

Supporting Information

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Supporting Information

A neuroimaging signature of cognitive aging from whole-brain functional connectivity

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Figure S1. Distribution of the fraction of explained variance (R^2) across 200 repetitions of cross-validation for age and each of the eight cognitive metrics.

		RMSE	Control for age	Control for gender	Control for <i>FD</i>		
Age	0.885 ± 0.0028	8.569 ± 0.0964	NA	0.885 ± 0.0028	0.841 ± 0.0039		
Emotion expression	0.422 ± 0.0060	9.860 ± 0.041	0.205 ± 0.0091	0.417 ± 0.0060	0.373 ± 0.0076		
Face recognition	0.361 ± 0.0066	2.26 ± 0.0093	0.029 ± 0.0097 ^{NS}	0.359 ± 0.0066	0.281 ± 0.0081		
Fluid intelligence	0.634 ± 0.0029	5.165 ± 0.017	0.253 ± 0.0054	0.634 ± 0.0029	0.528 ± 0.0040		
Force matching	0.333 ± 0.0194	$0.040 \pm 5.0e - 4$	0.149 ± 0.0228	0.329 ± 0.0194	0.263 ± 0.0210		
Hotel task	0.250 ± 0.0077	166.55 ± 0.58	0.119 ± 0.0101	0.250 ± 0.0077	0.183 ± 0.0093		
Motor learning	0.441 ± 0.0134	$0.035 \pm 3.6e - 4$	0.081 ± 0.0218 ^{NS}	0.440 ± 0.0134	0.332 ± 0.0164		
Tip-of-tongue	0.254 ± 0.0104	0.240 ± 0.001	0.047 ± 0.0139 ^{NS}	0.254 ± 0.0104	0.212 ± 0.0117		
VSTM	0.366 ± 0.0080	$0.758 \pm 1.0e-4$	0.026 ± 0.0117^{NS}	0.359 ± 0.0078	0.306 ± 0.0094		
FD, framewise displacement: NA, not applicable: NS. nonsignificant: RMSE, root mean square error:							

Table S1. Prediction accuracies of age and cognitive metrics, and influence of covariates

FD, framewise displacement; NA, not applicable; NS, nonsignificant; RMSE, root mean square error; VSTM, visual short-term memory.

Figure S2. Prediction correlations remain largely unchanged when only including subjects with a mean framewise displacement (FD) <0.15 or FD <0.20, suggesting that the predictive models are robust to head motion. The network-level representations of weight maps derived from models build on subjects with mean FD <0.15, and subjects with mean FD <0.20, were highly similar to those based on all subjects. For better comparison, network pairs in the bar plot were shown by the same sequence as in Figure 3C. Subplot A shows results for age-predictive models, and subplot B shows results for *g*F-predictive models.

Table S2. Top 10 weighted functional nodes in predicting age or fluid intelligence

Figure S3. Similarity of within-network weight maps between age- and cognition-predictive models. To examine whether within-network weight maps between age- and cognitionpredictive models show higher similarities than randomly selected connections, we conducted a bootstrap test. Specifically, for each functional network we randomly selected 200 withinnetwork connections without replacement 1000 times; and then calculated the correlation of weight maps from age-predictive and cognition-predictive models for each iteration. Further, we randomly selected 200 connections from the whole connectome 1000 times and calculated correlations of weight maps from age-predictive and cognition-predictive models for each iteration. Differences between the within-network weight maps and randomly selected weight maps were compared using a two-sample t-test. Overall, among all eight networks, only DAN and LIM have lower similarity in weight patterns than a matched number of randomly selected connections. For the VSTM-predictive model, DAN and VIS have lower similarity in weight patterns than a matched number of randomly selected connections.

