

1 History of childbirths relates to 2 region-specific brain aging patterns 3 in middle and older-aged women

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12
13 **Abstract** Pregnancy involves maternal brain adaptations, but little is known about how parity
14 influences women's brain aging trajectories later in life. In this study, we replicated previous
15 findings showing less apparent brain aging in women with a history of childbirths, and identified
16 regional brain aging patterns linked to parity in 19,787 middle and older-aged women. Using
17 novel applications of brain-age prediction methods, we found that a higher number of previous
18 childbirths was linked to less apparent brain aging in striatal and limbic regions. The strongest
19 effect was found in the accumbens - a key region in the mesolimbic reward system, which plays
20 an important role in maternal behavior. While only prospective longitudinal studies would be
21 conclusive, our findings indicate that subcortical brain modulations during pregnancy and
22 postpartum may be traceable decades after childbirth.

23 24 **Introduction**

25 Pregnancy involves a number of maternal brain adaptations (*Barha and Galea, 2017; Fox et al.,*
26 *2018; Hillerer et al., 2014; Eid et al., 2019; Boddy et al., 2015*). In rodents, changes in volume,
27 cell proliferation, and dendritic morphology (*Hillerer et al., 2014; Kinsley et al., 2006*), as well as
28 altered neurogenesis in the hippocampus (*Eid et al., 2019; Rolls et al., 2008*) are found across
29 pregnancy and postpartum. In humans, reduction in total brain volume has been observed during
30 pregnancy, reversing within six months of parturition (*Oatridge et al., 2002*). Reductions in striatal
31 volumes, particularly putamen, have been reported shortly after delivery (*Lisofsky et al., 2016*),
32 and pregnancy-related reductions in gray matter volume have been found in regions subserving
33 social cognition; the bilateral lateral prefrontal cortex, the anterior and posterior midline, and the
34 bilateral temporal cortex (*Hoekzema et al., 2017*). Conversely, a recent study showed no evidence
35 of decrease in gray matter volume following childbirth, but instead detected a pronounced gray
36 matter *increase* in both cortical and subcortical regions (*Luders et al., 2020*). Prefrontal cortical
37 thickness and subcortical volumes in limbic areas have been positively associated with postpartum
38 months (*Kim et al., 2018*), indicating that changes in brain structure may depend on region and
39 time since delivery (*Luders et al., 2020; Duarte-Guterman et al., 2019; Hoekzema et al., 2017; Kim*
40 *et al., 2018, 2010*). For instance, from 2–4 weeks to 3–4 months postpartum, gray matter volume

41 increases have been found in areas involved in maternal behaviours and motivation, such as the
42 amygdala, substantia nigra, hypothalamus, and prefrontal cortex (*Kim et al., 2010*).

43 While gray matter reductions have been reported up to 2 years post-pregnancy, most stud-
44 ies are limited to the postpartum period, and little is known about how previous pregnancies in-
45 fluence women's brain aging later in life. Evidence from animal studies shows that middle-aged
46 multiparous rats have stronger cellular response to estrogens in the hippocampus compared to
47 virgin female rats (*Barha and Galea, 2011*), suggesting that neuroplastic potential across the adult
48 lifespan may be influenced by previous pregnancies. Moreover, hippocampal neurogenesis has
49 been shown to increase during middle age in primiparous rats and decrease in nulliparous rats
50 over the same period (*Eid et al., 2019*). While longitudinal studies on parity and brain aging in
51 humans are lacking, cumulative number of months pregnant has been associated with decreased
52 risk for Alzheimer's disease (*Fox et al., 2018*), and we recently documented less evident brain ag-
53 ing in parous relative to nulliparous women in >12,000 UK Biobank participants using an magnetic
54 resonance imaging (MRI)-derived biomarker of global brain aging (*de Lange et al., 2019*).

