Supplementary information for "Four distinct trajectories of tau deposition identified in Alzheimer's disease"

Jacob W. Vogel[1,], Alexandra L. Young[2], Neil P. Oxtoby[3,4], Ruben Smith[5,6], Rik Ossenkoppele[5,6,7], Olof T. Strandberg[5,6], Renaud La Joie[8], Leon M. Aksman[3,9], Michel J Grothe[10,11], Yasser Iturria-Medina[1], the Alzheimer's Disease Neuroimaging Initiative[*], Michael J. Pontecorvo[12], Michael D. Devous[12], Gil D. Rabinovici[8,13], Daniel C. Alexander[3,4], Chul Hyoung Lyoo[14], Alan C. Evans[1], and Oskar Hansson[3,4]

[1]Montreal Neurological Institute, McGill University, Montréal, QC, Canada
[2]Department of Neuroimaging, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK.
[3]Centre for Medical Image Computing, University College London, London, WC1E 6BT, UK
[4]Department of Computer Science, University College London, London, WC1E 6BT, UK
[5]Clinical Memory Research Unit, Lund University, Lund, Sweden
[6]Memory Clinic, Skåne University Hospital, Lund, Sweden
[7]Alzheimer Center Amsterdam, Department of Neurology, Amsterdam Neuroscience, Vrije Universiteit Amsterdam, Amsterdam UMC, Amsterdam, The Netherlands
[8]Memory and Aging Center, Department of Neurology, Weill Institute for Neurosciences, University of California, San Francisco, San Francisco, CA
[9]Department of Medical Physics and Biomedical Engineering, University College London, London, WC1E 6BT, UK
[10]German Center for Neurodegenerative Diseases (DZNE), Rostock, Germany
[11]Instituto de Biomedicina de Sevilla, Hospital Universitario Virgen del Rocío/CSIC/Universidad de Sevilla, Seville, Spain
[12]Avid Radiopharmaceuticals, Philadelphia, PA, USA
[13]Department of Radiology and Biomedical Imaging; University of California, San Francisco, San Francisco, CA
[14]Departments of Neurology, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea
[*]Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at:
http://adni.loni.usc.edu/wp-content/uploads/how$_to_apply/ADNI_Acknowledgement_List.pdf$

Supplementary Notes

Supplementary Note 1: Once SuStaIn had assigned individuals into subtypes, these subtype were further subjected to post-hoc visual inspection and analysis to identify, characterize and remove potential "false-positives". A large minority of the S2 (MTL-Sparing) subtype were systematically identified as likely outliers, and were converted to S0 individuals (see Methods: Post-hoc subtype correction, Supplementary Fig S2a-c). After this process, the S0 (tau-negative) class included 78.5% of all cognitively normal individuals, 36.3% of individuals with MCI, and 4.7% of individuals with AD dementia. Altogether, the S0 group was composed of 85.9% cognitively normal individuals, 12.5% (A+) MCI patients and 1.5% (A+) AD patients.

Supplementary Note 2: In the replication analysis in BioFII, a subtype emerged similar to the S4 (L Temporal) subtype ind the discovery sample, but with right- rather than left-lateralized pattern. Two possible differences between the discovery and replication datasets that could lead to this discrepancy are the employed tau-PET radiotracer and sample size. To rule out the latter, we split the discovery sample in half (n=571, 572) and reran SuStaIn on each half, constraining the model to four subtypes. While the first three subtypes were once again very similar, a discrepancy was observed once again in the L Temporal phenotype. One half demonstrated a left lateralized phenotype, while the other half resulted in a right lateralized phenotype similar to the replication sample (Supplementary Fig S7). These results suggest a consistent overall pattern for the S4: L Temporal phenotype, but that this phenotype has a high propensity for marked lateralization. The emergence of a more left-predominant or right-predominant phenotype in data-driven analyses such as this one may vary due to sample size and composition. The variation in lateralization affected the overall stability of S4 and, to a lesser degree, S1, but S2 and S3 were remarkably stable over the four datasets (original, split 1, split 2, replication; Supplementary Fig S7).

