercept)	1.15	0.05	<0.001	1.22	0.05	<0.001	2.36	0.07	<0.001	0.06	0.06	0.33
	Time	0.02	0.009	0.02	0.02	0.01	0.13	0.04	0.02	0.02	-0.0002	0.01	0.99
iMCI [iMCI]	0.10	0.06	0.07	0.07	0.07	0.31	0.16	0.09	0.08	-0.04	0.08	0.56	
Time:iMCI [iMCI]	0.07	0.01	<0.001	0.03	0.01	0.015	0.11	0.02	<0.001	-0.03	0.01	0.03	
ADNI	Ab- participants - Fixed Effect	Est.	SE	P	Est.	SE	P	Est.	SE	P	Est.	SE	P
	(Intercept)	1.18	0.03	<0.001	1.37	0.04	<0.001	2.63	0.05	<0.001	0.18	0.03	<0.001
	Time	0.009	0.01	0.38	0.009	0.007	0.17	0.02	0.009	0.009	-0.006	0.005	0.23
	iMCI [iMCI]	0.31	0.07	<0.001	0.14	0.09	0.13	0.40	0.12	<0.001	-0.21	0.07	0.003
	Time:iMCI [iMCI]	0.05	0.02	0.013	0.0006	0.01	0.97	0.03	0.02	0.16	-0.009	0.010	0.36
	Ab+ participants - Fixed Effect	Est.	SE	P	Est.	SE	P	Est.	SE	P	Est.	SE	P
	(Intercept)	1.23	0.05	<0.001	1.43	0.07	<0.001	2.71	0.09	<0.001	0.18	0.07	0.010
	Time	0.03	0.02	0.08	0.06	0.02	0.002	0.08	0.02	<0.001	0.02	0.01	0.14
iMCI [iMCI]	0.03	0.07	0.64	0.17	0.10	0.10	0.21	0.13	0.10	0.13	0.09	0.18	
Time:iMCI [iMCI]	0.07	0.03	0.012	-0.007	0.02	0.77	0.04	0.03	0.17	-0.04	0.02	0.05	

To reduce the number of lines, those referring to covariates are not presented above. Analyses are all adjusted for age, sex, years of education, cohort (only for combined analyses), setting (only for DELCODE), and their interaction with time.

eTable 7. Results from Models 1-3 restricted to SCD patients from the DELCODE cohort, including subgroup slopes and pairwise comparisons with Bonferroni-adjusted p-values using the `ggeffects::hypothesis_test()` function.

	SP-Ecog			Self-Ecog			Cum-Ecog			CAI-Ecog		
	Est.	SE	P	Est.	SE	P	Est.	SE	P	Est.	SE	P
Model 1 - Fixed Effect^a												
(Intercept)	1.41	0.03	< 0.001	1.53	0.04	< 0.001	2.92	0.05	< 0.001	0.09	0.04	0.04
Time	0.02	0.006	0.002	0.01	0.007	0.11	0.04	0.01	0.002	-0.003	0.008	0.69
iMCI [iMCI]	0.09	0.04	0.05	0.03	0.05	0.52	0.13	0.07	0.06	-0.04	0.06	0.53
Time:iMCI [iMCI]	0.05	0.01	< 0.001	0.03	0.01	0.003	0.08	0.02	< 0.001	-0.02	0.01	0.19
Slopes	Est.	95% CI	P _{adj}	Est.	95% CI	P _{adj}	Est.	95% CI	P _{adj}	Est.	95% CI	P _{adj}
Stable	0.02	0.009, 0.03	< 0.001	0.01	0.0005, 0.03	0.08	0.04	0.02, 0.06	< 0.001	-0.002	-0.02, 0.01	1.00
iMCI	0.07	0.05, 0.09	< 0.001	0.05	0.03, 0.07	< 0.001	0.12	0.09, 0.15	< 0.001	-0.02	-0.04, 0.004	0.22
Model 2 - Fixed Effect^b												
(Intercept)	1.45	0.03	< 0.001	1.56	0.04	< 0.001	2.98	0.06	< 0.001	0.09	0.05	0.08
Time	0.02	0.007	0.01	0.01	0.008	0.21	0.04	0.01	0.008	0.001	0.009	0.89
Amyloid status [Ab+]	-0.02	0.04	0.55	0.001	0.05	0.98	-0.03	0.07	0.70	0.02	0.06	0.77
Time:Amyloid status [Ab+]	0.05	0.009	< 0.001	0.02	0.01	0.03	0.07	0.02	< 0.001	-0.03	0.01	0.006
Slopes	Est.	95% CI	P _{adj}	Est.	95% CI	P _{adj}	Est.	95% CI	P _{adj}	Est.	95% CI	P _{adj}
Ab-	0.02	0.006, 0.04	0.009	0.01	-0.003, 0.03	0.22	0.04	0.01, 0.07	0.005	0.002	-0.02, 0.02	1.00
Ab+	0.07	0.05, 0.09	< 0.001	0.03	0.02, 0.05	< 0.001	0.11	0.08, 0.14	< 0.001	-0.03	-0.05, -0.008	0.01
Model 3 - Fixed Effect^b												
(Intercept)	1.42	0.04	< 0.001	1.55	0.05	< 0.001	2.94	0.06	< 0.001	0.10	0.06	0.07
Time	0.02	0.007	0.04	0.005	0.009	0.58	0.03	0.01	0.05	-0.0001	0.01	0.99
iMCI [iMCI]	0.11	0.06	0.07	0.04	0.07	0.58	0.17	0.09	0.07	-0.04	0.09	0.66
Amyloid status [Ab+]	-0.03	0.05	0.55	0.006	0.06	0.92	-0.02	0.08	0.81	0.04	0.07	0.63
Time:iMCI [iMCI]	0.01	0.01	0.41	0.02	0.01	0.09	0.03	0.02	0.15	0.01	0.02	0.55
Time:Amyloid status [Ab+]	0.03	0.009	0.008	0.01	0.01	0.21	0.04	0.02	0.04	-0.02	0.01	0.18
iMCI:Amyloid status [Ab+iMCI]	-0.03	0.09	0.74	-0.03	0.11	0.81	-0.08	0.14	0.56	-0.03	0.13	0.80
Time:iMCI:Amyloid status [Ab+iMCI]	0.06	0.02	< 0.001	0.01	0.02	0.61	0.09	0.03	0.078	-0.04	0.02	0.08
Slopes	Est.	95% CI	P _{adj}	Est.	95% CI	P _{adj}	Est.	95% CI	P _{adj}	Est.	95% CI	P _{adj}
Ab-Stable	0.02	0.002, 0.03	0.09	0.007	-0.01, 0.02	1.00	0.03	0.004, 0.06	0.10	-0.0009	-0.02, 0.02	1.00
Ab+Stable	0.04	0.02, 0.06	< 0.001	0.02	0.0005, 0.04	0.18	0.07	0.03, 0.10	< 0.001	-0.02	-0.04, 0.008	0.73
Ab-iMCI	0.03	0.003, 0.05	0.10	0.03	0.004, 0.06	0.09	0.06	0.02, 0.10	0.01	0.01	-0.02, 0.04	1.00
Ab+iMCI	0.12	0.09, 0.14	< 0.001	0.06	0.03, 0.08	< 0.001	0.18	0.14, 0.22	< 0.001	-0.05	-0.08, -0.02	0.006