55 In the current study, we first aimed to replicate our previously reported findings described
56 in *de Lange et al. (2019)*, where less apparent brain aging was found in women with a history of
57 childbirths. Brain-age prediction methods were used to derive estimates of global brain aging,
58 which was analysed in relation to number of previous (live) childbirths in 8880 newly added UK
59 Biobank participants. Brain-age prediction is commonly used to estimate an individual's age based
60 on their brain characteristics (*Cole and Franke, 2017*), and individual variation in "brain age" esti-
61 mates has been associated with a range of clinical and biological factors (*Cole and Franke, 2017*;
62 *Kaufmann et al., 2019*; *Franke and Gaser, 2019*; *Cole et al., 2018, 2019*; *Cole, 2019*; *Smith et al.,*
63 *2019*; *Cole et al., 2017*; *de Lange et al., 2020a,b*). As compared to MRI-derived measures such as
64 cortical volume or thickness, brain-age prediction adds a dimension by capturing deviations from
65 normative trajectories identified by machine learning. While traditional brain age approaches sum-
66 marize measures across regions to produce a single, global aging estimate - often with high predic-
67 tion accuracy, models of distinct and regional aging patterns can provide more refined biomarkers
68 that may capture additional biological detail (*Kaufmann et al., 2019*; *Smith et al., 2020*; *Eavani*
69 *et al., 2018*). In this study, we utilized novel applications of brain-age prediction methods based
70 on cortical and subcortical volumes to identify regions of particular importance for maternal brain
71 aging, using a total sample of 19,787 UK Biobank women.

72 Results

73 Associations between previous childbirths and global brain aging:

74 To replicate our findings described in *de Lange et al. (2019)*, we trained a brain-age prediction
75 model on the part of the current sample that overlapped with the previous study (N = 10,907), and
76 applied it to the newly added participants (N = 8880) using the procedure described in *Methods and*
77 *Materials*. When applied to the test set, the modeled age prediction showed an accuracy of $R^2 =$
78 0.34 , root mean square error (RMSE) = 6.00, and Pearson's r (predicted versus chronological age)
79 = 0.58; 95% confidence interval (CI) = [0.57, 0.59], $p < 0.001$. Corresponding to our previous results,
80 an association was found between a higher number of previous childbirths and less apparent brain
81 aging in the group of newly added participants: $\beta = -0.13$ standard error (SE) = 0.03, $t = -4.07$, $p =$
82 4.79×10^{-5} . To adjust for age-bias in the brain age prediction as well as age-dependencies in number
83 of childbirths (*Le et al., 2018*), chronological age was included as a covariate in the linear regression.

84 To test for non-linear relationships, polynomial fits were run for number of childbirths and brain
85 age gap; one including intercept and a linear term (β) only, and one including intercept, linear, and
86 quadratic terms (γ). For these analyses, the brain age gap estimations were first corrected for
87 chronological age using linear regression (*Le et al., 2018*), and the residuals were used in the fits.
88 A comparison of the two models showed that the inclusion of the quadratic term did not provide
89 a better fit ($F = 0.06$, $p = 0.804$). The results from the fit including the linear term only showed

90 a significant linear effect ($\beta = -0.12 \pm 0.03$; $F = 16.10$, $p = 6.05 \times 10^{-5}$), while the results from the
91 fit including both terms showed that only the linear term was significant ($\beta = -0.14 \pm 0.072$; $\gamma =$
92 0.004 ± 0.02 ; $F = 8.08$, $p = 3.11 \times 10^{-4}$). The two fits are shown in Figure 1. As a cross check, the
93 fits were rerun with orthogonal polynomials, showing corresponding results ($\beta = -13.44 \pm 3.35$,
94 $\gamma = 0.83 \pm 3.35$; $F = 8.08$, $p = 3.11 \times 10^{-4}$).

