Supplementary Text

Covariate adjustment. For each feature type, let j be the index of a brain region, $j = 1, \ldots, m$. Let $n = 3418$ be the aggregate training sample size and $\boldsymbol{f}_j$ be an $n \times 1$ vector containing all subjects' hemisphere-averaged values of a given feature. We begin by regressing out the confounding effects of sex, cohort, FreeSurfer version, and of the cohort × CA interaction. We account for the joint confounding effects of cohort and FreeSurfer version after generating an $n \times 1$ group vector $\boldsymbol{g}$ which assigns a distinct integer to each unique combination of cohort and FreeSurfer version, yielding $N_g = 6$ 'groups' in our training set (**Table 1**). Let k be an index for each of these groups ($k = 1, \ldots, N_g$), $\boldsymbol{CA}$ be an $n \times 1$ vector containing the CAs of the subjects, and $\boldsymbol{g}_k$ be an $n \times 1$ vector with entries of 1 for subjects belonging to group k and 0 otherwise. For each feature $\boldsymbol{f}_j$ we fit N_g distinct multiple linear regression models of the form

$$\boldsymbol{f}_j = \gamma_{0,j,k} + \gamma_{1,j,k}\boldsymbol{g}_k + \gamma_{2,j,k}\boldsymbol{CA} + \gamma_{3,j,k}\boldsymbol{g}_k \odot \boldsymbol{CA} + \boldsymbol{\varepsilon}_{j,k}$$

For each of k, $\gamma_{0,j,k}$ is the intercept, $\gamma_{1,j,k}$, ..., $\gamma_{3,j,k}$ are regression coefficients, $\boldsymbol{\varepsilon}_{j,k}$ is the residual vector obtained by fitting the regression model to $\boldsymbol{f}_j$, and $\boldsymbol{a} \odot \boldsymbol{b}$ denotes elementwise multiplication of the elements in $\boldsymbol{a}$ and $\boldsymbol{b}$, which are of the same dimensions. To note, $\boldsymbol{CA}$ is included as a predictor variable to ensure that its covariance with $\boldsymbol{f}_j$ is not captured in the group-by-CA interaction term, which has been shown to improve model performance and to remove confounding effects (18). Because of this inclusion, each group requires a separate multiple linear regression model to avoid a rank-deficient design matrix. If only the group effect is regressed out, each feature $\boldsymbol{f}_j$ is corrected as

$$\boldsymbol{f}_j^{(\mathrm{c})} = \boldsymbol{f}_j - \sum_{k=1}^{N_g} \left(\gamma_{1,j,k}\boldsymbol{g}_k + \gamma_{3,j,k}\boldsymbol{g}_k \odot \boldsymbol{CA}\right)$$

The intercept $\gamma_{0,k}$ is not subtracted because this would remove the main effect, which is unaccounted for by confounds. To ensure that the covariance of $\boldsymbol{f}_j$ with $\boldsymbol{CA}$ is not removed, the $\gamma_{2,j,k}\boldsymbol{CA}$ term in the regression is not subtracted. The covariate-corrected features $\boldsymbol{f}_j^{(c)}$ are assembled into an $n \times (m+1)$ design matrix

$$\boldsymbol{X} = \left[\,\boldsymbol{1}\ \boldsymbol{f}_1^{(\mathrm{c})} \ldots \boldsymbol{f}_m^{(\mathrm{c})}\right]$$

where $\boldsymbol{1}$ is an $n \times 1$ column vector for the model intercept. Ridge regressions were implemented both across sexes and for each sex. In the former case, the statistical effect of sex on brain features is regressed out; in the latter case, a separate regression model is implemented for each sex. Once the sex effect has been regressed out, a linear regression model $\boldsymbol{f}_j = \alpha_0 + \alpha_1\boldsymbol{s} + \boldsymbol{\varepsilon}$ is fit, where $\boldsymbol{s}$ is an $n \times 1$ binary variable vector (which codes male subjects as 1 and female subjects as 0.), α_0 is the intercept, α_1 is a linear regression coefficient, and $\boldsymbol{\varepsilon}$ is a vector of residuals. We chose this coding scheme to model females as the reference sex group due to their typically slower aging. When the effects of *both* sex and group are regressed out, each feature is corrected according to the equation

$$\boldsymbol{f}_j^{(c)} = \boldsymbol{f}_j - \sum_{k=1}^{N_g} \left(\gamma_{1,j,k}\boldsymbol{g}_k + \gamma_{3,j,k}\boldsymbol{g}_k \odot \boldsymbol{CA}\right) - \alpha_1\boldsymbol{s}$$

where $\boldsymbol{f}_j^{(c)}$ is the corrected value of the feature indexed by j.