	Age		Fluid intelligence		
	Mean	95% CI	Mean	95% CI	
VIS-VIS	-0.0070	$[-0.00707, -0.00689]$	0.0036	$\overline{[0.00355, 0.00357]}$	
VIS-SMN	0.0062	[0.00613, 0.00624]	-0.0003	$[-0.00026, -0.00024]$	
SMN-SMN	-0.0127	$[-0.01273, -0.01258]$	0.0034	[0.00336, 0.00339]	
VIS-DAN	-0.0052	$[-0.00525, -0.00514]$	0.0013	[0.00133, 0.00135]	
SMN-DAN	0.0115	[0.01149, 0.0116]	-0.0032	$[-0.00323, -0.00321]$	
DAN-DAN	-0.0002	$[-0.00032, -0.00013]$	0.0034	[0.00334, 0.00337]	
VIS-VAN	-0.0020	$[-0.00207, -0.00194]$	-0.0002	$[-0.00016, -0.00014]$	
SMN-VAN	0.0097	[0.0096, 0.00973]	0.0010	[0.00099, 0.00101]	
DAN-VAN	-0.0043	$[-0.00432, -0.00419]$	0.0006	[0.00058, 0.0006]	
VAN-VAN	-0.0224	$[-0.02249, -0.02226]$	0.0056	[0.00561, 0.00563]	
VIS-LIM	0.0071	[0.00699, 0.00712]	-0.0007	$[-0.00073, -0.00071]$	
SMN-LIM	0.0072	[0.00717, 0.0073]	0.0006	[0.00057, 0.00059]	
DAN-LIM	-0.0007	$[-0.00076, -0.00064]$	-0.0002	$[-0.00022, -0.0002]$	
VAN-LIM	0.0019	[0.00186, 0.002]	0.0002	[0.00022, 0.00024]	
LIM-LIM	0.0045	[0.00437, 0.00457]	-0.0020	$[-0.00206, -0.00203]$	
VIS-FPN	0.0038	[0.00377, 0.0039]	-0.0008	$[-0.00085, -0.00083]$	
SMN-FPN	0.0072	[0.00713, 0.00725]	-0.0024	$[-0.0024, -0.00238]$	
DAN-FPN	0.0039	[0.00381, 0.00394]	0.0004	[0.00038, 0.00039]	
VAN-FPN	-0.0004	$[-0.00043, -0.00028]$	-0.0007	$[-0.00069, -0.00067]$	
LIM-FPN	-0.0076	$[-0.00763, -0.00752]$	-0.0003	$[-0.00029, -0.00028]$	
FPN-FPN	-0.0028	$[-0.00293, -0.00275]$	0.0018	[0.0018, 0.00182]	
VIS-DMN	-0.0018	$[-0.00188, -0.00176]$	-0.0012	$[-0.00117, -0.00116]$	
SMN-DMN	-0.0018	$[-0.00182, -0.00172]$	-0.0001	$[-0.00016, -0.00014]$	
DAN-DMN	0.0017	[0.00165, 0.00176]	-0.0025	$[-0.00255, -0.00254]$	
VAN-DMN	0.0060	[0.00592, 0.00604]	-0.0018	$[-0.00185, -0.00183]$	
LIM-DMN	-0.0078	$[-0.00781, -0.0077]$	0.0007	[0.00064, 0.00066]	
FPN-DMN	-0.0028	$[-0.00283, -0.00271]$	0.0001	[0.0001, 0.00012]	
DMN-DMN	-0.0167	$[-0.0168, -0.01664]$	0.0047	[0.00468, 0.0047]	
VIS-SUB	-0.0013	$[-0.00135, -0.00124]$	0.0013	[0.00134, 0.00136]	
SMN-SUB	0.0011	[0.00104, 0.00115]	0.0026	[0.00256, 0.00257]	
DAN-SUB	-0.0062	$[-0.00623, -0.00612]$	0.0012	[0.00116, 0.00117]	
VAN-SUB	0.0022	[0.00214, 0.00226]	0.0024	[0.00243, 0.00245]	
LIM-SUB	0.0038	[0.00377, 0.0039]	-0.0002	$[-0.00023, -0.00021]$	
FPN-SUB	0.0008	[0.0007, 0.00081]	0.0007	[0.00072, 0.00074]	
DMN-SUB	0.0006	[0.00052, 0.00062]	0.0012	[0.00115, 0.00117]	
SUB-SUB	-0.0132	$[-0.01326, -0.0131]$	0.0012	[0.00118, 0.0012]	

Table S3. Predictive weights and 95% confidence interval for each network pair

Figure S4. Stability of weight maps across 2000 distinct models. The prediction analysis was placed within a 10-fold cross-validation with 200 repetitions, generating 2000 predictive models in total. Stability of the predictive models was evaluated by calculating the intercorrelations of weight maps across 2000 models. DAN, dorsal attention network; DMN, default mode network; FPN, frontoparietal network; gF, fluid intelligence; LIM, limbic network; SMN, somatomotor network; SUB, subcortical network; VAN, ventral attention network; VIS, visual network; VSTM, visual short-term memory.

Figure S5. Mean weights distribution of within-network and between-network connections derived from bootstrap tests. We iteratively generated bootstrap samples by randomly sampling participants with replacement (5000 iterations), and then built predictive models using each bootstrap sample. Error bars indicate standard deviation. DAN, dorsal attention network; DMN, default mode network; FPN, frontoparietal network; gF, fluid intelligence; LIM, limbic network; SMN, somatomotor network; SUB, subcortical network; VAN, ventral attention network; VIS, visual network; VSTM, visual short-term memory.