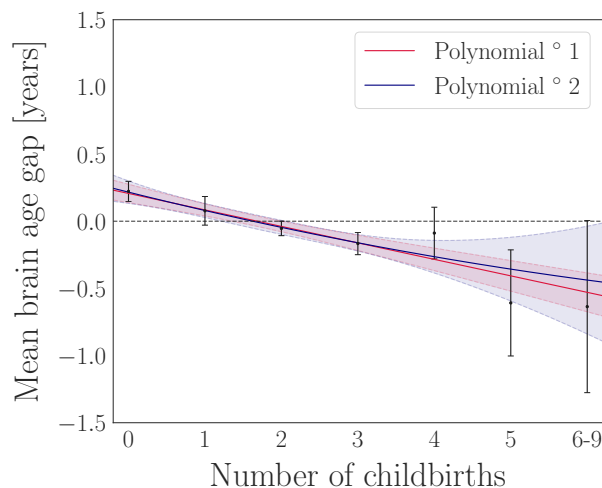


Figure 1. Results from first and second degree polynomial fits for number of childbirths and global brain aging in the newly added participants ($N = 8880$). The black points indicate the mean brain age gap \pm standard error within groups of women based on number of childbirths (x-axis). The red and blue lines represent the results of the fits, and the shaded areas indicate the $\pm 95\%$ confidence intervals for each fit. The horizontal dashed line indicates 0 on the y-axis. Number of participants in each group: 0 births = 2065, 1 birth = 1014, 2 births = 3912, 3 births = 1493, 4 births = 311, 5 births = 67, 6 births = 13, 7 births = 3, 8 births = 1, and 9 births = 1. The group of women with 6-9 children were merged to obtain sufficient statistics for least square fits using the standard error on the means as weights.

95 **Regional brain aging patters:**

96 To identify groups of imaging features based on their covariance, we performed hierarchical clustering on the Spearman rank-order correlations using an average of right and left hemisphere measures for each feature. Five clusters were identified, as shown in Figure 2. All features were grouped according to their associated cluster ID, and separate models were run to estimate brain age for each cluster using the brain-age prediction procedure described in *Methods and Materials*. The features contained in each cluster are listed in Table 1. The cluster-specific model performances are shown in Table 2.

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103 To test whether the relative prediction accuracy of the models depended on number of features, the models were rerun using the four strongest contributing features from each model as input variables. The feature contributions were calculated using permutation feature importance, defining the decrease in model performance when a single feature value is randomly shuffled (*Breiman, 2001*). The results are shown in Table 3.

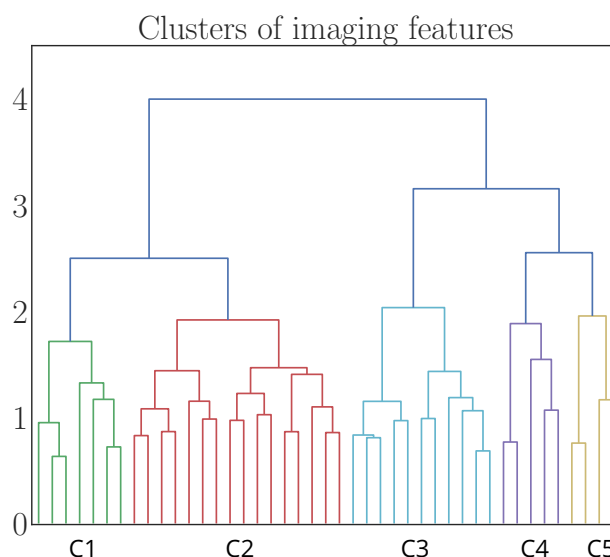


Figure 2. Dendrogram based on hierarchical clustering on the Spearman rank-order correlations of all features. The colours represent clusters (C) of features that are grouped together based on common covariance. A list of imaging features contained in each of the clusters are provided in Table 1. The y-axis shows the degree of co-linearity between the features, with higher y-values indicating less co-linearity between clusters.

Table 1. List of imaging features contained in each of the clusters identified based on hierarchical clustering (Figure 2). All feature names represent regional volume.

Cluster 1			
Cuneus	Isthmuscingulate	Lateraloccipital	Lingual
Pericalcarine	Precuneus	Superiorparietal	
Cluster 2			
Caudalanteriorcingulate	Lateralorbitofrontal	Medialorbitofrontal	Paracentral
Parsopercularis	Parsorbitalis	Parstriangularis	Postcentral
Posteriorcingulate	Precentral	Rostralmiddlefrontal	Superiorfrontal
Superiortemporal	Supramarginal	Transversetemporal	Insula
Cluster 3			
Banks of superior temporal sulcus	Fusiform	Inferiorparietal	Inferiortemporal
Middletemporal	Parahippocampal	Thalamus	Putamen
Hippocampus	Amygdala	Accumbens	
Cluster 4			
Caudalanteriorcingulate	Entorhinal	Rostralanteriorcingulate	Frontalpole
Temporalpole			
Cluster 5			
Brain-Stem	Cerebellum	Caudate	Pallidum

Table 2. The accuracy of the age prediction measured by Pearson’s r (predicted versus chronological age), R^2 , root mean square error (RMSE), and mean absolute error (MAE) for each of the cluster-specific models. 95 % confidence intervals are indicated in square brackets. RMSE and MAE are reported in years. N_{feat} = number of features contained in the cluster. P -values were < 0.001 for all models.