Supplementary Tables

eTable 1. Formulas for covariate correction procedures, regression objective functions, bias correction, and performance statistics, as well as quantities on which these depend.

quantity/equation	formula
ridge regression objective function	$\widehat{\boldsymbol{\beta}} = \arg\min_{\boldsymbol{\beta}} \left\{ \frac{1}{n} \lVert \boldsymbol{CA} - \boldsymbol{X\beta} \rVert_2^2 + \lambda \lVert \boldsymbol{\beta} \rVert_2^2 \right\}$
LASSO objective function	$\widehat{\boldsymbol{\beta}} = \operatorname{argmin}_{\boldsymbol{\beta}} \left\{ \frac{1}{n} \lVert \boldsymbol{CA} - \boldsymbol{X\beta} \rVert_2^2 + \lambda \lVert \boldsymbol{\beta} \rVert_1 \right\}$
zero correlation constraint corrected age gaps	$\widehat{\boldsymbol{AG}}_C = \frac{1}{corr(\boldsymbol{CA},\ \widehat{\boldsymbol{BA}})} \frac{\lVert \widehat{\boldsymbol{AG}} \rVert}{\lVert \widehat{\boldsymbol{BA}} \rVert} \widehat{\boldsymbol{AG}}_B$
mean squared error	$MSE = \frac{1}{n} \sum_{i=1}^{n} \left(\widehat{BA}_i - CA_i \right)^2$
mean absolute error	$MAE = \frac{1}{n} \sum_{i=1}^{n} \left(\lvert \widehat{BA}_i - CA_i \rvert \right)$
error sum of squares	$SSE = \sum_{i=1}^{n} \left(\widehat{BA}_i - CA_i \right)^2$
sample mean CA	$\overline{CA} = \frac{1}{n} \sum_{i=1}^{n} CA_i$
total sum of squares	$SST = \sum_{i=1}^{n} (CA_i - \overline{CA})^2$
adjusted coefficient of determination	$\bar{R}^2 = 1 - \left(\frac{SSE}{SST} \right) \left(\frac{n-1}{n-m} \right)$
adjusted coefficient of partial determination	$\bar{R}_p^2 = \left(\frac{SSE_r}{n-m-2} - \frac{SSE_f}{n-m-1} \right) \left(\frac{SSE_r}{n-m-2} \right)^{-1}$
unadjusted coefficient of partial determination	$R_p^2 = \left(SSE_r - SSE_f \right) / SSE_r$

Note. BA=biological age, CA=chronological age, f=full, g=group m=number of features, N_g=number of groups, n=number of subjects, r=reduced.

eTable 2. Summary of cognitive assessments available for the Cam-CAN validation sample. For emotional processing, the percentage of correct responses to Ekman's emotion expression task conveys emotional recognition accuracy, which declines with age. For stimuli with negative emotional valence in the emotional memory task, d' indexes memory accuracy (correct rejections vs. correct recognitions). Negative stimuli were selected for this study because negative emotional memory is more affected by age than positive or neutral emotional memories are. Emotional regulation during negatively valanced trials indicates the ability to suppress negative emotions, which is often preserved in typical aging. For executive functioning, the total score on Cattell's fluid intelligence test conveys frontoparietal-mediated executive control measured across four subtests. On the hotel test, the time taken on each of five tasks is a measure of complex planning and multitasking ability. The number of correctly interpreted proverbs measures abstraction. For memory, the number of correctly matched unfamiliar faces can index age-related memory decline. The number of correctly recognized famous faces measures semantic recall. In the picture priming task, the word finding time is used to indicate age-related semantic memory decline. The proportion of tip-of-the-tongue responses quantifies word finding difficulty, which commonly reflects cognitive decline. Average capacity on the color version of the visual short-term memory task measures working memory span, which often declines with age. For motor functioning, the mean over-compensation time on the force matching task measures sensorimotor integration ability. The mean reaction time on the motor learning task is a measure of motor adaptation. The mean reaction time on the simple task measures automatic response speed, while the mean reaction time on the choice task measures response speed for trials requiring decision-making.

