Supplementary information

Accelerated functional brain aging in pre-clinical familial Alzheimer's disease

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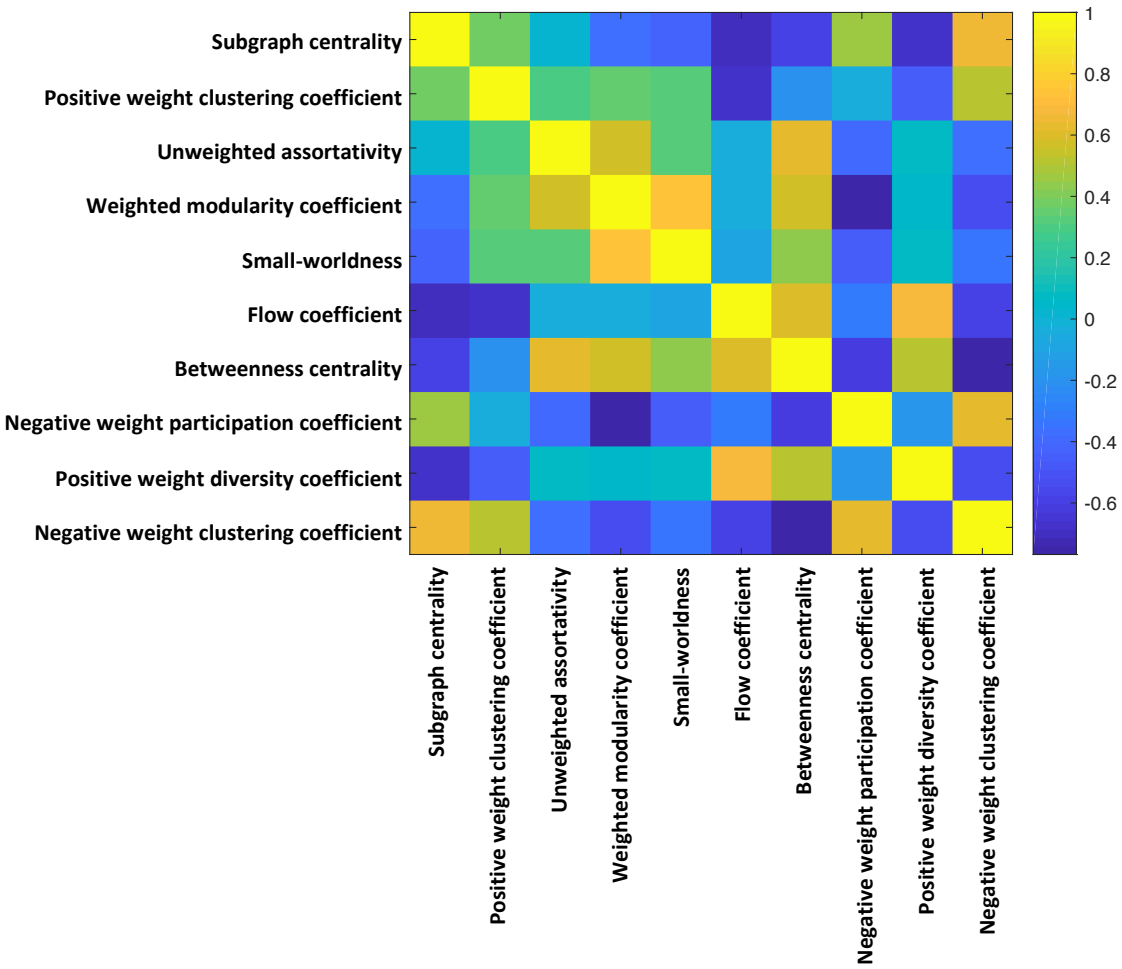
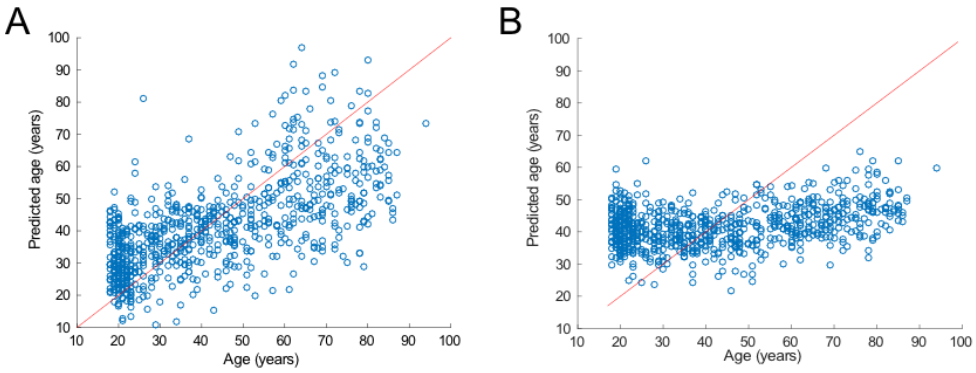
Supplementary Fig. 1