Supplementary Note 3: We investigate the longitudinal progression of SuStaIn stage. Starting originally with the 519 individuals with longitudinal flortaucipir-PET data, we excluded subtype 0 individuals (n=330), and also excluded individuals that were not classified as the same subtype across all measurements (n=36), for a final sample of n=153. Across the whole sample, we observed significant yearly increase in SuStaIn stage (mean /year = 0.8, $t[148]=6.54$, $p<0.0001$). This relationship was consistent across subtype, though only a trend for S2 (MTL-Sparing) (Fig 3h; S1: mean = 0.78, $t[57]=4.09$, $p=0.0001$; S2: mean = 0.45, $t[39]=1.81$, $p=0.079$; S3: mean = 0.64, $t[31]=2.61$, $p=0.014$, S4: mean = 1.73, $t[21]=5.85$, $p<0.0001$). A significant difference in mean annual rate of SuStaIn stage change was seen across subtypes ($F=3.80$, $p=0.012$), and posthoc tests revealed annual SuStaIn stage increased faster in S4 (L Temporal) compared to S2 (MTL-Sparing) and S3 (Posterior) subtypes . Supplementary Table S3 shows the proportion of individuals who progressed, remained stable, or regressed in SuStaIn stage at their second visit, before and after accounting for model uncertainty. Notably, no S4 individuals regressed.

Supplementary Tables

	Discovery						Validation
	ADNI	**BioF**	**UCSF**	**Seoul**	**AVID**	**Total***	**BF2**
N	486	144	84	188	241	1143	467
Age	74.4 (7.4) [c,d]	72.4 (8.1) [c,d]	63.4 (8.7) [f]	69.2 (9.8) [f]	72.7 (9.1) [c,d]	72.1 (8.9)	69.0 (10.1) [g]
Prop. Female	0.56	0.47 [d]	0.52	0.66 [b,e]	0.49 [d]	0.55	0.5
Education	16.6 (2.5) [b,d,e]	12.2 (3.6) [a,c,e]	17.0 (2.9) [b,d,e]	11.5 (4.9) [a,c,e]	15.4 (2.7) [f]	14.9 (3.8)	12.4 (3.9) [g]
Prop. CN	0.84 [f]	0.46 [a,c,e]	0.05 [f]	0.48 [a,c,e]	0.58 [f]	0.62	0.4 [g]
Prop. MCI	0.16 [e]	0.19	0.18	0.23	0.25	0.2	0.25 [g]
Prop. AD	0.01 [f]	0.35 [a,c,e]	0.77 [f]	0.29 [a,c,e]	0.17 [f]	0.19	0.16
Prop. Aβ+	0.58 [b,c]	0.8 [f]	0.96 [f]	0.57 [b,c]	0.6 [b,c]	0.65	0.56 [g]
Prop. APOE4	0.35 [b,e]	0.59 [a,c,d]	0.42 [b]	0.35 [b,e]	0.48 [a,d]	0.41	0.51 [g]
Prop. APOE4/4	0.05 [b]	0.18 [a,d,e]	0.12	0.08 [b]	0.08 [b]	0.08	0.06
MMSE	28.63 (2.21) [f]	25.67 (4.77) [a,c,e]	22.18 (5.65) [f]	24.75 (5.31) [a,c,e]	27.0 (3.7) [f]	26.85 (4.28)	26.32 (4.29) [g]
Total Tau	1.12 (0.1) [f]	1.27 (0.31) [a,c]	1.68 (0.38) [f]	1.28 (0.26) [a,c,e]	1.22 (0.25) [a,c,d]	1.23 (0.27)	1.16 (0.27) [g]
IT Tau	1.26 (0.2) [f]	1.62 (0.55) [f]	2.11 (0.6) [f]	1.43 (0.48) [a,b,c]	1.42 (0.43) [a,b,c]	1.43 (0.46)	1.44 (0.56)

Supplementary Table S1. Sample characteristics for individuals across cohorts. Significance testing assessing inter-cohort difference performed with one-way ANOVAs for scalar variables and χ^2 tests for categorical variables. P-values assessed with Tukey's posthoc tests.