Figure S6. Predictive results based on connectome-based predictive modeling (CPM) ^{[\[1-5\]](#page-17-0)}, CPM works by (i) calculating the correlation of each connection to the target measure (e.g., age) across training subjects, and retaining the most significantly correlated ones under a predefined threshold; (ii) separating the selected features into a positive tail (the positively-correlated connections) and a negative tail (the negatively-correlated connections); (iii) separately summing the selected connections in the positive and negative tails into a single aggregate metric (positive network strength, negative network strength); (iv) submitting the aggregate metrics to a linear regression model. Detailed implementation can be found in $[1, 2]$ $[1, 2]$. Overall, results showed that the CPM method achieved slightly lower prediction accuracy than PLSR, but the identified predictive patterns were highly similar to those revealed by PLSR.

Figure S7. Prediction accuracies based on within- or between-network connections. To examine which functional network contributes more to the prediction than others, we reran the prediction framework using only within-network or between-network connections to predict age. All network pairs achieved a prediction accuracy lower than models based on whole-brain features. However, we found that networks having more connections are more likely to better predict age. Nevertheless, there are some interesting findings. For example, there are only a medium number of connections within DMN. But it achieved a relative higher accuracy in predicting age than its size-matched counterparts.

Table S4. Prediction results based on multimodal neuroimaging features

Figure S8. Distributions of age and each of the eight cognitive metrics scores. For most of the cognitive tasks, there were a comparable number of subjects, while for force matching and motor learning, the number of participants was reduced by half. This is mainly because most of the cognitive measures were derived from a paper-and-pencil task or simple computerized experiment. However, the motor learning and force matching required specialist equipment. To facilitate the efficiency of data acquisition, the cognitive measures were collected from 4 Cam-Can sessions. Specifically, all participants attended Session 1 and Session 2, and either Session 3a or Session 3b^{[\[6\]](#page-18-0)}. Cognitive measures of force matching and motor learning only appeared in either Session 3a or Session 3b. Therefore, only half of the participants have available data for these two cognitive tasks. Description for each of the eight behavioral tasks were directly copied from $^{[7]}$ $^{[7]}$ $^{[7]}$, while more details can be found in $^{[6]}$ $^{[6]}$ $^{[6]}$.

- 1) Fluid intelligence: Fluid intelligence was assessed using the standard form of the Cattell Culture Fair, Scale 2 Form A. Participants completed nonverbal puzzles involving series completion, classification, matrices, and conditions. Correct responses are given a score of 1 for a total maximum score of 46.
- 2) Motor learning: This task taps into motor adaptation, the process of learning new kinematic control in response to deviations in a voluntary action. Time-pressured movement of a cursor to a target by moving an (occluded) stylus under veridical, perturbed (30°), and reset (veridical again) mappings between visual and real space.
- 3) Visual short-term memory: View (1–4) colored discs briefly presented on a computer

screen, then after a delay, attempt to remember the color of the disc that was at a cued location, with response indicated by selecting the color on a color wheel (touchscreen input).

- 4) Force matching: Match mechanical force applied to left index finger by using right index finger either directly, pressing a lever which transmits force to left index finger, or indirectly, by moving a slider which adjusts the force transmitted to the left index finger. Accuracy was assessed by average difference between target force and matched force applied by participant via (direct, indirect) means.
- 5) Face recognition: Given a target image of a face, identify same individual in an array of 6 face images (with possible changes in head orientation and lighting between target and same face in the test array).
- 6) Hotel task: This task examines aspects of executive function that are important for complex planning and multitasking. Perform tasks in role of hotel manager: write customer bills, sort money, proofread advert, sort playing cards, alphabetise list of names. Total time must be allocated equally between tasks; there is not enough time to complete any one task.
- 7) Emotion expression recognition: View face and label emotion expressed (happy, sad, anger, fear, disgust, surprise) where faces are morphs along axes between emotional expressions.
- 8) Tip-of-tongue task: View faces of famous people (actors, musicians, politicians, etc.) and respond with the person's name, or "don't know" if they do not know the person's name (even if familiar), or "TOT" if they know the person's name but are (temporarily) unable to retrieve it.

Figure S9. Correlations between cognitive metrics and age. As expected, all cognitive domain scores were negatively correlated with individual's age, reflecting a pattern of aging-related cognitive decline (p<0.001, Bonferroni corrected).

MRI data acquisition

Cam-CAN: Details of fMRI data acquisition can be found in $[6, 7]$ $[6, 7]$. Briefly, resting-state scans were collected while participants rested with their eyes closed. In the movie-watching task, participants were scanned while they watched an excerpt of a compelling but unfamiliar film: "Bang! You're Dead", which is condensed from its original time of about 30 min to 8 min with the essential plot preserved. In the sensorimotor task, participants respond to 129 trials consisting of an initial practice trial, 120 bimodal audio/visual trials, and eight unimodal trials included to discourage strategic responding to one modality.