Model	N_{feat}	r	R^2	RMSE	MAE
Cluster 1	7	0.32 [0.31, 0.33]	0.10 [0.10, 0.11]	7.00	5.79
Cluster 2	16	0.38 [0.36, 0.39]	0.14 [0.13, 0.15]	6.86	5.64
Cluster 3	11	0.48 [0.47, 0.49]	0.23 [0.23, 0.24]	6.48	5.29
Cluster 4	5	0.13 [0.11, 0.14]	0.02 [0.01, 0.02]	7.36	6.13
Cluster 5	4	0.21 [0.19, 0.22]	0.04 [0.04, 0.05]	7.25	6.04

Table 3. The accuracy of the age prediction when including the four strongest contributing features for each model. 95 % confidence intervals are indicated in square brackets. RMSE and MAE are reported in years. N_{feat} = number of features included. P -values were < 0.001 for all models.

Model	N_{feat}	r	R^2	RMSE	MAE
Cluster 1	4	0.32 [0.31, 0.33]	0.10 [0.10, 0.11]	7.01	5.80
Cluster 2	4	0.34 [0.33, 0.35]	0.11 [0.11, 0.12]	6.96	5.75
Cluster 3	4	0.46 [0.45, 0.47]	0.21 [0.21, 0.22]	6.55	5.36
Cluster 4	4	0.12 [0.11, 0.13]	0.02 [0.01, 0.02]	7.36	6.14
Cluster 5	4	0.21 [0.19, 0.22]	0.04 [0.04, 0.05]	7.25	6.04

108 **Associations between previous childbirths and regional brain aging:**

109 The cluster-specific associations with number of previous childbirths are shown in Table 4.

Table 4. Relationships between number of previous childbirths and estimated brain aging for each cluster. Cluster-specific *brain age gap* was entered as the dependent variable and *number of (live) childbirths* was entered as independent variable for each analysis. Chronological age was included for covariate purposes. P -values are provided before and after FDR correction. Significant relationships (< 0.05) are marked with an asterisk in the p_{corr} column. SE = standard error.

Number of childbirths vs cluster-specific brain age estimates					
Cluster	β	SE	t	p	p_{corr}
1	-0.054	0.016	-3.282	0.001	0.002*
2	-0.010	0.018	-0.552	0.581	0.726
3	-0.133	0.021	-6.385	1.754×10^{-10}	8.768×10^{-10} *
4	-0.003	0.010	-0.278	0.781	0.781
5	-0.056	0.012	-4.620	3.868×10^{-16}	9.670×10^{-6} *

110 As shown in Table 4, brain aging estimates based on three clusters were each significantly associ-
 111 ated with number of previous childbirths. To test whether the associations were statistically differ-
 112 ent from each other, pairwise Z tests for correlated samples (Eq. 1, *Methods and Materials*) were
 113 run on the cluster-specific associations with number of childbirths. The results showed that cluster
 114 3 was more strongly related to number of previous childbirths relative to the other clusters, as
 115 shown in Figure 3.