Pairwise comparisons	SP-Ecog			Self-Ecog			Cum-Ecog			CAI-Ecog		
	Est.	95% CI	P _{adj}	Slope	95% CI	P _{adj}	Slope	95% CI	P _{adj}	Slope	95% CI	P _{adj}
Ab-Stable / Ab+Stable	-0.03	-0.04, -0.007	0.04	-0.01	-0.04, 0.008	1.00	-0.04	-0.07, -0.002	0.22	0.02	-0.008, 0.04	1.00
Ab-Stable / Ab-iMCI	-0.01	-0.03, 0.01	1.00	-0.02	-0.05, 0.004	0.54	-0.03	-0.07, 0.01	0.87	-0.01	-0.04, 0.02	1.00
Ab-Stable / Ab+iMCI	-0.10	-0.12, -0.08	<0.001	-0.05	-0.08, -0.02	0.003	-0.15	-0.20, -0.11	<0.001	0.05	0.02, 0.08	0.02
Ab+Stable / Ab-iMCI	0.02	-, 0.04	1.00	-0.01	-0.04, 0.02	1.00	0.004	-0.04, 0.05	1.00	-0.03	-0.06, 0.009	0.85
Ab+Stable / Ab+iMCI	-0.07	-0.10, -0.05	<0.001	-0.04	-0.07, -0.005	0.13	-0.12	-0.16, -0.07	<0.001	0.03	-0.002, 0.07	0.41
Ab-iMCI / Ab+iMCI	-0.09	-0.12, -0.06	<0.001	-0.03	-0.06, 0.01	0.97	-0.12	-0.18, -0.07	<0.001	0.06	0.02, 0.10	0.02
Model 1 in Ab- SCD patients	Est.	SE	P	Est.	SE	P	Est.	SE	P	Est.	SE	P
(Intercept)	1.44	0.03	<0.001	1.53	0.04	<0.001	2.94	0.06	<0.001	0.07	0.05	0.21
Time	0.003	0.007	0.67	0.008	0.008	0.32	0.02	0.01	0.13	0.009	0.009	0.35
iMCI [iMCI]	0.11	0.06	0.06	0.05	0.07	0.42	0.19	0.09	0.04	-0.02	0.09	0.79
Time:iMCI [iMCI]	0.01	0.01	0.18	0.03	0.01	0.03	0.04	0.02	0.05	0.008	0.02	0.59
Model 1 in Ab+ SCD patients	Est.	SE	P	Est.	SE	P	Est.	SE	P	Est.	SE	P
(Intercept)	1.35	0.05	<0.001	1.50	0.07	<0.001	2.83	0.09	<0.001	0.13	0.08	0.12
Time	0.03	0.01	0.003	0.008	0.01	0.56	0.04	0.02	0.07	-0.02	0.01	0.16
iMCI [iMCI]	0.07	0.07	0.32	0.009	0.09	0.92	0.08	0.12	0.50	-0.07	0.10	0.53
Time:iMCI [iMCI]	0.07	0.02	<0.001	0.03	0.02	0.10	0.11	0.03	<0.001	-0.04	0.02	0.05

To reduce the number of lines, those referring to covariates are not presented above. ^a Adjusted for age, sex, years of education, and their interaction with time. ^b Adjusted in addition for amyloid modality (PET, CSF, plasma).

eTable 8. Risk of clinical progression to incident mild cognitive impairment (iMCI) based on one-year changes in Ecog scores, stratified by amyloid status.

eTable 6A. Combined sample.

		SP-Ecog			Self-Ecog			Cum-Ecog			CAI-Ecog		
iMCI		N _{obs} [event]	HR [95% CI]	P	N _{obs} [event]	HR [95% CI]	P	N _{obs} [event]	HR [95% CI]	P	N _{obs} [event]	HR [95% CI]	P
Ecog scores				0.002			0.13			<i>0.019</i>			0.59
	Unchanged	243 [26]			222 [27]			247 [27]			255 [32]		
	Decrease	47 [6]	1.35 [0.50, 3.61]	0.55	64 [11]	0.99 [0.45, 2.17]	0.98	48 [8]	1.03 [0.44, 2.42]	0.95	54 [14]	1.44 [0.72, 2.89]	0.30
	Increase	63 [20]	3.24 [1.73, 6.07]	<0.001	67 [14]	1.97 [1.01, 3.86]	<i>0.048</i>	58 [17]	2.54 [1.31, 4.91]	0.005	44 [6]	1.02 [0.41, 2.53]	0.97
Baseline levels		353 [52]	1.11 [0.43, 2.85]	0.83	353 [52]	1.29 [0.50, 3.35]	0.59	353 [52]	1.23 [0.70, 2.15]	0.47	353 [52]	0.83 [0.39, 1.76]	0.63
iMCI*Ab													
Ecog scores				0.20			0.90			0.002			0.50
	Unchanged	243 [26]			222 [27]			247 [27]			255 [32]		
	Decrease	47 [6]	2.07 [0.61, 7.05]	0.80	64 [11]	1.11 [0.39, 3.14]	0.80	48 [8]	1.61 [0.50, 5.16]	0.40	54 [14]	1.75 [0.70, 4.37]	0.20
	Increase	63 [20]	2.42 [0.89, 6.57]	<i>0.08</i>	67 [14]	1.32 [0.47, 3.74]	0.60	58 [17]	6.04 [2.27, 16.1]	<0.001	44 [6]	1.32 [0.47, 3.74]	0.90
Baseline levels		353 [52]	1.64 [0.46, 5.79]	0.40	353 [52]	1.43 [0.45, 4.53]	0.50	353 [52]	1.24 [0.60, 2.54]	0.60	353 [52]	1.43 [0.45, 4.53]	0.20
Ecog scores * Amyloid status				0.50			0.30			<i>0.09</i>			0.80
	Decrease * Aβ+	18 [2]	0.45 [0.05, 3.80]	0.50	21 [4]	0.98 [0.19, 5.11]	>0.90	15 [3]	0.45 [0.08, 2.72]	0.40	17 [6]	0.82 [0.20, 3.35]	0.80
	Increase * Aβ+	26 [12]	1.64 [0.43, 6.22]	0.50	27 [9]	2.76 [0.70, 10.90]	0.15	25 [7]	0.22 [0.06, 0.87]	<i>0.03</i>	20 [4]	1.60 [0.24, 10.50]	0.60
Baseline levels * Amyloid status		123 [26]	0.43 [0.06, 3.05]	0.40	123 [26]	0.77 [0.10, 5.80]	0.80	123 [26]	0.77 [0.26, 2.32]	0.60	123 [26]	3.08 [0.68, 13.80]	0.14
iMCI in Ab-													
Ecog scores				0.13			0.83			<i>0.014</i>			0.62
	Unchanged	164 [14]			147 [14]			164 [11]			169 [16]		
	Decrease	29 [4]	2.55 [0.72, 9.03]	0.15	43 [7]	1.17 [0.39, 3.50]	0.78	33 [5]	1.44 [0.40, 5.15]	0.58	37 [8]	1.51 [0.57, 3.96]	0.41
	Increase	37 [8]	2.83 [0.99, 8.07]	<i>0.05</i>	40 [5]	1.40 [0.49, 4.01]	0.54	33 [10]	4.73 [1.66, 13.5]	0.004	24 [2]	0.77 [0.17, 3.59]	0.74
Baseline levels		230 [26]	1.70 [0.43, 6.78]	0.45	230 [26]	1.26 [0.36, 4.40]	0.72	230 [26]	1.25 [0.55, 2.84]	0.59	230 [26]	0.59 [0.21, 1.68]	0.33
iMCI in Ab+													
Ecog scores				0.003			0.11			0.57			0.82
	Unchanged	79 [12]			75 [13]			83 [16]			86 [16]		
	Decrease	18 [2]	0.60 [0.11, 3.22]	0.55	21 [4]	0.75 [0.21, 2.72]	0.66	15 [3]	0.63 [0.16, 2.41]	0.49	17 [6]	1.42 [0.46, 4.42]	0.54
	Increase	26 [12]	4.18 [1.80, 9.73]	<0.001	27 [9]	2.44 [0.92, 6.46]	<i>0.07</i>	25 [7]	1.37 [0.52, 3.62]	0.53	20 [4]	0.98 [0.31, 3.10]	0.97
Baseline levels		123 [26]	1.41 [0.26, 7.73]	0.69	123 [26]	1.89 [0.35, 10.3]	0.46	123 [26]	1.32 [0.49, 3.55]	0.58	123 [26]	1.29 [0.40, 4.15]	0.66

eTable 6B. DELCODE cohort.