Supplementary Figure 1: Pearson correlations between the 10 graph metrics used as input in the neural network. The color-scale represents r-values; stronger positive correlations being represented by lighter (yellow) colors while darker (blue) colors correspond to stronger negative correlations.

Supplementary Fig. 2



Supplementary Figure 2. Age prediction from support vector machine models using original graph metrics as input (A) and age prediction from support vector machine models using harmonized graph metrics from ComBat as input. (B)

Supplementary Table 1. Percentage of frames retained from resting-state fMRI scans in each cohort

Cohort	Average % frames retained ± SD
CamCAN	86.2 ± 15.5
FCP-Cambridge	100 ± 0
DIAN	93.8 ± 12.0
Prevent-AD	85.0 ± 17.2
ADNI	80.7 ± 15.4
ICBM	96.76 ± 8.0

SD: standard deviation

Supplementary Table 2. Functional brain parcellation (based on Power and Petersen functional atlas)

ROI	MNI space X	Y	Z	Suggested System
13	-7	-52	61	Sensory/somatomotor Hand
14	-14	-18	40	Sensory/somatomotor Hand
15	0,1	-15	47	Sensory/somatomotor Hand
16	9,5	-2	45	Sensory/somatomotor Hand
17	-7	-21	65	Sensory/somatomotor Hand
18	-7	-33	72	Sensory/somatomotor Hand
19	13	-33	75	Sensory/somatomotor Hand
20	-54	-23	43	Sensory/somatomotor Hand
21	29	-17	71	Sensory/somatomotor Hand
22	9,9	-46	73	Sensory/somatomotor Hand
23	-23	-30	72	Sensory/somatomotor Hand
24	-40	-19	54	Sensory/somatomotor Hand
25	29	-39	59	Sensory/somatomotor Hand
26	50	-20	42	Sensory/somatomotor Hand
27	-38	-27	69	Sensory/somatomotor Hand
28	20	-29	60	Sensory/somatomotor Hand
29	44	-8	57	Sensory/somatomotor Hand
30	-29	-43	61	Sensory/somatomotor Hand
31	10	-17	74	Sensory/somatomotor Hand
32	22	-42	69	Sensory/somatomotor Hand
33	-45	-32	47	Sensory/somatomotor Hand
34	-21	-31	61	Sensory/somatomotor Hand
35	-13	-17	75	Sensory/somatomotor Hand
36	42	-20	55	Sensory/somatomotor Hand
37	-38	-15	69	Sensory/somatomotor Hand
38	-16	-46	73	Sensory/somatomotor Hand
39	2,4	-28	60	Sensory/somatomotor Hand
40	3,5	-17	58	Sensory/somatomotor Hand
41	38	-17	45	Sensory/somatomotor Hand
42	-49	-11	35	Sensory/somatomotor Mouth
43	36	-9	14	Sensory/somatomotor Mouth
44	51	-6	32	Sensory/somatomotor Mouth
45	-53	-10	24	Sensory/somatomotor Mouth
46	66	-8	25	Sensory/somatomotor Mouth
47	-3	2,4	53	Cingulo-opercular Task Control
48	54	-28	34	Cingulo-opercular Task Control
49	19	-8	64	Cingulo-opercular Task Control