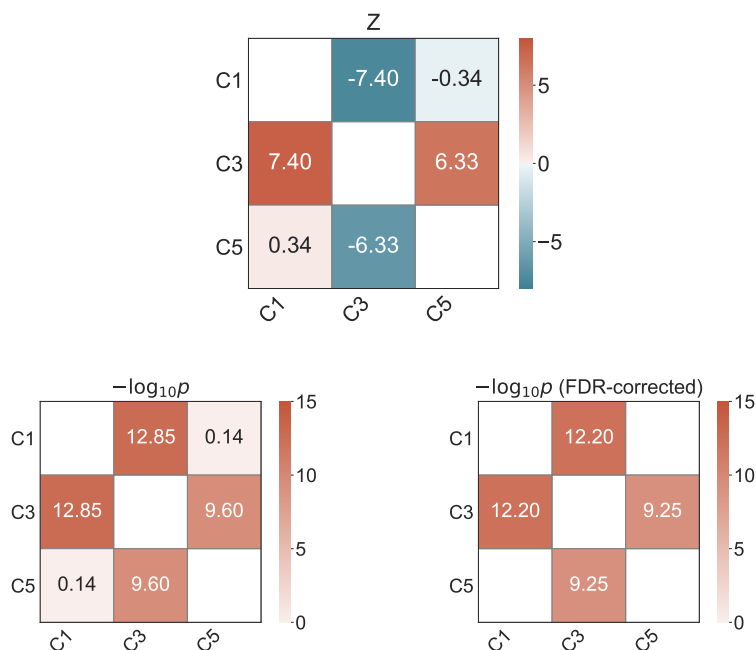


Figure 3. Top plot: Matrix showing pairwise differences between the cluster-specific associations with number of childbirths, based on Z tests for correlated samples (Eq.1). Bottom left plot: Uncorrected $-\log_{10} p$ -values of the differences between the cluster-specific associations. Bottom right plot: $-\log_{10} p$ -values corrected for multiple comparisons using FDR, with only significant values (< 0.05) displayed. C = cluster.

116 To investigate further specificity, the clustering procedure was repeated on the features in cluster
 117 3 - the cluster showing the strongest association with number of childbirths. Two subclusters were
 118 identified based on the covariance of the features, as shown in Figure 4. Subcluster 1 included
 119 5 features; subcluster 2 included 6 features. The features were matched with the cluster they
 120 belonged to, and separate models were run to generate brain-age predictions for each subclus-
 121 ter. The subcluster-specific model performances are shown in Table 5, and their associations with
 122 number of previous childbirths are shown in Table 6.

Table 5. The accuracy of the age prediction measured by Pearson's r (predicted versus chronological age), R^2 , root mean square error (RMSE), and mean absolute error (MAE) for each of the subcluster-specific models. 95 % confidence intervals are indicated in square brackets. RMSE and MAE are reported in years. N_{feat} = number of features contained in the cluster. P-values were < 0.001 for both models.

Model	N_{feat}	r	R^2	RMSE	MAE
Subcluster 1	5	0.33 [0.31, 0.34]	0.11 [0.10, 0.12]	6.99	5.79
Subcluster 2	6	0.47 [0.45, 0.48]	0.22 [0.20, 0.23]	6.54	5.35