DELCODE		SP-Ecog			Self-Ecog			Cum-Ecog			CAI-Ecog		
		N _{obs} [event]	HR [95% CI]	P	N _{obs} [event]	HR [95% CI]	P	N _{obs} [event]	HR [95% CI]	P	N _{obs} [event]	HR [95% CI]	P
iMCI	Overall			0.008			0.15			0.007			0.54
	Unchanged	148 [20]			143 [21]			154 [19]			165 [26]		
	Decrease	30 [5]	1.72 [0.45, 3.14]	0.33	40 [7]	0.99 [0.38, 2.61]	0.99	30 [7]	1.89 [0.72, 4.94]	0.19	33 [9]	1.51 [0.67, 3.40]	0.32
	Increase	37 [13]	3.61 [1.69, 5.94]	<0.001	32 [10]	2.18 [1.01, 4.70]	<i>0.047</i>	31 [12]	3.70 [1.69, 8.08]	0.001	17 [3]	0.82 [0.24, 2.82]	0.74
Baseline levels		215 [38]	0.70 [0.46, 2.99]	0.52	215 [38]	1.12 [0.35, 3.60]	0.85	215 [38]	0.87 [0.44, 1.72]	0.68	215 [38]	0.91 [0.39, 2.11]	0.83
iMCI in Ab-	Overall			<i>0.07</i>			0.74			0.007			0.91
	Unchanged	102 [10]			97 [12]			102 [8]			109 [13]		
	Decrease	19 [4]	3.92 [0.56, 6.75]	<i>0.05</i>	29 [4]	0.97 [0.27, 3.49]	0.96	23 [4]	2.66 [0.68, 10.4]	0.16	25 [5]	1.28 [0.40, 4.05]	0.68
	Increase	22 [6]	3.45 [0.92, 7.51]	<i>0.05</i>	17 [4]	1.57 [0.50, 4.98]	0.44	18 [8]	7.56 [2.20, 26.0]	0.001	9 [2]	0.98 [0.20, 4.90]	0.98
Baseline levels		143 [20]	0.71 [0.48, 7.35]	0.69	143 [20]	1.36 [0.33, 5.52]	0.67	143 [20]	0.89 [0.33, 2.38]	0.81	143 [20]	0.88 [0.27, 2.87]	0.84
iMCI in Ab+	Overall			<i>0.03</i>			0.21			0.56			0.21
	Unchanged	46 [10]			46 [9]			52 [11]			56 [13]		
	Decrease	11 [1]	0.43 [0.05, 4.10]	0.46	11 [3]	0.84 [0.21, 5.07]	0.97	7 [3]	1.95 [0.44, 8.56]	0.38	8 [4]	2.69 [0.81, 8.90]	0.11
	Increase	15 [7]	3.77 [1.28, 11.1]	<i>0.02</i>	15 [6]	1.79 [0.87, 9.70]	<i>0.08</i>	13 [4]	1.61 [0.50, 5.22]	0.43	8 [1]	0.48 [0.06, 3.74]	0.49
Baseline levels		72 [18]	1.20 [0.14, 10.4]	0.87	72 [18]	1.48 [0.16, 11.7]	0.79	72 [18]	0.87 [0.24, 3.24]	0.84	72 [18]	1.07 [0.28, 4.04]	0.92
DELCODE, SCD patients only													
		N _{obs} [event]	HR [95% CI]	P	N _{obs} [event]	HR [95% CI]	P	N _{obs} [event]	HR [95% CI]	P	N _{obs} [event]	HR [95% CI]	P
iMCI	Overall			0.19			0.13			0.26			0.89
	Unchanged	90 [16]			85 [16]			94 [16]			94 [16]		
	Decrease	24 [4]	1.59 [0.48, 5.29]	0.45	31 [4]	0.74 [0.22, 2.47]	0.62	24 [4]	1.04 [0.32, 3.35]	0.95	24 [4]	1.51 [0.67, 3.40]	0.90
	Increase	29 [9]	2.40 [0.96, 5.98]	<i>0.06</i>	27 [9]	2.22 [0.96, 5.13]	<i>0.06</i>	25 [9]	2.08 [0.88, 4.94]	0.10	25 [9]	0.82 [0.24, 2.82]	0.64
Baseline levels		143 [29]	0.37 [0.11, 1.29]	0.12	143 [29]	0.69 [0.19, 2.56]	0.58	143 [29]	0.61 [0.29, 1.27]	0.18	143 [29]	0.91 [0.39, 2.11]	0.70
iMCI in Ab-	Overall			0.29			0.43			0.22			0.43
	Unchanged	61 [8]			58 [8]			60 [6]			67 [10]		
	Decrease	16 [3]	3.66 [0.77, 17.3]	0.10	24 [3]	1.12 [0.25, 5.02]	0.88	20 [3]	1.70 [0.38, 7.60]	0.49	20 [3]	0.40 [0.09, 1.75]	0.22
	Increase	19 [4]	1.76 [0.41, 7.60]	0.45	14 [4]	2.39 [0.67, 8.45]	0.18	16 [6]	3.49 [0.88, 13.9]	<i>0.07</i>	9 [2]	0.60 [0.12, 3.03]	0.54
Baseline levels		96 [15]	0.19 [0.03, 1.51]	0.12	96 [15]	0.88 [0.19, 4.10]	0.87	96 [15]	0.51 [0.17, 1.54]	0.23	96 [15]	1.95 [0.50, 7.58]	0.34
iMCI in Ab+	Overall			<i>0.09</i>			<i>0.44</i>			0.97			0.26
	Unchanged	29 [8]			27 [8]			34 [10]			36 [10]		
	Decrease	8 [1]	0.59 [0.06, 5.75]	0.65	7 [1]	0.59 [0.05, 5.37]	0.59	4 [1]	0.84 [0.09, 7.93]	0.88	5 [3]	3.10 [0.73, 13.1]	0.12
	Increase	10 [5]	3.95 [1.11, 14.1]	<i>0.03</i>	13 [5]	3.95 [0.51, 6.71]	<i>0.35</i>	9 [3]	1.15 [0.30, 4.43]	0.83	6 [1]	0.54 [0.07, 4.32]	0.57
Baseline levels		47 [14]	0.71 [0.08, 6.55]	0.76	47 [14]	0.71 [0.05, 7.19]	0.69	47 [14]	0.54 [0.12, 2.50]	0.43	47 [14]	1.05 [0.25, 4.43]	0.94

eTable 6C. ADNI cohort.

		SP-Ecog			Self-Ecog			Cum-Ecog			CAI-Ecog		
		N _{obs} [event]	HR [95% CI]	P	N _{obs} [event]	HR [95% CI]	P	N _{obs} [event]	HR [95% CI]	P	N _{obs} [event]	HR [95% CI]	P
iMCI				0.13			0.85			0.08			0.97
Overall													
	Unchanged	95 [6]			79 [6]			93 [8]			90 [6]		
	Decrease	17 [1]	0.49 [0.05, 4.52]	0.53	24 [4]	0.93 [0.20, 4.26]	0.93	18 [1]	0.13 [0.01, 1.26]	0.08	21 [5]	1.08 [0.21, 5.57]	0.92
	Increase	26 [7]	3.12 [0.88, 11.1]	0.08	35 [4]	1.43 [0.33, 6.22]	0.63	27 [5]	1.01 [0.29, 3.56]	0.98	27 [3]	1.21 [0.29, 5.08]	0.79
Baseline levels		138 [14]	6.61 [1.50, 29.1]	0.012	138 [14]	2.18 [0.38, 12.6]	0.38	138 [14]	2.97 [1.26, 7.02]	0.013	138 [14]	0.41 [0.06, 2.94]	0.38
iMCI in Ab-				0.24			0.83			0.12			0.52
Overall													
	Unchanged	62 [4]			50 [2]			62 [3]			60 [3]		
	Decrease	10 [0]	0.00 [0.00, Inf]	1.00	14 [3]	2.01 [0.16, 25.2]	0.59	10 [1]	0.00 [0.00, Inf]	1.00	12 [3]	1.97 [0.20, 19.4]	0.56
	Increase	15 [2]	4.61 [0.48, 44.8]	0.19	23 [1]	1.03 [0.06, 17.1]	0.98	15 [2]	1.64 [0.23, 11.8]	0.62	15 [0]	0.00 [0.00, Inf]	1.00
Baseline levels		87 [6]	16.58 [1.61, 171]	0.02	87 [6]	1.56 [0.08, 31.8]	0.77	87 [6]	4.06 [1.08, 15.2]	0.04	87 [6]	0.07 [0.00, 1.62]	0.10
iMCI in Ab+				0.13			0.25			0.02			0.23
Overall													
	Unchanged	33 [2]			29 [4]			31 [5]			30 [3]		
	Decrease	7 [1]	1.26 [0.04, 38.8]	0.89	10 [1]	0.20 [0.01, 2.84]	0.23	8 [0]	0.00 [0.00, Inf]	1.00	9 [2]	0.08 [0.00, 2.24]	0.14
	Increase	11 [5]	7.22 [0.66, 79.3]	0.11	12 [3]	1.64 [0.25, 10.8]	0.61	12 [3]	1.13 [0.14, 9.16]	0.91	12 [3]	0.65 [0.10, 4.16]	0.65
Baseline levels		51 [8]	1.24 [0.01, 210]	0.93	51 [8]	7.03 [0.34, 146]	0.21	51 [8]	4.58 [0.46, 45.7]	0.20	51 [8]	3.29 [0.25, 43.4]	0.37