50	-16	-5	71	Cingulo-opercular Task Control
51	-10	-2	42	Cingulo-opercular Task Control
52	37	0,8	-4	Cingulo-opercular Task Control
53	13	-1	70	Cingulo-opercular Task Control
54	6,5	7,7	51	Cingulo-opercular Task Control
55	-45	0,1	8,8	Cingulo-opercular Task Control
56	49	8,3	-1	Cingulo-opercular Task Control
57	-34	3,3	4,2	Cingulo-opercular Task Control
58	-51	8,3	-2	Cingulo-opercular Task Control
59	-5	18	34	Cingulo-opercular Task Control
60	36	10	1,2	Cingulo-opercular Task Control
61	32	-26	13	Auditory
62	65	-33	20	Auditory
63	58	-16	7,5	Auditory
64	-38	-33	17	Auditory
65	-60	-25	14	Auditory
66	-49	-26	5,2	Auditory
67	43	-23	20	Auditory
68	-50	-34	26	Auditory
69	-53	-22	23	Auditory
70	-55	-9	12	Auditory
71	56	-5	13	Auditory
72	59	-17	29	Auditory
73	-30	-27	12	Auditory
74	-41	-75	26	Default mode
75	5,6	67	-4	Default mode
76	8,4	48	-15	Default mode
77	-13	-40	0,9	Default mode
78	-18	63	-9	Default mode
79	-46	-61	21	Default mode
80	43	-72	28	Default mode
81	-44	12	-34	Default mode
82	46	16	-30	Default mode
86	-44	-65	35	Default mode
87	-39	-75	44	Default mode
88	-7	-55	27	Default mode
89	5,9	-59	35	Default mode
90	-11	-56	16	Default mode
91	-3	-49	13	Default mode
92	7,9	-48	31	Default mode
93	15	-63	26	Default mode
94	-2	-37	44	Default mode
95	11	-54	17	Default mode
96	52	-59	36	Default mode
97	23	33	48	Default mode
98	-10	39	52	Default mode
99	-16	29	53	Default mode
100	-35	20	51	Default mode
101	22	39	39	Default mode
102	13	55	38	Default mode
103	-10	55	39	Default mode
104	-20	45	39	Default mode
105	5,9	54	16	Default mode
106	6,1	64	22	Default mode
107	-7	51	-1	Default mode
108	8,8	54	3,5	Default mode
109	-3	44	-9	Default mode
110	7,5	42	-5	Default mode
111	-11	45	7,6	Default mode
112	-2	38	36	Default mode
113	-3	42	16	Default mode
114	-20	64	19	Default mode
115	-8	48	23	Default mode
117	-56	-13	-10	Default mode
118	-58	-30	-4	Default mode
119	65	-31	-9	Default mode
120	-68	-41	-5	Default mode
121	13	30	59	Default mode
122	12	36	20	Default mode
123	52	-2	-16	Default mode
124	-26	-40	-8	Default mode
125	27	-37	-13	Default mode
126	-34	-38	-16	Default mode
127	28	-77	-32	Default mode
128	52	6,8	-30	Default mode
129	-53	2,6	-27	Default mode
130	47	-50	29	Default mode
131	-49	-42	0,8	Default mode
133	-2	-35	31	Memory retrieval
134	-7	-71	42	Memory retrieval
135	11	-66	42	Memory retrieval
136	4,2	-48	51	Memory retrieval
137	-46	31	-13	Default mode