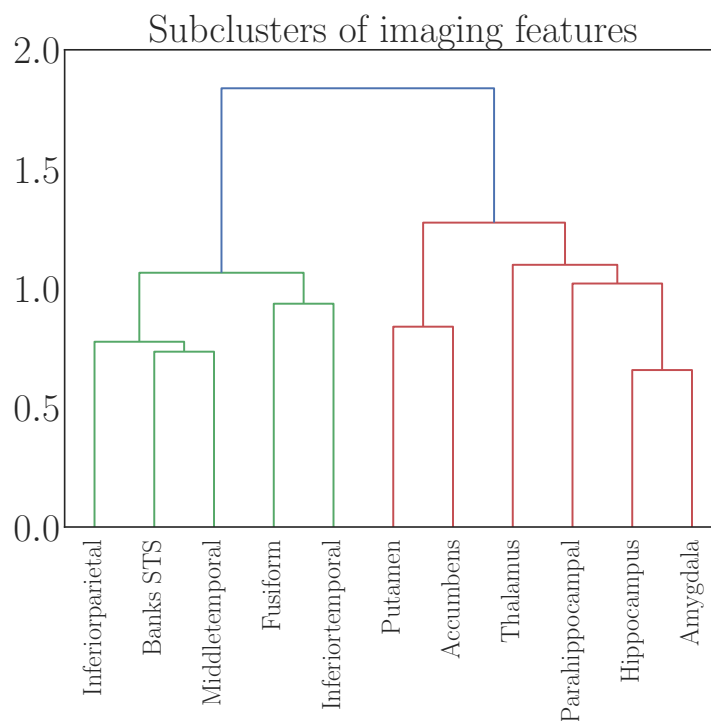


Figure 4. Dendrogram based on hierarchical clustering on the Spearman rank-order correlations of the features contained in Cluster 3, which showed the strongest association with number of childbirths (see Figure 3). The colours represent clusters of features that are grouped together based on common covariance; subcluster 1 in green and subcluster 2 in red. The y-axis shows the degree of co-linearity between the features, with higher y-values indicating less co-linearity between clusters. STS = superior temporal sulcus.

Table 6. Relationships between number of previous childbirths and estimated brain aging for each subcluster. Subcluster-specific *brain age gap* was entered as the dependent variable and *number of childbirths* was entered as independent variable for each analysis. Chronological age was included for covariate purposes. *P*-values are provided before and after FDR correction.

Number of childbirths vs subcluster-specific brain age estimates					
Subcluster	β	SE	<i>t</i>	<i>p</i>	<i>P_{corr}</i>
1	-0.071	0.016	-4.321	1.563×10^{-5}	1.563×10^{-5}
2	-0.124	0.020	-6.169	7.024×10^{-10}	1.405×10^{-9}

Table 7. Difference in quadrature between the subcluster-specific associations with number of childbirths, calculated using Eq. 1 (*Methods and Materials*).

Comparison	<i>Z</i>	<i>p</i>	<i>P_{corr}</i>
Subcluster 1 vs subcluster 2	-5.32	1.01×10^{-7}	2.03×10^{-7}

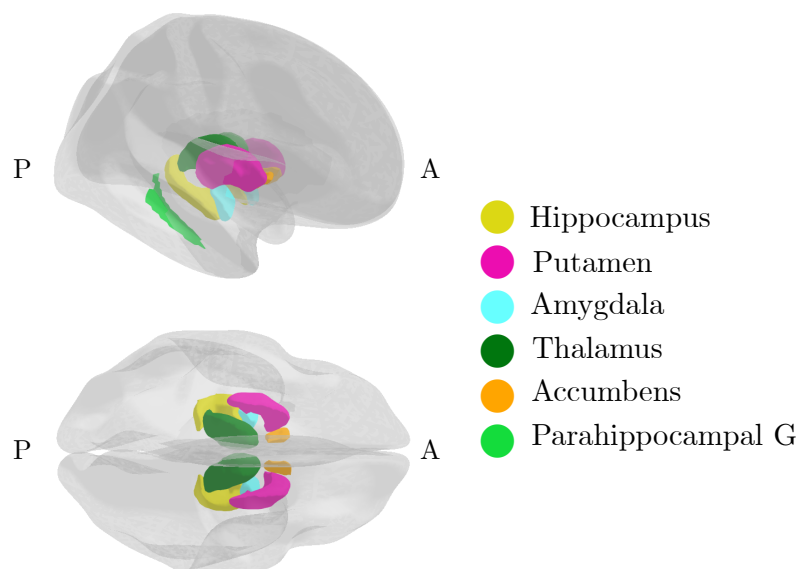


Figure 5. Regions in subcluster 2 - the cluster that showed the strongest association with number of previous childbirths. A = anterior, G = gyrus, P = posterior. Figure created using the *ggseg* plotting tool for brain atlases in R (Mowinckel and Vidal-Piñeiro, 2019).

123 To control for potential confounding factors, the analyses of number of previous childbirths versus
124 subcluster 2 brain age estimates were rerun including assessment location, education, body mass
125 index (BMI), diabetic status, hypertension, smoking and alcohol intake, menopausal status ('yes',
126 'no', 'not sure, had hysterectomy', and 'not sure, other reason'), and oral contraceptive (OC) and
127 hormonal replacement therapy (HRT) status (previous or current user vs never used) as covariates.
128 16,512 women had data on all variables and were included in the analyses. The results showed
129 an association of $\beta = -0.12$, $SE = 0.02$, $t = -5.36$, $p = 8.27 \times 10^{-8}$ between number of childbirths
130 and subcluster 2, indicating that the covariates could not fully explain the association. Number of
131 previous childbirths and age at first birth correlated $r = -0.294$, $p = 6.90 \times 10^{-296}$ (corrected for age).
132 To test for an association with brain aging, an analysis was run with subcluster 2 brain age as the
133 dependent variable and *age at first birth* as independent variable, including all the covariates (age,
134 assessment location, education, BMI, diabetic status, hypertension, smoking and alcohol intake,
135 menopausal status, OC and HRT use). No association was found ($\beta = 0.010$, $SE = 0.01$, $t = 1.64$, $p =$
136 0.102 , $N = 12,937$).