eTable 9. Risk of clinical progression to incident mild cognitive impairment (iMCI) based on one-year changes in Ecog scores, joint model including self- and study partner-reports.

iMCI	Combined sample			DELCODE			ADNI			DELCODE, SCD patients		
	N _{obs} [event]	HR [95% CI]	P	N _{obs} [event]	HR [95% CI]	P	N _{obs} [event]	HR [95% CI]	P	N _{obs} [event]	HR [95% CI]	P
SP-Ecog scores			0.002			0.008			0.13			0.008
Unchanged	243 [26]			148 [20]			95 [6]			148 [20]		
Decrease	47 [6]	1.45 [0.54, 3.90]	0.50	30 [5]	2.12 [0.70, 6.38]	0.20	17 [1]	0.43 [0.04, 4.62]	0.50	30 [5]	1.72 [0.45, 3.14]	0.33
Increase	63 [20]	3.43 [1.82, 6.49]	<0.001	37 [13]	4.24 [1.99, 9.04]	<0.001	26 [7]	2.75 [0.70, 10.9]	0.15	37 [13]	3.61 [1.69, 5.94]	<0.001
Baseline SP-Ecog levels	353 [52]	1.15 [0.45, 2.97]	0.80	215 [38]	0.71 [0.23, 2.17]	0.50	138 [14]	10.4 [1.55, 69.8]	0.02	215 [38]	0.70 [0.46, 2.99]	0.52
Self-Ecog scores			0.002			0.15			0.85			0.15
Unchanged	222 [27]			143 [21]			79 [6]			143 [21]		
Decrease	64 [11]	1.28 [0.59, 2.79]	0.50	40 [7]	1.19 [0.45, 3.14]	0.70	24 [4]	1.14 [0.23, 5.58]	0.90	40 [7]	0.99 [0.38, 2.61]	0.99
Increase	67 [14]	2.25 [1.13, 4.46]	0.02	32 [10]	2.93 [1.32, 6.48]	0.008	35 [4]	2.11 [0.45, 9.82]	0.30	32 [10]	2.18 [1.01, 4.70]	0.047
Baseline Self-Ecog levels	353 [52]	0.93 [0.36, 2.41]	0.90	215 [38]	1.05 [0.34, 3.21]	0.90	138 [14]	0.55 [0.06, 4.62]	0.60	215 [38]	1.12 [0.35, 3.60]	0.85

eTable 10. Results from Models 2-3 replacing amyloid status by a combination of amyloid and tau status (AT status), including subgroup slopes and pairwise comparisons with Bonferroni-adjusted p-values using the `ggeffects::hypothesis_test()` function.

eTable 8A. Combined sample.

		SP-Ecog			Self-Ecog			Cum-Ecog			CAI-Ecog		
		Est.	SE	P	Est.	SE	P	Est.	SE	P	Est.	SE	P
Model 2 - Fixed Effect													
(Intercept)		1.19	0.03	< 0.001	1.22	0.03	< 0.001	2.40	0.05	< 0.001	0.02	0.04	0.57
Time		0.005	0.006	0.37	0.01	0.006	0.08	0.02	0.009	0.05	0.006	0.006	0.31
AT status				0.72			0.49			0.58			0.70
	Ab+T-	0.02	0.03	0.41	0.03	0.03	0.39	0.03	0.04	0.41	-0.007	0.03	0.84
	Ab+T+	-0.003	0.03	0.92	0.04	0.04	0.33	0.05	0.06	0.40	0.03	0.04	0.45
Time:AT status				< 0.001			< 0.001			< 0.001			0.23
	Ab+T-	0.03	0.005	< 0.001	0.02	0.006	0.002	0.04	0.008	< 0.001	-0.006	0.006	0.35
	Ab+T+	0.05	0.008	< 0.001	0.03	0.008	< 0.001	0.06	0.01	< 0.001	-0.01	0.008	0.11
Slopes		Est.	95% CI	P _{adj}	Est.	95% CI	P _{adj}	Est.	95% CI	P _{adj}	Est.	95% CI	P _{adj}
Ab-T-		0.004	-0.007, 0.01	1.00	0.01	-0.002, 0.02	0.30	0.02	-0.002, 0.03	0.24	0.006	-0.006, 0.02	0.91
Ab+T-		0.03	0.02, 0.04	< 0.001	0.03	0.01, 0.04	< 0.001	0.06	0.04, 0.08	< 0.001	0.0009	-0.01, 0.02	1.00
Ab+T+		0.05	0.03, 0.07	< 0.001	0.04	0.02, 0.06	< 0.001	0.07	0.05, 0.10	< 0.001	-0.007	-0.03, 0.01	1.00
Pairwise comparisons		Est.	95% CI	P _{adj}	Slope	95% CI	P _{adj}	Slope	95% CI	P _{adj}	Slope	95% CI	P _{adj}
(Ab-T-)-(Ab+T-)		-0.03	-0.04, -0.02	< 0.001	-0.02	-0.03, -0.006	0.007	-0.05	-0.06, -0.03	< 0.001	0.006	-0.006, 0.02	1.00
(Ab-T-)-(Ab+T+)		-0.05	-0.06, -0.03	< 0.001	-0.03	-0.05, -0.01	< 0.001	-0.06	-0.08, -0.04	< 0.001	0.01	-0.003, 0.03	0.33
(Ab+T-)-(Ab+T+)		-0.02	-0.04, -0.003	0.06	-0.01	-0.03, 0.006	0.55	-0.01	-0.04, 0.01	0.88	0.008	-0.01, 0.03	1.00
Model 3 - Fixed Effect													
(Intercept)		1.18	0.03	< 0.001	1.21	0.03	< 0.001	2.38	0.05	< 0.001	0.03	0.04	0.47
Time		0.005	0.005	0.31	0.01	0.006	0.10	0.02	0.008	0.05	0.005	0.006	0.37
iMCI [iMCI]		0.15	0.04	< 0.001	0.08	0.05	0.10	0.23	0.06	< 0.001	-0.05	0.05	0.31
AT status				0.91			0.47			0.60			0.66
	Ab+T-	0.01	0.03	0.62	0.02	0.03	0.48	0.02	0.05	0.59	0.001	0.04	0.97
	Ab+T+	0.003	0.04	0.94	0.05	0.05	0.28	0.06	0.07	0.34	0.05	0.05	0.38
Time:iMCI [iMCI]		-0.0003	0.008	0.97	0.008	0.009	0.33	0.005	0.01	0.67	0.007	0.009	0.41
Time:AT status				0.008			0.001			0.001			0.29
	Time:Ab+T-	0.01	0.006	0.02	0.006	0.006	0.32	0.02	0.008	0.02	-0.006	0.006	0.37
	Time:Ab+T+	0.02	0.009	0.02	0.04	0.01	< 0.001	0.04	0.01	0.002	0.01	0.01	0.26
iMCI:AT status				0.32			0.60			0.28			0.97
	Ab+T-.iMCI	-0.01	0.06	0.87	-0.009	0.08	0.91	-0.03	0.11	0.79	-0.02	0.09	0.78