138	-10	11	67	Ventral attention
139	49	35	-12	Default mode

	MNI space			Suggested System
ROI	X	Y	Z	
143	18	-47	-10	Visual
144	40	-72	14	Visual
145	8,5	-72	11	Visual
146	-8	-81	7,4	Visual
147	-28	-79	19	Visual
148	20	-66	1,7	Visual
149	-24	-91	19	Visual
150	27	-59	-9	Visual
151	-15	-72	-8	Visual
152	-18	-68	4,8	Visual
153	43	-78	-12	Visual
154	-47	-76	-10	Visual
155	-14	-91	31	Visual
156	15	-87	37	Visual
157	29	-77	25	Visual
158	20	-86	-2	Visual
159	15	-77	31	Visual
160	-16	-52	-1	Visual
161	42	-66	-8	Visual
162	24	-87	24	Visual
163	5,6	-72	24	Visual
164	-42	-74	0,4	Visual
165	26	-79	-16	Visual
166	-16	-77	34	Visual
167	-3	-81	21	Visual
168	-40	-88	-6	Visual
169	37	-84	13	Visual
170	6,2	-81	6,1	Visual
171	-26	-90	3,1	Visual
172	-33	-79	-13	Visual
173	37	-81	1,2	Visual
174	-44	1,8	46	Fronto-parietal Task Control
175	48	25	27	Fronto-parietal Task Control
176	-47	11	23	Fronto-parietal Task Control
177	-53	-49	43	Fronto-parietal Task Control
178	-23	11	64	Fronto-parietal Task Control
179	58	-53	-14	Fronto-parietal Task Control
180	24	45	-15	Fronto-parietal Task Control
181	34	54	-13	Fronto-parietal Task Control
186	47	9,9	33	Fronto-parietal Task Control
187	-41	5,8	33	Fronto-parietal Task Control
188	-42	38	21	Fronto-parietal Task Control
189	38	43	15	Fronto-parietal Task Control
190	49	-42	45	Fronto-parietal Task Control
191	-28	-58	48	Fronto-parietal Task Control
192	44	-53	47	Fronto-parietal Task Control
193	32	14	56	Fronto-parietal Task Control
194	37	-65	40	Fronto-parietal Task Control
195	-42	-55	45	Fronto-parietal Task Control
196	40	18	40	Fronto-parietal Task Control
197	-34	55	4,4	Fronto-parietal Task Control
198	-42	45	-2	Fronto-parietal Task Control
199	33	-53	44	Fronto-parietal Task Control
200	43	49	-2	Fronto-parietal Task Control
201	-42	25	30	Fronto-parietal Task Control
202	-3	26	44	Fronto-parietal Task Control
203	11	-39	50	Salience
204	55	-45	37	Salience
205	42	-0	47	Salience
206	31	33	26	Salience
207	48	22	9,7	Salience
208	-35	20	0,1	Salience
209	36	22	2,6	Salience
210	37	32	-2	Salience