137 **Single-region associations:**

138 To investigate the unique contributions of each region in subcluster 2 to the association with pre-
139 vious childbirths, separate brain-age prediction models were run with each feature as input, yield-
140 ing 11 region-specific brain age estimates. Table 8 shows the correlation between predicted and
141 chronological age for each region-specific model, and their associations with number of childbirths.
142 As the regions within the cluster were correlated (see Figure 4), we tested for unique contributions
143 by first running a multiple regression analysis with all region-specific brain age estimates as in-
144 dependent variables and *number of childbirths* as the dependent variable, before eliminating the
145 regions one at a time to compare the log-likelihood of the full and reduced models. The signifi-
146 cance of model differences was calculated using Wilk's theorem (Wilks, 1938) as $\sqrt{2(\Delta LL)}$, where
147 $\Delta LL = LL_1 - LL_2$; the difference in log-likelihood between the reduced model (LL_1) and the full
148 model (LL_2). The results showed that only the accumbens contributed uniquely to the association

149 with number of previous childbirths. The association when excluding accumbens from subcluster
 150 2 was $\beta = -0.098$, $SE = 0.020$, $t = -5.001$, $p = 5.766 \times 10^{-07}$, indicating that the association was not
 151 solely driven by this region.

Table 8. Region-specific age prediction accuracy (correlation between predicted and chronological age; r_{Age}) and association with number of childbirths (β_{CB} , standard error (SE), t , p , and p_{corr}) for each of the region-specific brain age gap estimates. Chronological age was included in the analyses for covariate purposes. 95 % confidence intervals are indicated in square brackets. P -values are reported before and after FDR correction.

Subcluster 2 region	r_{Age}	β_{CB}	SE	t	p	P_{corr}
Parahippocampal	0.24 [0.23, 0.25]	-0.020	0.012	-1.650	0.099	0.099
Thalamus	0.35 [0.34, 0.36]	-0.048	0.016	-2.991	0.003	0.003
Putamen	0.24 [0.22, 0.25]	-0.053	0.012	-4.401	1.08×10^{-5}	2.253×10^{-5}
Hippocampus	0.33 [0.32, 0.34]	-0.061	0.016	-3.923	8.77×10^{-5}	1.315×10^{-4}
Amygdala	0.29 [0.27, 0.30]	-0.061	0.014	-4.393	1.13×10^{-5}	2.252×10^{-5}
Accumbens	0.31 [0.30, 0.32]	-0.101	0.015	-6.812	9.90×10^{-12}	5.937×10^{-11}

Table 9. Difference in log-likelihood (ΔLL) between regression analyses against *number of children*. The difference is calculated between models where all cluster features are included and models where single features are left out one at the time. P -values are reported before and after FDR correction.

Left-out feature	ΔLL	Z	p	P_{corr}
Parahippocampal	0.051	0.322	0.758	0.758
Thalamus	0.753	1.227	0.376	0.563
Putamen	1.819	1.907	0.129	0.388
Hippocampus	0.352	0.839	0.561	0.673
Amygdala	0.813	1.275	0.354	0.563
Accumbens	10.568	4.597	2.05×10^{-5}	1.232×10^{-4}

152 As a cross check, we investigated associations between previous childbirths and regional volumes
 153 in subcluster 2. Separate analyses were run with the volume measure for each region as depen-
 154 dent variables and number of previous childbirths as the independent variable, including age,
 155 assessment location, education, BMI, diabetic status, hypertension, smoking and alcohol intake,
 156 menopausal status, and OC and HRT status as covariates. 16,516 women had data on all variables
 157 and were included in the analysis. The associations between number of previous childbirths and
 158 regional volume corresponded to the associations with brain age estimates, as shown in Table 10.