		SP-Ecog			Self-Ecog			Cum-Ecog			CAI-Ecog		
Time:iMCI:AT status	Ab+T+. iMCI	-0.11	0.07	0.13	-0.09	0.09	0.32	-0.19	0.12	0.11	-0.007	0.10	0.95
				<0.001			<0.001			<0.001			<0.001
	Ab+T-.iMCI	0.07	0.01	<0.001	0.05	0.01	<0.001	0.13	0.02	<0.001	-0.003	0.02	0.87
	Ab+T+.iMCI	0.07	0.02	<0.001	-0.02	0.02	0.21	0.06	0.02	0.02	-0.08	0.02	<0.001
Slopes		Est.	95% CI	P _{adj}	Est.	95% CI	P _{adj}	Est.	95% CI	P _{adj}	Est.	95% CI	P _{adj}
Ab-T-.Stable		0.005	-0.006, 0.01	1.00	0.009	-0.002, 0.02	0.73	0.01	-0.001, 0.03	0.43	0.006	-0.006, 0.02	1.00
Ab+T-.Stable		0.02	0.004, 0.03	0.05	0.02	0.0006, 0.03	0.25	0.03	0.01, 0.06	0.004	-0.0001	-0.02, 0.02	1.00
Ab+T+.Stable		0.03	0.007, 0.05	0.05	0.05	0.02, 0.07	<0.001	0.05	0.03, 0.08	0.001	0.02	-0.005, 0.04	0.77
Ab-T-.iMCI		0.004	-0.01, 0.02	1.00	0.02	-0.002, 0.04	0.43	0.02	-0.006, 0.05	0.84	0.01	-0.007, 0.03	1.00
Ab+T-. iMCI		0.09	0.07, 0.11	<0.001	0.08	0.05, 0.10	<0.001	0.17	0.13, 0.20	<0.001	0.005	-0.02, 0.03	1.00
Ab+T+. iMCI		0.10	0.07, 0.12	<0.001	0.03	0.005, 0.06	0.13	0.11	0.08, 0.15	<0.001	-0.05	-0.08, -0.03	<0.001
Pairwise comparisons		Est.	95% CI	P _{adj}	Slope	95% CI	P _{adj}	Slope	95% CI	P _{adj}	Slope	95% CI	P _{adj}
Ab-T-.Stable / Ab+T-.Stable		-0.01	-0.02, -0.002	0.32	-0.006	-0.02, 0.006	1.00	-0.02	-0.04, -0.004	0.24	0.006	-0.007, 0.02	1.00
Ab-T-.Stable / Ab+T+.Stable		-0.02	-0.04, -0.004	0.24	-0.04	-0.06, -0.02	0.003	-0.04	-0.06, -0.01	0.03	-0.01	-0.03, 0.008	1.00
Ab-T-.Stable / Ab-T-.iMCI		0.0003	-0.01, 0.02	1.00	-0.008	-0.03, 0.009	1.00	-0.005	-0.03, 0.02	1.00	-0.007	-0.02, 0.01	1.00
Ab-T-.Stable / Ab+T-.iMCI		-0.08	-0.10, -0.06	<0.001	-0.07	-0.09, -0.05	<0.001	-0.15	-0.18, -0.12	<0.001	0.001	-0.02, 0.02	1.00
Ab-T-.Stable / Ab+T+.iMCI		-0.09	-0.12, -0.07	<0.001	-0.02	-0.05, 0.003	1.00	-0.10	-0.13, -0.07	<0.001	0.06	0.03, 0.09	<0.001
Ab+T-.Stable / Ab+T+.Stable		-0.009	-0.03, 0.01	1.00	-0.03	-0.05, -0.009	0.08	-0.02	-0.05, 0.009	1.00	-0.02	-0.04, 0.004	1.00
Ab+T-.Stable / Ab-T-.iMCI		0.01	-0.004, 0.03	1.00	-0.002	-0.02, 0.02	1.00	0.02	-0.01, 0.04	1.00	-0.01	-0.03, 0.007	1.00
Ab+T-.Stable / Ab+T-.iMCI		-0.07	-0.09, -0.05	<0.001	-0.06	-0.09, -0.04	<0.001	-0.13	-0.17, -0.10	<0.001	-0.005	-0.03, 0.02	1.00
Ab+T-.Stable / Ab+T+.iMCI		-0.08	-0.11, -0.06	<0.001	-0.02	-0.04, 0.01	1.00	-0.08	-0.12, -0.04	<0.001	0.05	0.03, 0.08	0.002
Ab+T+.Stable / Ab-T-.iMCI		0.02	0.0000, 0.04	0.74	0.03	0.004, 0.05	0.35	0.03	0.002, 0.07	0.58	0.004	-0.02, 0.03	1.00
Ab+T+.Stable / Ab+T-.iMCI		-0.06	-0.09, -0.03	<0.001	-0.03	-0.06, -0.003	0.41	-0.11	-0.15, -0.07	<0.001	0.01	-0.02, 0.04	1.00
Ab+T+.Stable / Ab+T+.iMCI		-0.07	-0.10, -0.04	<0.001	0.01	-0.02, 0.04	1.00	-0.06	-0.10, -0.02	0.05	0.07	0.04, 0.10	<0.001
Ab-T-.iMCI / Ab+T-.iMCI		-0.08	-0.11, -0.06	<0.001	-0.06	-0.09, -0.03	<0.001	-0.15	-0.18, -0.11	<0.001	0.008	-0.02, 0.04	1.00
Ab-T-.iMCI / Ab+T+.iMCI		-0.09	-0.12, -0.07	<0.001	-0.01	-0.04, 0.02	1.00	-0.09	-0.13, -0.06	<0.001	0.07	0.04, 0.10	<0.001
Ab+T-.iMCI / Ab+T+.iMCI		-0.01	-0.04, 0.02	1.00	0.05	0.01, 0.08	0.09	0.05	0.008, 0.10	0.32	0.06	0.02, 0.09	0.010

To reduce the number of lines, those referring to covariates are not presented above. Adjusted for age, sex, years of education, amyloid and tau modalities (PET, CSF, plasma, Mixed), cohort (only for combined analyses), setting (only for DELCODE, except when restricted to SCD patients), and their interaction with time.

eTable 8B. DELCODE cohort.