* All variables exhibited significant inter-cohort differences.

[a] p<0.05 different from ADNI

[b] p<0.05 different from BioF

[c] p<0.05 different from UCSF

[d] p<0.05 different from Seoul

[e] p<0.05 different from AVID

[f] p<0.05 different from all other cohorts

[g] p<0.05 different from Discovery sample

Prop. = Proportion; CN = Cognitively Normal; MCI = Mild Cognitive Impairment; AD = Alzheimer's Disease; MMSE = Mini-mental State Examination; Aβ+ = -β positive; IT = Inferior temporal lobe; ADNI = Alzheimer's Disease Neuroimaging Initiative; BioF = BioFINDER Cohort; UCSF = University of California, San Francisco, Memory and Aging Center Cohort; Seoul = Gangnam Severence Hospital Cohort; AVID = Avid Radiopharmaceuticals Cohort; BF2 = BioFINDER II Cohort

Dx	Group 1	Group 2	Mean Diff	p(adj)	lower CI	upper CI
CN	S1	S2	-0.2938	0.6866	-1.0163	0.4287
	S1	S3	0.7892	0.001	0.3	1.2784
	S1	S4	-0.1138	0.9	-0.9062	0.6786
	S2	S3	1.083	0.001	0.406	1.7599
	S2	S4	0.18	0.9	-0.7402	1.1003
	S3	S4	-0.9029	0.012	-1.654	-0.1519
MCI	S1	S2	-0.8581	0.0935	-1.8123	0.0961
	S1	S3	0.8386	0.0199	0.0984	1.5788
	S1	S4	-1.1093	0.0039	-1.9363	-0.2823
	S2	S3	1.6967	0.001	0.6539	2.7395
	S2	S4	-0.2512	0.9	-1.3573	0.8549
	S3	S4	-1.9479	0.001	-2.8758	-1.0201
AD	S1	S2	-1.2161	0.0233	-2.3112	-0.1209
	S1	S3	-0.2955	0.8675	-1.3321	0.7411
	S1	S4	-2.3472	0.001	-3.3969	-1.2975
	S2	S3	0.9206	0.1921	-0.2771	2.1182
	S2	S4	-1.1311	0.0755	-2.3401	0.0779
	S3	S4	-2.0517	0.001	-3.2079	-0.8954

Supplementary Table S2. Tukey's pairwise posthoc tests showing subtype differences in longitudinal MMSE decline, stratified by clinical diagnosis. Values represent differences in predicted slopes based on the mixed models described in Results section "Cognitive prognosis of AD subtypes", and correspond directly to the boxplots in Main Text Figure 3d.
Dx = Diagnosis; CN = Cognitively Normal; MCI = Mild Cognitive Impairment; AD = probable Alzheimer's dementia; Diff = Difference; adj = adjusted.
N subjects CN: S1=22, S2=11, S3=38, S4=7
N subjects MCI: S1=45, S2=13, S3=24, S4=17
N subjects AD: S1=44, S2=22, S3=27, S4=25

Cutoff	N	Perc. Total	Stability
None	191	100%	83.9
0.5	167	87%	86.8
0.6	163	85%	86.5
0.7	156	82%	86.8
0.8	149	75%	86.6
0.9	137	72%	88.3

Supplementary Table S3. Longitudinal stability of subtypes when only including individuals above different threholds of subtype probability (excluding individuals classified as S0.