	MNI space			Suggested System
ROI	X	Y	Z	
211	34	16	-8	Salience
212	-11	26	25	Salience
213	-1	15	44	Salience
214	-28	52	21	Salience
215	-0	30	27	Salience
216	5,2	23	37	Salience
217	10	22	27	Salience
218	31	56	14	Salience
219	26	50	27	Salience
220	-39	51	17	Salience
221	1,8	-24	30	Memory retrieval
222	6,3	-24	-0	Subcortical
223	-2	-13	12	Subcortical
224	-10	-18	7	Subcortical
225	12	-17	7,5	Subcortical
226	-5	-28	-4	Subcortical
227	-22	7,5	-5	Subcortical
228	-15	3,6	8	Subcortical
229	31	-14	1,7	Subcortical
230	23	10	1,5	Subcortical
231	29	0,8	4	Subcortical
232	-31	-11	-0	Subcortical
233	15	4,9	7,2	Subcortical
234	8,6	-4	5,8	Subcortical
235	54	-43	22	Ventral attention
236	-56	-50	9,9	Ventral attention
237	-55	-40	14	Ventral attention
238	52	-33	7,6	Ventral attention
239	51	-29	-4	Ventral attention
240	56	-46	11	Ventral attention
241	53	33	0,6	Ventral attention
242	-49	25	-1	Ventral attention
251	9,6	-62	61	Dorsal attention
252	-52	-63	5,3	Dorsal attention
255	47	-30	49	Sensory/somatomotor Hand
256	22	-65	48	Dorsal attention
257	46	-59	3,9	Dorsal attention
258	25	-58	60	Dorsal attention
259	-33	-46	47	Dorsal attention
260	-27	-71	37	Dorsal attention
261	-32	-1	54	Dorsal attention
262	-42	-60	-9	Dorsal attention
263	-17	-59	64	Dorsal attention
264	29	-5	54	Dorsal attention
265	-10	14	-2	Limbic
266	10	14	-2	Limbic
267	-22	-2	-22	Limbic
268	26	-2	-22	Limbic
269	-24	-14	-18	Limbic
270	26	-14	-18	Limbic
271	-28	-34	-6	Limbic
272	30	-34	-6	Limbic

Supplementary Table 3: Gene primers in DIAN

Gene	Ensembl_Transcript_ID	Exon	Direction	Sequence
PSEN2	ENST00000366783.3	4	Forward	GACAGGCATCTCTTGGAAGC
		4	Reverse	CATCAGGGAATGAATGTCTGG
		5	Forward	ACTTCTCATTTCTGGTTCCA
		5	Reverse	TAGGTCACAATCCAGGAGG
		6	Forward	ACTCCATCAGGGCAGCAT
		6	Reverse	AAAAATCTGGGTCTATTTTCCTCT
		8	Forward	GTTGGGACTGAATGGTGGTA
		8	Reverse	CCCTCTGTTTTACAAAGGCG
PSEN1	ENST00000324501.5	4	Forward	AACTCATAGTGACGGGTCTG
		4	Reverse	GTAATAACCCCTCGCTCTCT
		5	Forward	TTGGTGAGTTGGGGAAA
		5	Reverse	CACAGTGAGGAGGAAGAAAA
		6	Forward	CGACAAAGTGAGACCCTGT
		6	Reverse	AGTACATGGCTTTAAATGATAGCT
		7	Forward	ATGTTTGGGAGCCATCA
		7	Reverse	CCAGCCGAAATCTTCAA
		8	Forward	TCACCTGCCATTTATTTCA
		8	Reverse	CAGGAATGCTGTGCATTTA
		9	Forward	CTGCTAAAACCAAAGAGAACC
		9	Reverse	TGTATTTACTGGGCATTATCATAG
		11	Forward	AAAACACAGCTGAAGCCTAA
		11	Reverse	GCTCCTCAGATAGCTGGAAT
		12	Forward	TCCAGATTGAATGAACGTCT
		12	Reverse	TGGAAGGAAGCTGCAAA
APP	ENST00000346798.3	7	Forward	ATGCTGCCTAATAAACCAGTCC
		7	Reverse	TCCCAAGAACCAGGAAAATCAA
		16	Forward	GGTTTCCCTTACCCTTTCATTT
		16	Reverse	TCAGCCTAGCCTATTTATTTTCT
		17	Forward	TGAAACTTTTTATATAACCTCATCCAA
		17	Reverse	CATGGAAGCACACTGATTCG

The table is annotated based on Ensembl version 75 in genome build GRCh37

Supplementary Table 4: Gene primers in PREVENT-AD

Gene	Variant	Analyses	Sequence
APOE	rs429358	amplification forward	5'-ACGGCTGTCCAAGGAGCTG-3'
		amplification reverse biotinylated	5'-CACCTCGCCGCGGTACTG-3'
		sequencing	5'-CGGACATGGAGGACG-3'
	rs7412	amplification forward	5'-CTCCGCGATGCCGATGAC-3'
		amplification reverse biotinylated	5'-CCCCGGCCTGGTACACTG-3'
		sequencing	5'-CGATGACCTGCAGAAG-3'