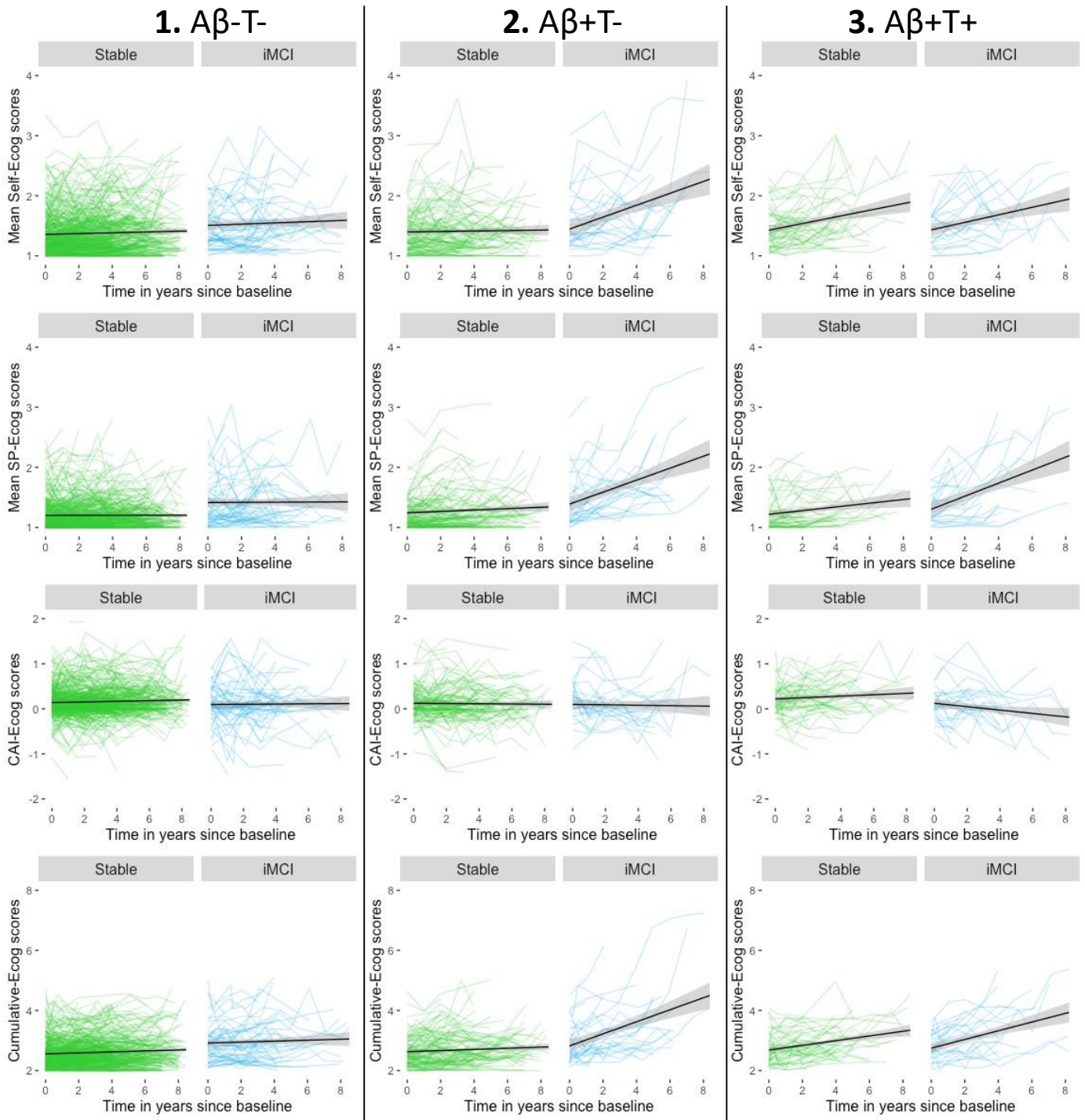
	SP-Ecog			Self-Ecog			Cum-Ecog			CAI-Ecog			
	Est.	SE	P	Est.	SE	P	Est.	SE	P	Est.	SE	P	
Model 2 - Fixed Effect													
(Intercept)	1.21	0.03	< 0.001	1.24	0.03	< 0.001	2.44	0.04	< 0.001	0.02	0.04	0.53	
Time	0.007	0.005	0.18	0.01	0.006	0.09	0.02	0.009	0.03	0.007	0.006	0.29	
AT status			0.67			0.83			0.80			0.93	
	Ab+T-	-0.006	0.03	0.92	0.01	0.04	0.71	-0.003	0.05	0.96	0.004	0.04	0.93
	Ab+T+	-0.04	0.05	0.37	-0.02	0.06	0.69	-0.05	0.08	0.51	0.03	0.07	0.71
Time:AT status			< 0.001			0.008			< 0.001			0.008	
	Ab+T-	0.03	0.006	< 0.001	0.02	0.007	0.008	0.05	0.01	< 0.001	-0.01	0.007	0.05
	Ab+T+	0.05	0.01	< 0.001	0.03	0.01	0.03	0.07	0.02	< 0.001	-0.04	0.01	0.006
Slopes	Est.	95% CI	P _{adj}	Est.	95% CI	P _{adj}	Est.	95% CI	P _{adj}	Est.	95% CI	P _{adj}	
Ab-T-	0.007	-0.004, 0.02	0.64	0.009	-0.002, 0.02	0.35	0.02	0.0004, 0.04	0.14	0.007	-0.006, 0.02	0.93	
Ab+T-	0.04	0.03, 0.05	< 0.001	0.03	0.01, 0.04	< 0.001	0.07	0.05, 0.09	< 0.001	-0.008	-0.02, 0.007	0.95	
Ab+T+	0.06	0.04, 0.08	< 0.001	0.03	0.01, 0.06	0.01	0.09	0.05, 0.13	< 0.001	-0.03	-0.06, -0.004	0.07	
Pairwise comparisons	Est.	95% CI	P _{adj}	Slope	95% CI	P _{adj}	Slope	95% CI	P _{adj}	Slope	95% CI	P _{adj}	
(Ab-T-)-(Ab+T-)	-0.03	-0.04, -0.02	< 0.001	-0.02	-0.03, -0.005	0.02	-0.05	-0.07, -0.03	< 0.001	0.01	0.0001, 0.03	0.15	
(Ab-T-)-(Ab+T+)	-0.05	-0.07, -0.03	< 0.001	-0.03	-0.05, -0.003	0.09	-0.07	-0.11, -0.03	< 0.001	0.04	0.01, 0.06	0.02	
(Ab+T-)-(Ab+T+)	-0.02	-0.04, 0.002	0.23	-0.008	-0.03, 0.02	1.00	-0.02	-0.06, 0.02	1.00	0.02	-0.005, 0.05	0.33	
Model 3 - Fixed Effect													
(Intercept)	1.20	0.03	< 0.001	1.24	0.03	< 0.001	2.42	0.04	< 0.001	0.02	0.04	0.56	
Time	0.008	0.005	0.11	0.008	0.006	0.15	0.02	0.009	0.02	0.005	0.007	0.44	
iMCI [iMCI]	0.09	0.04	0.04	0.05	0.05	0.28	0.16	0.07	0.02	-0.01	0.06	0.86	
AT status			0.48			0.97			0.89			0.55	
	Ab+T-	-0.02	0.03	0.48	0.01	0.04	0.80	-0.02	0.06	0.72	0.03	0.05	0.55
	Ab+T+	-0.07	0.06	0.27	0.004	0.08	0.95	-0.04	0.10	0.69	0.09	0.09	0.31
Time:iMCI [iMCI]	0.003	0.008	0.72	0.02	0.009	0.07	0.02	0.01	0.24	0.009	0.01	0.38	
Time:AT status			0.015			0.17			0.05			0.32	
	Time:Ab+T-	0.01	0.006	0.02	0.007	0.007	0.35	0.02	0.01	0.04	-0.01	0.008	0.19
	Time:Ab+T+	0.03	0.01	0.04	0.03	0.01	0.08	0.04	0.02	0.09	-0.02	0.02	0.35
iMCI:AT status			0.68			0.72			0.70			0.46	
	Ab+T-.iMCI	0.06	0.07	0.39	0.003	0.09	0.98	0.03	0.12	0.81	-0.10	0.11	0.33
	Ab+T+. iMCI	0.007	0.10	0.94	-0.09	0.12	0.44	-0.12	0.16	0.46	-0.14	0.14	0.33
Time:iMCI:AT status			< 0.001			0.03			< 0.001			0.10	
	Ab+T-.iMCI	0.08	0.01	< 0.001	0.04	0.02	0.012	0.13	0.02	< 0.001	-0.02	0.02	0.26