Subtype	N	Progressed	Stable	Regressed
All	153	53.8%	27.6%	18.6
S1 (Limbic)	58	50.0%	36.7%	13.3%
S2 (MTL-Sparing)	42	47.6%	19.0%	33.3%
S3 (Posterior)	32	57.6%	21.2%	21.2%
S4 (L Temporal)	21	71.4%	28.6%	0.0%

Subtype	N	Progressed	Stable	Regressed
All	153	37.9%	51.0%	11.1%
S1 (Limbic)	58	36.2%	53.4%	10.3%
S2 (MTL-Sparing)	42	33.3%	47.6%	19.0%
S3 (Posterior)	32	46.9%	43.8%	9.4%
S4 (L Temporal)	21	38.1%	61.9%	0.0%

Supplementary Table S4. Proportion of individuals progressing, regressing and remaining stable in SuStaIn stage, before (top) and after (bottom) accounting for model uncertainty

	Memory	Executive	Language	Visuospatial
5***ADNI**	Logical Memory Total Logical Memory Delayed Recall RAVLT Immediate Recall RAVLT Delayed Recall	DigitSpan Backward DigitSpan Forward Digit Symbol Trails A Trails B	BNT Total Category Fluency: Animals Category Fluency: Vegetables Multilingual Naming Test	Clock Draw Figure Drawing
4***BioF**	ADAS Delayed Recall	AQT Cognitive Speed Letter Fluency: S Trails A Stroop Correct	ADAS Naming Objects Category Fluency: Animals	Clock Drawing Cube
5***AVID**	Clock Draw Recall WMS Immediate Recall WMS Delayed Recall	DigitSpan Backward DigitSpan Forward Digit Symbol Trails A Trails B	ANART BNT Total Category Fluency: Animals	Benton JoLO Clock Draw Copy
2***Seoul**	Modified RFC Delayed Recall SVLT Delay	Digit Symbol Letter Fluency	BNT Total	Modified RFC
6***UCSF**	CVLT Correct Total CVLT Delayed Recall Modified RFC Delayed Recall	Abstract Reasoning Test DigitSpan Backward DigitSpan Forward Letter Fluency Modified Trails Stroop Correct	BNT Total Category Fluency: Animals Repetition test Syntax test Verbal Agility test	Dot Counting Fragmented Letters Modified RFC Number Location Object Decision

Supplementary Table S5. Cohort-specific cognitive tests composing each cognitive domain score. ADAS = Alzheimer's Disease Assessment Scale; ANART = American National Adult Reading Test; AQT = A Quick Test (of); BNT = Boston Naming Test; CVLT = California Verbal Learning Test; JoLO = Judgement of Line Orientation; RAVLT = Rey Auditory Verbal Learning Test; RFC = Rey Figure Copy; SVLT = Seoul Verbal Learning Test; WMS = Wechsler Memory Scale;

Original	Anchor 1	Anchor 2	Anchor 3	Data-Driven	Anchor 1	Anchor 2	Anchor 3
L MTL	2.00	5.00	10.00	**L MTL**	2.02	-	-
R MTL	2.00	5.00	10.00	**R MTL**	2.02	-	-
L Temporal	2.00	5.00	10.00	**L Temporal**	1.99	7.11	-
R Temporal	2.00	5.00	10.00	**R Temporal**	1.35	3.86	-
L Parietal	2.00	5.00	10.00	**L Parietal**	1.91	7.36	-
R Parietal	2.00	5.00	10.00	**R Parietal**	1.98	7.09	-
L Occipital	2.00	5.00	10.00	**L Occipital**	2.22	10.32	-
R Occipital	2.00	5.00	10.00	**R Occipital**	1.25	3.72	15.79
L Frontal	2.00	5.00	10.00	**L Frontal**	1.90	6.19	-
R Frontal	2.00	5.00	10.00	**R Frontal**	1.41	4.07	-

Supplementary Table S6. Z-score values for used to anchor each ROI for the original (left) and data-driven replication runs of the SuStaIn model