Imaging data were acquired using a 3T Siemens TIM Trio scanner with a 32-channel head coil. A 3D structural MRI was performed on each participant using a T1-weighted sequence with generalized autocalibrating partially parallel acquisition acceleration factor 2; repetition time (TR) = 2250 ms; echo time (TE) = 2.99 ms; flip angle = 9° ; field-of-view (FOV) = 256 \times 240×192 mm; resolution = 1 mm. For resting-state and sensorimotor task fMRI acquisition, T2*-weighted gradient echo planar image (EPI) data of 261 volumes were acquired with 32 slices (descending order) of thickness 3.7 mm and a slice gap of 20% for whole-brain coverage (TR = 1970 ms; TE = 30 ms; flip angle = 78°; FOV = 192 \times 192 mm; resolution = 3 \times 3 \times 4.44 mm). Imaging data during the movie-watching task were acquired using a multi-echo EPI scan

with the following parameters: $TR = 2470$ ms; 5 echoes ($TE = 9.4$ ms, 21.2 ms, 33 ms, 45 ms, 57 ms); flip angle = 78°; FOV = 192 × 192 mm; resolution = $3 \times 3 \times 4.44$ mm; slices = 32; 193 volumes.

NKI: Imaging data were acquired using a 3T Siemens TIM Trio scanner. Resting fMRI data were acquired using an EPI sequence with the following parameters: $TR = 2500$ ms; $TE =$ 30 ms; flip angle = 80° ; FOV = 216 mm; slice thickness = 3.0 mm, slices = 38, voxel size = 3.0 \times 3.0 \times 3.0 mm, acquisition time=5 minutes. High resolution T1 MPRAGE anatomical images were acquired with the following parameters: $TR = 1900$ ms, $TE = 2.52$ ms, slice thickness = 1.0 mm, flip angle = 9° , FOV= 256 mm, and voxel size = $1.0 \times 1.0 \times 1.0$ mm.

Shanxi: MRI data were obtained with a Siemens Trio 3.0 Tesla scanner (Erlangen, Germany). Participants were instructed to stay awake with their eyes closed, and not to fall asleep or move during scanning. No participants were excluded due to falling asleep or opening their eyes. Functional scans were collected using an EPI sequence with the following parameters: TR = 2500 ms; TE = 30 ms; flip angle = 90° ; FOV = 240×240 mm; slice thickness $= 3$ mm, slices=32; voxel size $= 3.75 \times 3.75 \times 4$ mm, 212 volumes.

Preprocessing

The DiffusionKit (diffusion.brainnetome.org) and in-house code were used for fMRI preprocessing, following the general framework in aging studies $[8, 9]$ $[8, 9]$. We applied similar preprocessing strategy to all three datasets, which was the same as our previous publications. The BOLD echo planar image data for all three states were unwrapped based on field-map images to compensate for magnetic field inhomogeneities, realigned to correct motion effects where the motion parameters for each volume image were stored for the following regression, and slice-time corrected. The first 10 volumes were discarded to allow for magnetic equilibration and then nonlinearly registered to MNI 3-mm space (for validation datasets, we did not discard any volumes because they only included a small number of volumes). We further scrubbed the frames with excessive head motions based on framewise displacement (FD) >0.5 mm criterion and corrected the frames by interpolation. We discarded images with less than 40% of their original data after scrubbing. Moreover, fMRI scans with a mean FD>0.3 mm were excluded from further analysis. We then band-pass filtered the data at 0.009–0.08 Hz to reduce low-frequency drift and high-frequency noise. CompCor was used to reduce physiological effects as performed in $[10, 11]$ $[10, 11]$. Specifically, the mean signal and 5 principal components of white matter and cerebrospinal fluid and movement parameters and their derivatives were regressed out as confounding factors to remove physiological noise. The aforementioned principal components were derived separately by decomposing the regional signal masked by the eroded

white matter and cerebrospinal fluid. In light of the fact that the location of functional regions was more variable in older adults, which can be alleviated by smoothing $[11]$, we smoothed the volume images by a Gaussian filter with a kernel size of 6 mm. Considering a controversial physiological interpretation, global signal regression was not performed here. As previous studies confirmed the advantages of longer scan length, we concatenated fMRI time series from all three fMRI conditions ^{[\[12-14\]](#page-18-6)}. Time courses from the task fMRI were calculated based on the raw task fMRI data, with no regression of task-evoked activity [\[15\]](#page-18-7), resulting in a total length of 685 time points for Cam-CAN data. For validation cohorts, only resting-state fMRI was available, therefore, the total length of time points did not change.

11 1: Visual network; 2: Somatomotor network; 3: Dorsal attention network; 4: Ventral attention network; 5: Limbic network; 6: Frontoparietal network; 7: Default mode network; 8: Subcortical network.

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