	SP-Ecog			Self-Ecog			Cum-Ecog			CAI-Ecog		
Ab+T+.iMCI	0.06	0.02	0.004	-0.008	0.02	0.73	0.07	0.03	<i>0.05</i>	-0.06	0.03	<i>0.04</i>
Slopes	Est.	95% CI	P _{adj}	Est.	95% CI	P _{adj}	Est.	95% CI	P _{adj}	Est.	95% CI	P _{adj}
Ab-T-.Stable	0.008	-0.002, 0.02	0.79	0.008	-0.004, 0.02	1.00	0.02	0.002, 0.04	0.19	0.005	-0.008, 0.02	1.00
Ab+T-.Stable	0.02	0.01, 0.04	0.004	0.01	-0.0004, 0.03	0.34	0.04	0.02, 0.06	0.002	-0.006	-0.02, 0.01	1.00
Ab+T+.Stable	0.03	0.009, 0.06	0.04	0.03	0.005, 0.06	0.12	0.06	0.01, 0.10	<i>0.06</i>	-0.01	-0.04, 0.02	1.00
Ab-T-.iMCI	0.01	-0.006, 0.03	1.00	0.02	0.005, 0.04	<i>0.08</i>	0.04	0.006, 0.06	0.11	0.01	-0.008, 0.04	1.00
Ab+T-. iMCI	0.10	0.08, 0.12	<0.001	0.07	0.05, 0.10	<0.001	0.19	0.15, 0.22	<0.001	-0.02	-0.05, 0.01	1.00
Ab+T+. iMCI	0.10	0.07, 0.13	<0.001	0.04	0.008, 0.08	0.10	0.14	0.09, 0.19	<0.001	-0.06	-0.10, -0.02	0.02
Pairwise comparisons	Est.	95% CI	P _{adj}	Slope	95% CI	P _{adj}	Slope	95% CI	P _{adj}	Slope	95% CI	P _{adj}
Ab-T-.Stable / Ab+T-.Stable	-0.01	-0.03, -0.002	0.28	-0.007	-0.02, 0.008	1.00	-0.02	-0.04, -0.0006	0.66	0.01	-0.005, 0.03	1.00
Ab-T-.Stable / Ab+T+.Stable	-0.03	-0.05, -0.002	0.56	-0.03	-0.05, 0.003	1.00	-0.04	-0.08, 0.005	1.00	0.02	-0.02, 0.05	1.00
Ab-T-.Stable / Ab-T-.iMCI	-0.003	-0.02, 0.01	1.00	-0.02	-0.04, 0.002	1.00	-0.02	-0.04, 0.01	1.00	-0.009	-0.03, 0.01	1.00
Ab-T-.Stable / Ab+T-.iMCI	-0.09	-0.12, -0.07	<0.001	-0.06	-0.09, -0.04	<0.001	-0.17	-0.20, -0.13	<0.001	0.02	-0.005, 0.05	1.00
Ab-T-.Stable / Ab+T+.iMCI	-0.09	-0.12, -0.06	<0.001	-0.03	-0.07, -0.0003	0.72	-0.12	-0.17, -0.07	<0.001	0.06	0.02, 0.10	0.02
Ab+T-.Stable / Ab+T+.Stable	-0.01	-0.04, 0.01	1.00	-0.02	-0.05, 0.01	1.00	-0.02	-0.06, 0.03	1.00	0.005	-0.03, 0.04	1.00
Ab+T-.Stable / Ab-T-.iMCI	0.01	-0.006, 0.03	1.00	-0.01	-0.03, 0.01	1.00	0.006	-0.03, 0.04	1.00	-0.02	-0.04, 0.004	1.00
Ab+T-.Stable / Ab+T-.iMCI	-0.08	-0.10, -0.06	<0.001	-0.06	-0.08, -0.03	<0.001	-0.15	-0.19, -0.11	<0.001	0.01	-0.02, 0.04	1.00
Ab+T-.Stable / Ab+T+.iMCI	-0.07	-0.10, -0.04	<0.001	-0.03	-0.06, 0.008	1.00	-0.10	-0.15, -0.05	0.002	0.05	0.01, 0.09	0.17
Ab+T+.Stable / Ab-T-.iMCI	0.02	-0.004, 0.05	1.00	0.008	-0.02, 0.04	1.00	0.02	-0.03, 0.07	1.00	-0.03	-0.06, 0.01	1.00
Ab+T+.Stable / Ab+T-.iMCI	-0.07	-0.10, -0.04	<0.001	-0.04	-0.07, -0.004	0.41	-0.13	-0.18, -0.08	<0.001	0.006	-0.04, 0.05	1.00
Ab+T+.Stable / Ab+T+.iMCI	-0.06	-0.10, -0.03	0.01	-0.009	-0.05, 0.03	1.00	-0.09	-0.15, -0.02	0.11	0.05	-0.002, 0.10	0.94
Ab-T-.iMCI / Ab+T-.iMCI	-0.09	-0.12, -0.07	<0.001	-0.05	-0.08, -0.02	0.01	-0.15	-0.19, -0.11	<0.001	0.03	-0.001, 0.06	0.87
Ab-T-.iMCI / Ab+T+.iMCI	-0.09	-0.12, -0.05	<0.001	-0.02	-0.05, 0.02	1.00	-0.11	-0.16, -0.05	0.002	0.07	0.03, 0.11	0.01
Ab+T-.iMCI / Ab+T+.iMCI	0.006	-0.03, 0.04	1.00	0.03	-0.009, 0.07	1.00	0.04	-0.02, 0.10	1.00	0.04	-0.005, 0.09	1.00

eTable 8C. DELCODE cohort restricted to SCD patients.

	SP-Ecog			Self-Ecog			Cum-Ecog			CAI-Ecog			
	Est.	SE	P	Est.	SE	P	Est.	SE	P	Est.	SE	P	
Model 2 - Fixed Effect													
(Intercept)	1.45	0.04	<0.001	1.55	0.04	<0.001	2.98	0.06	<0.001	0.09	0.05	0.12	
Time	0.02	0.008	0.04	0.007	0.009	0.45	0.03	0.01	0.04	0.002	0.009	0.86	
AT status			0.75			0.95			0.82			0.82	
	Ab+T-	-0.02	0.05	0.75	-0.02	0.06	0.78	-0.05	0.08	0.53	-0.02	0.08	0.78
	Ab+T+	-0.05	0.07	0.46	0.006	0.08	0.94	-0.02	0.11	0.83	0.06	0.10	0.53
Time:AT status			<0.001			0.07			<0.001			<0.001	
	Ab+T-	0.05	0.010	<0.001	0.02	0.01	0.05	0.07	0.02	<0.001	-0.02	0.01	0.08
	Ab+T+	0.07	0.02	<0.001	0.03	0.02	0.10	0.09	0.03	0.001	-0.06	0.02	0.002
Slopes	Est.	95% CI	P _{adj}	Est.	95% CI	P _{adj}	Est.	95% CI	P _{adj}	Est.	95% CI	P _{adj}	
Ab-T-	0.02	0.002, 0.03	0.08	0.009	-0.008, 0.03	0.86	0.03	0.005, 0.06	0.06	0.003	-0.02, 0.02	1.00	
Ab+T-	0.06	0.04, 0.08	<0.001	0.03	0.01, 0.05	0.01	0.11	0.07, 0.14	<0.001	-0.02	-0.04, 0.004	0.33	
Ab+T+	0.09	0.06, 0.12	<0.001	0.04	0.005, 0.07	0.07	0.12	0.07, 0.17	<0.001	-0.06	-0.09, -0.02	0.005	
Pairwise comparisons	Est.	95% CI	P _{adj}	Slope	95% CI	P _{adj}	Slope	95% CI	P _{adj}	Slope	95% CI	P _{adj}	
(Ab-T-)-(Ab+T-)	-0.05	-0.07, -0.03	<0.001	-0.02	-0.05, -0.0006	0.13	-0.07	-0.11, -0.04	<0.001	0.02	-0.002, 0.05	0.23	
(Ab-T-)-(Ab+T+)	-0.07	-0.10, -0.04	<0.001	-0.03	-0.06, 0.005	0.31	-0.09	-0.14, -0.03	0.004	0.06	0.02, 0.10	0.005	
(Ab+T-)-(Ab+T+)	-0.02	-0.06, 0.007	0.38	-0.004	-0.04, 0.03	1.00	-0.01	-0.07, 0.04	1.00	0.04	-0.002, 0.08	0.19	
Model 3 - Fixed Effect													
(Intercept)	1.42	0.04	<0.001	1.54	0.05	<0.001	2.94	0.06	<0.001	0.09	0.06	0.13	
Time	0.01	0.008	0.08	0.001	0.009	0.90	0.02	0.01	0.10	-0.0007	0.01	0.95	
iMCI [iMCI]	0.10	0.06	0.12	0.05	0.08	0.53	0.17	0.10	0.09	-0.02	0.09	0.85	
AT status			0.70			0.91			0.94			0.55	
	Ab+T-	-0.03	0.06	0.62	0.01	0.07	0.87	-0.03	0.09	0.78	0.03	0.09	0.73
	Ab+T+	-0.07	0.09	0.44	0.05	0.11	0.66	0.02	0.15	0.89	0.15	0.14	0.28
Time:iMCI [iMCI]	0.007	0.01	0.60	0.03	0.01	0.08	0.03	0.02	0.19	0.01	0.02	0.46	
Time:AT status			0.014			0.30			0.11			0.21	
	Time:Ab+T-	0.02	0.01	0.03	0.010	0.01	0.46	0.03	0.02	0.09	-0.02	0.01	0.23
	Time:Ab+T+	0.05	0.02	0.02	0.03	0.02	0.14	0.05	0.03	0.12	-0.04	0.03	0.14
iMCI:AT status			0.97			0.67			0.66			0.52	
	Ab+T-.iMCI	0.02	0.11	0.83	-0.10	0.13	0.46	-0.11	0.17	0.52	-0.16	0.17	0.33
	Ab+T+. iMCI	-0.009	0.14	0.95	-0.11	0.17	0.51	-0.17	0.22	0.43	-0.17	0.21	0.42
Time:iMCI:AT status			0.002			0.19			0.005			0.45	
	Ab+T-.iMCI	0.08	0.02	<0.001	0.04	0.02	0.15	0.13	0.04	0.001	-0.02	0.03	0.49