cognitive domain	task	variable	interpretation of higher scores	n^a
emotional processing	Ekman's Emotion Expression Recognition	percentage of correct answers	**better** emotional recognition	47
	Emotional Memory	negative stimuli d' (hits - misses, standardized)	**better** recognition memory for negative stimuli	310
	Emotional Regulation	rating of emotional regulation for negative images	**greater** emotional regulation	300
executive function	Cattell's Fluid Intelligence	total score	**better** fluid intelligence	632
	Hotel Task	time per task	**worse** multitasking	629
	Proverbs	number of correct responses	**larger** number of correctly interpreted proverbs	627
memory	Benton's Face Recognition	number of correct responses	**better** recognition of familiar faces	630
	Face Recognition: Famous Faces	number of correct responses (famous faces)	**better** recognition of famous faces	631
	Picture Priming	word finding time	**shorter** word finding time	558
	Tip of the Tongue Task	proportion of 'tip-of-the-tongue' responses	**worse** recall	619
	visual short-term memory: color	average working memory capacity	**worse** visual short term memory capacity	635
motor functioning	Force Matching	mean over-compensation	**worse** motor control	308
	Motor Learning	mean reaction time	**slower** motor learning	305
	Reaction Time: Choice	mean reaction time	**shorter** reaction time	597
	Reaction time: Simple	mean reaction time	**shorter** reaction time	605

[a]n=sample size

eTable 3. Estimated ridge regression coefficients $\hat{\beta}_j$ and (un)adjusted partial coefficients of determination R_p^2 for the sex-agnostic model to estimate brain age from regional volumes. R_p^2 is expressed as a percentage of the variance, explained by the full model, that is not explained by a reduced model which excludes the variable in question. The model intercept is in units of years (y); the other regression coefficients $\hat{\beta}_j$ are in units of y × 10^3. In accordance with the text, the subscript j in $\hat{\beta}_j$ is used to emphasize that these are *multivariate* regression coefficients. Entries are sorted in descending order by adjusted $\bar{R}_p^2$.

		R_p^{2} [b]	
anatomical structure/feature	$\hat{\beta}_j$ [a]	**unadjusted**	**adjusted**
model intercept	78.94	—	—
nucleus accumbens	-27.82	7.30	7.27
inferior temporal gyrus	-2.09	4.05	4.03
thalamus	-2.85	3.63	3.61
brain stem	1.66	3.32	3.29
posterior lateral sulcus	9.33	3.25	3.22
caudate nucleus	3.40	3.08	3.05
orbital gyri	-3.19	2.99	2.96
precentral gyrus	-2.95	2.83	2.80
pericallosal sulcus	5.01	2.52	2.49
central sulcus	3.44	2.24	2.21
isthmus, cingulate gyrus	10.51	2.21	2.18
putamen	-2.40	1.96	1.93
pallidum	5.20	1.74	1.71
cingulate gyrus, posterodorsal part	-4.81	1.60	1.57

anatomical structure/feature	$\hat{\beta}_j$ [a]	R_p^2 [b] unadjusted	adjusted
subcallosal area & gyrus	3.94	1.54	1.51
temporal pole	1.64	1.36	1.33
hippocampus	-2.87	1.26	1.23
calcarine sulcus	-2.06	1.25	1.22
cerebellum	-0.17	1.14	1.11
fusiform gyrus	-1.28	1.07	1.04
precentral sulcus, inferior part	1.95	1.07	1.04
posterotransverse collateral sulcus	-5.82	0.89	0.86
collateral/lingual sulci	-1.93	0.88	0.85
superior parietal lobule	1.35	0.84	0.81
inferior frontal gyrus, opercular part	-1.95	0.84	0.81
short insular gyri	2.98	0.83	0.80
middle temporal gyrus	-1.00	0.74	0.71
precuneus	-1.19	0.58	0.55
Heschl's gyrus	-3.47	0.52	0.49
postcentral sulcus	1.22	0.48	0.45
lingual gyrus	0.89	0.47	0.44
middle occipital/lunatus sulci	-2.14	0.43	0.40
occipital pole	1.26	0.41	0.38
middle frontal gyrus	-0.49	0.41	0.38
transverse frontopolar gyri/sulci	1.88	0.40	0.37
insular long gyrus/central sulcus	2.62	0.37	0.34