Supplementary Methods

Race/ethnicity from the different cohorts

DIAN: The sample mainly identified as non-Hispanic/White, both for mutation non-carriers (90% from the training set and 100% from the test set) and mutation carriers (80% from the test set).
The ten remaining mutation non-carriers (all from the training set) identified as Hispanic/White (n=4), Hispanic with no further specification (n=2), non-Hispanic/Middle Eastern (n=1) or non-Hispanic/Aboriginal (n=2). Regarding the 24 mutation carriers with a different race/ethnicity, they identified themselves as Hispanic/White (n=10), Hispanic with no further specification (n=6), non-Hispanic/Middle Eastern-North Africa (n=2), Aboriginal (n=1), native Hawaiian or other pacific islanders (n=3), Hispanic/Black or African American (n=1) and non-Hispanic/Asian (n=1).

PREVENT-AD: The sample was mainly White/Caucasian with the exception of 4 participants (2 Hispanics, 1 Haitian and 1 unspecified).

ADNI: The sample mainly identified as non-Hispanic/White (83% of those included in the training set and 93% of those included in the test set), with the exception of 6 subjects (1 Hispanic/White, 1 unknow ethnicity/White and 3 non-Hispanic/not White [1 Black, 1 with more than one race and 1 unknown] in the training set, and 1 Hispanic/White in the test set).

FCP-Cambridge, CamCAN and ICBM: Participants from the FCP-Cambridge were recruited from the Cambridge (MA, USA) area, CamCAN is a population-based cohort recruited within the Cambridge City (UK) area (excluding term-time residents of colleges and universities) and the ICBM cohort was recruited in the Montreal (QC, Canada) area; however further demographic information, including specific information on race/ethnicity, was not provided for these cohorts.

Estimated years to symptom onset

Estimated expected years to symptom onset (EYO) was computed in the two cohorts by subtracting each participant's age at assessment from his/her parent's age at symptom onset. In DIAN, the parental age at onset was determined using semi-structured interview in which family members were asked about the age of first progressive cognitive decline.[1] In PREVENT-

AD, EYO was calculated using the age of the parent at which the family observed significant cognitive/memory changes, as reported by the participant during the medical interview.[2–4]

We conducted partial correlations between EYO and the predicted age difference (PAD), controlling for the influence of chronological age, in DIAN and PREVENT-AD.

Calculation of small-worldness and resilience

For a thresholded correlation matrix *G*, small-worldness was calculated as Supplementary Equation 1:

$$\text{small-worldness} = [(\text{clustering}_{G} / \text{clustering}_{\text{random}}) / (\text{efficiency}_{\text{random}} / \text{efficiency}_{G})] \quad (1)$$

in which clustering is the clustering coefficient, and indicates the extent to which nodes are clustered together. The efficiency indicates the average of the inverse path length between nodes of the matrix. The subscript random indicates when these measures are taken on randomly scrambled matrices with preserved degree count for each node in *G,* and were generated using the function randmio_und. Random clustering coefficient and efficiency were averaged over 100 random matrices, generated for each scan.

Resilience is a measure of the robustness of network *G* as node hubs are removed. Networks with scale-free properties *(i.e.* node degree probabilities follow a power-law distribution) are resilient to random attacks and can be described as Supplementary Equation 2:

$$p(k) \; \alpha \; k^{-y} \quad (2)$$

where *p(k)* is the probability of a node having a degree of *k* (or *k* total connections), and *y* is an exponent. On a log-log scale this probability distribution is linear, and thus resilience of *G* can be estimated as the negative slope of the degree distribution.

Supplementary Notes. DIAN Study Group

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