	SP-Ecog			Self-Ecog			Cum-Ecog			CAI-Ecog		
Ab+T+.iMCI	0.05	0.03	0.11	-0.02	0.03	0.48	0.05	0.05	0.32	-0.05	0.04	0.23
Slopes	Est.	95% CI	P _{adj}	Est.	95% CI	P _{adj}	Est.	95% CI	P _{adj}	Est.	95% CI	P _{adj}
Ab-T-.Stable	0.01	-0.0003, 0.03	0.33	0.003	-0.01, 0.02	1.00	0.03	-0.001, 0.05	0.38	0.0004	-0.02, 0.02	1.00
Ab+T-.Stable	0.04	0.02, 0.06	0.001	0.01	-0.01, 0.04	1.00	0.06	0.02, 0.10	0.01	-0.02	-0.04, 0.010	1.00
Ab+T+.Stable	0.06	0.02, 0.10	0.01	0.04	-0.006, 0.08	0.55	0.08	0.01, 0.15	0.11	-0.04	-0.09, 0.01	0.77
Ab-T-.iMCI	0.02	-0.003, 0.05	0.49	0.03	0.001, 0.06	0.25	0.06	0.01, 0.10	0.07	0.01	-0.02, 0.04	1.00
Ab+T-. iMCI	0.12	0.09, 0.15	<0.001	0.08	0.04, 0.11	<0.001	0.22	0.16, 0.27	<0.001	-0.02	-0.06, 0.02	1.00
Ab+T+. iMCI	0.11	0.08, 0.15	<0.001	0.04	-0.005, 0.08	0.51	0.16	0.09, 0.22	<0.001	-0.07	-0.12, -0.02	0.02
Pairwise comparisons	Est.	95% CI	P _{adj}	Slope	95% CI	P _{adj}	Slope	95% CI	P _{adj}	Slope	95% CI	P _{adj}
Ab-T-.Stable / Ab+T-.Stable	-0.02	-0.05, -0.002	0.44	-0.010	-0.04, 0.02	1.00	-0.03	-0.07, 0.005	1.00	0.02	-0.01, 0.05	1.00
Ab-T-.Stable / Ab+T+.Stable	-0.05	-0.08, -0.007	0.31	-0.03	-0.07, 0.01	1.00	-0.05	-0.12, 0.01	1.00	0.04	-0.01, 0.09	1.00
Ab-T-.Stable / Ab-T-.iMCI	-0.007	-0.03, 0.02	1.00	-0.03	-0.06, 0.003	1.00	-0.03	-0.07, 0.01	1.00	-0.01	-0.05, 0.02	1.00
Ab-T-.Stable / Ab+T-.iMCI	-0.11	-0.14, -0.08	<0.001	-0.07	-0.11, -0.04	0.001	-0.19	-0.25, -0.13	<0.001	0.02	-0.02, 0.07	1.00
Ab-T-.Stable / Ab+T+.iMCI	-0.10	-0.14, -0.06	<0.001	-0.03	-0.08, 0.01	1.00	-0.13	-0.20, -0.07	0.002	0.07	0.02, 0.12	0.07
Ab+T-.Stable / Ab+T+.Stable	-0.02	-0.06, 0.02	1.00	-0.02	-0.07, 0.02	1.00	-0.02	-0.09, 0.05	1.00	0.02	-0.03, 0.08	1.00
Ab+T-.Stable / Ab-T-.iMCI	0.02	-0.01, 0.05	1.00	-0.02	-0.05, 0.02	1.00	0.004	-0.05, 0.06	1.00	-0.03	-0.07, 0.009	1.00
Ab+T-.Stable / Ab+T-.iMCI	-0.08	-0.12, -0.05	<0.001	-0.06	-0.10, -0.02	0.03	-0.16	-0.22, -0.09	<0.001	0.007	-0.04, 0.05	1.00
Ab+T-.Stable / Ab+T+.iMCI	-0.08	-0.12, -0.04	0.003	-0.02	-0.07, 0.02	1.00	-0.10	-0.17, -0.03	0.09	0.05	0.002, 0.11	0.63
Ab+T+.Stable / Ab-T-.iMCI	0.04	-0.004, 0.08	1.00	0.006	-0.04, 0.05	1.00	0.02	-0.05, 0.10	1.00	-0.05	-0.11, 0.005	1.00
Ab+T+.Stable / Ab+T-.iMCI	-0.06	-0.11, -0.01	0.16	-0.04	-0.09, 0.01	1.00	-0.14	-0.22, -0.05	0.02	-0.01	-0.08, 0.05	1.00
Ab+T+.Stable / Ab+T+.iMCI	-0.05	-0.10, -0.002	0.61	-0.003	-0.06, 0.06	1.00	-0.08	-0.17, 0.010	1.00	0.03	-0.03, 0.10	1.00
Ab-T-.iMCI / Ab+T-.iMCI	-0.10	-0.14, -0.06	<0.001	-0.05	-0.09, -0.004	0.46	-0.16	-0.23, -0.10	<0.001	0.04	-0.01, 0.09	1.00
Ab-T-.iMCI / Ab+T+.iMCI	-0.09	-0.13, -0.05	<0.001	-0.009	-0.06, 0.04	1.00	-0.10	-0.18, -0.03	0.10	0.09	0.03, 0.14	0.04
Ab+T-.iMCI / Ab+T+.iMCI	0.007	-0.04, 0.05	1.00	0.04	-0.02, 0.09	1.00	0.06	-0.03, 0.14	1.00	0.05	-0.01, 0.11	1.00



eFigure 2. Spaghetti plot of individual trajectories: SCD reports over time in years since baseline according to clinical progression and AD pathology (amyloid and tau status).

Abbreviations: Aβ-T-, participants amyloid- and tau-negative at baseline; Aβ+T-, participants amyloid-positive but tau-negative at baseline; Aβ+T+, participants amyloid- and tau-positive at baseline; CAI, Cognitive awareness index; iMCI, participants that progressed to incident mild cognitive impairment during the follow-up period; SP, study partner; Stable, participants cognitively stable during the follow-up period.

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