anatomical structure/feature	$\hat{\beta}_j$ [a]	R_p^2 [b] unadjusted	R_p^2 [b] adjusted
superior temporal sulcus	0.61	0.37	0.34
superior circular insular sulcus	2.38	0.35	0.32
anterior circular insular sulcus	4.10	0.34	0.31
lateral occipitotemporal sulcus	1.59	0.29	0.27
lateral superior temporal gyrus	-0.91	0.29	0.26
inferior circular insular sulcus	2.01	0.25	0.22
transverse temporal sulcus	-4.19	0.21	0.18
paracentral lobule/sulcus	0.77	0.21	0.18
inferior temporal sulcus	1.23	0.21	0.18
amygdala	1.51	0.21	0.18
anterior cingulate gyrus/sulcus	0.80	0.21	0.18
superior frontal gyrus	-0.29	0.17	0.14
frontomarginal gyrus/sulcus	1.40	0.17	0.14
superior occipital gyrus	-0.98	0.16	0.13
middle frontal sulcus	-0.62	0.16	0.13
superior frontal sulcus	-0.52	0.14	0.11
supramarginal gyrus	-0.43	0.14	0.11
middle occipital gyrus	0.61	0.14	0.11
precentral sulcus, superior part	0.89	0.13	0.10
medial orbital sulcus	1.40	0.12	0.09
inferior frontal sulcus	-0.59	0.09	0.06
superior/transverse occipital sulci	-0.90	0.09	0.06

anatomical structure/feature	$\widehat{\beta}_j$ [a]	R_p^2 [b] unadjusted	adjusted
parietooccipital sulcus	0.53	0.08	0.05
subparietal sulcus	-0.73	0.07	0.04
angular gyrus	-0.30	0.07	0.04
postcentral gyrus	-0.49	0.06	0.03
marginal cingulate sulcus	0.91	0.06	0.03
cuneus	-0.56	0.06	0.03
straight gyrus	0.62	0.06	0.03
anterior transverse collateral sulcus	0.61	0.05	0.02
middle posterior cingulate gyrus/sulcus	0.70	0.04	0.01
horizontal anterior lateral sulcus	-1.76	0.04	0.01
parahippocampal gyrus	-0.23	0.04	0.01
orbital sulci	0.60	0.03	0.00
subcentral gyrus/sulci	-0.31	0.03	0.00
inferior frontal gyrus, triangular part	-0.30	0.02	-0.01
inferior frontal gyrus, orbital part	-0.62	0.02	-0.01
suborbital sulcus	0.56	0.02	-0.01
Jensen's sulcus	-0.53	0.02	-0.01
temporal plane	-0.16	0.01	-0.02
intraparietal/transverse parietal sulci	-0.14	0.01	-0.02
vertical anterior lateral sulcus	-0.50	0.00	-0.03
temporo-occipital incisure	-0.12	0.00	-0.03
lateral orbital sulcus	-0.15	0.00	-0.03

anatomical structure/feature	$\hat{\beta}_j$[a]	R_p^2[b] unadjusted	R_p^2[b] adjusted
temporal polar plane	0.05	0.00	-0.03
inferior occipital gyrus/sulcus	0.02	0.00	-0.03
middle anterior cingulate gyrus/sulcus	0.07	0.00	-0.03

[a] $\hat{\beta}_j$=regression coefficient for region j

[b] R_p^2=coefficient of partial determination

eTable 4. Relative ability of CA and BA to capture performance within each cognitive domain for Cam-CAN validation sample participants with data available for each cognitive task. For each of CA, BA, and AG, the table lists Spearman's rank correlation coefficient ρ, p-value for the test of the null hypothesis $H_0: \rho = 0$, and df. Also listed are Fischer's z-statistic and p-value for the test of the null hypothesis $H_0: \rho(CA) = \rho(BA)$ of no change in ρ when this measure is computed using CA vs. BA.

			test of $H_0: \rho = 0$			test of $H_0: \rho(CA) = \rho(BA)$	
cognitive domain	**task**	**measure**	ρ[a]	p[b]	df[c]	z[d]	p[e]
emotional processing	emotion recognition	CA	0.111	0.463	45	0.106	0.916
		BA	0.133	0.378			
		AG	0.201	0.180			
	emotional memory	CA	0.539	<0.001*	308	0.338	0.736
		BA	0.519	<0.001*			
		AG	0.073	0.199			
	emotional regulation	CA	0.106	0.067	298	0.276	0.783
		BA	0.128	0.026			
		AG	0.081	0.164			
executive function	fluid intelligence	CA	0.668	<0.001*	630	1.282	0.200
		BA	0.626	<0.001*			
		AG	0.037	0.349			
	hotel task	CA	0.267	<0.001*	627	0.876	0.381
		BA	0.220	<0.001*			
		AG	0.045	0.256			
language processing	proverbs	CA	0.134	0.001*	625	0.287	0.774

cognitive domain	task	measure	test of H_0: ρ = 0			test of $H_0: \rho(CA) = \rho(BA)$	
			ρ[a]	p[b]	df[c]	z[d]	p[e]
		BA	0.118	0.003			
		AG	0.008	0.842			
memory	unfamiliar face recognition	CA	0.466	<0.001*	628	0.319	0.750
		BA	0.452	<0.001*			
		AG	0.063	0.116			
	famous face recognition	CA	0.439	<0.001*	629	0.697	0.486
		BA	0.407	<0.001*			
		AG	0.031	0.433			
	picture priming	CA	0.310	<0.001*	556	0.286	0.775
		BA	0.294	<0.001*			
		AG	0.074	0.082			
	tip of the tongue	CA	0.302	<0.001*	618	1.070	0.285
		BA	0.245	<0.001*			
		AG	0.055	0.171			
	visual short-term memory: color	CA	0.493	<0.001*	633	1.073	0.283
		BA	0.446	<0.001*			
		AG	0.017	0.673			
motor functioning	force matching	CA	0.271	<0.001*	306	0.276	0.783
		BA	0.250	<0.001*			
		AG	0.024	0.673			
	motor learning	CA	0.537	<0.001*	303	0.563	0.574
		BA	0.504	<0.001*			

cognitive domain	task	measure	test of $H_0: \rho = 0$			test of $H_0: \rho(CA) = \rho(BA)$	
			ρ[a]	p[b]	df[c]	z[d]	p[e]
		AG	0.054	0.348			
	reaction time: choice	CA	0.687	<0.001*	595	1.435	0.151
		BA	0.640	<0.001*			
		AG	0.044	0.280			
	reaction time: simple	CA	0.388	0.000	603	0.271	0.787
		BA	0.375	0.000			
		AG	0.081	0.046			

Note. AG = age gap, BA = biological age, CA = chronological age.

[a] ρ=Spearman's rank correlation coefficient between task and measure

[b] p=p-value for significance test of ρ

[c] df=degrees of freedom of significance test of ρ

[d] z=z-score for the difference between ρ_{CA} and ρ_{BA} for corresponding task

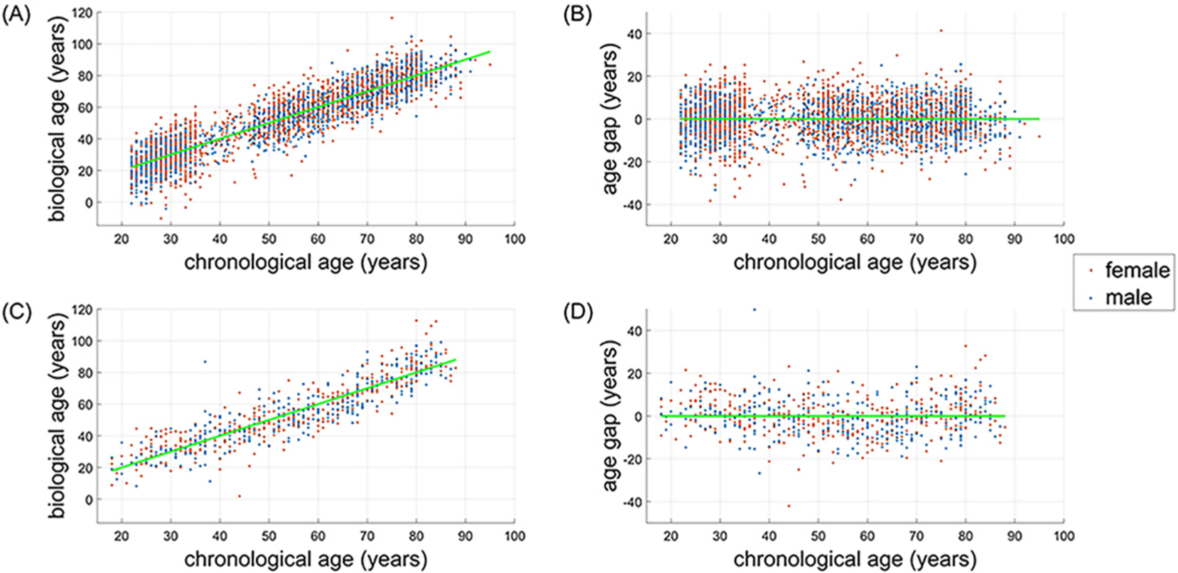
[e] p=p-value for significance test of z

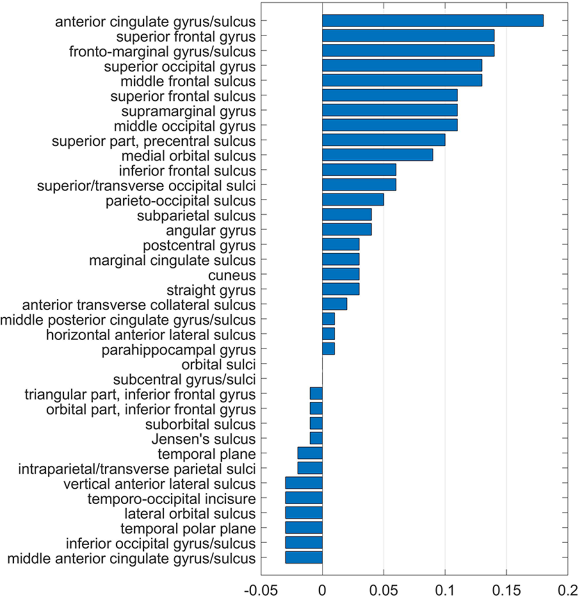
*$p < 0.0013$

Supplementary Figure Captions

eFigure 1. Performance of the sex-agnostic ridge regression model predicting age from regional volumes. Biological ages and age gaps are scatter-plotted against chronological age for the (**A**, **B**) training and (**C**, **D**) test sets. **A**. biological ages in the training set. **B**. age gaps in the training set. **C**. biological ages in the test set. **D**. age gaps for the test set. All quantities are in years. The continuous green line in **A**. and **C**. is for the equation $BA = CA$. The green line in **B** and **D** is for the equation $AG = 0$. Abbreviations: AG=age gap, BA=biological age, CA=chronological age, y=years.

eFigure 2. Adjusted coefficients of partial coefficient of determination $\bar{R}_p^2$ for the 37 structures with the largest $\bar{R}_p^2$ values included in the sex-agnostic ridge regression model estimating age using regional volumes. Plotted are adjusted $\bar{R}_p^2$ values, expressed as percentages of the total variance $\bar{R}^2$ explained by the full model that includes all predictors (regions or structures).


(A)
biological age (years)
chronological age (years)
(B)
age gap (years)
chronological age (years)
female
male
(C)
biological age (years)
chronological age (years)
(D)
age gap (years)
chronological age (years)



anterior cingulate gyrus/sulcus
superior frontal gyrus
fronto-marginal gyrus/sulcus
superior occipital gyrus
middle frontal sulcus
superior frontal sulcus
supramarginal gyrus
middle occipital gyrus
superior part, precentral sulcus
medial orbital sulcus
inferior frontal sulcus
superior/transverse occipital sulci
parieto-occipital sulcus
subparietal sulcus
angular gyrus
postcentral gyrus
marginal cingulate sulcus
cuneus
straight gyrus
anterior transverse collateral sulcus
middle posterior cingulate gyrus/sulcus
horizontal anterior lateral sulcus
parahippocampal gyrus
orbital sulci
subcentral gyrus/sulci
triangular part, inferior frontal gyrus
orbital part, inferior frontal gyrus
suborbital sulcus
Jensen's sulcus
temporal plane
intraparietal/transverse parietal sulci
vertical anterior lateral sulcus
temporo-occipital incisure
lateral orbital sulcus
temporal polar plane
inferior occipital gyrus/sulcus
middle anterior cingulate gyrus/sulcus
-0.05
0
0.05
0.1
0.15
0.2