Table 10. Relationships between number of previous childbirths and volume for each region in subcluster 2. P -values are provided before and after FDR correction.

Number of childbirths vs regional volume					
Region	β	SE	t	p	P_{corr}
Parahippocampal	1.730	1.647	1.051	0.293	0.293
Thalamus	7.364	3.627	2.030	0.042	0.051
Putamen	9.369	3.215	2.914	0.004	0.005
Hippocampus	7.359	2.295	3.207	0.001	0.003
Amygdala	4.946	1.094	4.522	6.165×10^{-6}	1.849×10^{-5}
Accumbens	3.311	0.554	5.979	2.291×10^{-9}	1.374×10^{-8}

159 Discussion

160 The results showed that a higher number of previous childbirths was associated with less apparent
161 brain aging in striatal and limbic regions, including the accumbens, putamen, thalamus, hippocam-
162 pus, and amygdala. The most prominent effect was seen in the accumbens, which is part of the
163 ventral striatum and a key region in the mesolimbic system involved in reward processing and re-
164 inforcement learning (*Haber and Knutson, 2010*). The mesolimbic system plays a pivotal role in
165 the rapid emergence of adequate maternal behavior directly after birth due to its role in motiva-
166 tion, reward, and the hedonic value of stimuli (*Brunton and Russell, 2008; Numan and Woodside,*
167 *2010*). In rodents, this circuit is activated by pup-related cues that strongly motivate and reinforce
168 maternal care, such as odor (*Fleming et al., 1989*), ultrasonic vocalization (*Robinson et al., 2011*),
169 and suckling (*Ferris et al., 2005*). Low levels of maternal care have been associated with reduced
170 dopamine release within the nucleus accumbens in response to pup cues (*Champagne et al., 2004*),
171 and in humans, motherhood has been linked to anatomical changes in the ventral striatum, with
172 volume reductions promoting responsivity to offspring cues (*Hoekzema et al., 2020*). Together with
173 the ventral striatum, regions including the thalamus, parietal cortex, and brainstem also serve im-
174 portant functions for processing pup-related somatosensory information (*Kim et al., 2010*), and
175 some evidence suggests that structural reorganization occurs in the thalamus, parietal lobe, and
176 somatosensory cortex as a result of physical interactions with pups during nursing (*Kinsley et al.,*
177 *2008; Xerri et al., 1994*). A recent study by *Luders et al. (2020)* found an increase in regional vol-
178 umes including the thalamus in women postpartum, corroborating functional MRI (fMRI) studies
179 showing maternal thalamic activation in response to their offspring (*Paul et al., 2019; Rocchetti*
180 *et al., 2014*). During mother–infant interaction, brain activation has also been shown to increase
181 in the striatum (including putamen and accumbens), amygdala, substantia nigra, insula, inferior
182 frontal gyrus, and temporal gyrus (*Rocchetti et al., 2014*). To summarize, the brain regions iden-
183 tified in the current study largely overlap with neural circuitry underpinning maternal behavior,
184 indicating that brain modulations during pregnancy and postpartum may be traceable decades
185 after childbirth.

186 In addition to the regions overlapping with the maternal circuit, we found a link between hip-
187 pocampal brain aging and previous childbirths. This association concurs with animal studies show-
188 ing enhanced hippocampal neurogenesis in middle age in parous relative to nulliparous rats (*Eid*
189 *et al., 2019*), and fewer hippocampal deposits of amyloid precursor protein in multiparous relative
190 to primiparous and virgin animals (*Love et al., 2005*). Contrary to the findings in middle-aged ani-
191 mals, *reduced* hippocampal neurogenesis has been reported during the postpartum period, coin-
192 ciding with enhanced memory performance in primiparous compared to nulliparous rodents (*Kins-*
193 *ley and Lambert, 2008*). In combination with the evidence of both increased and decreased re-
194 gional volume in humans postpartum (*Luders et al., 2020; Hoekzema et al., 2017; Kim et al., 2018*),
195 these findings emphasize that pregnancy-related brain changes may be highly dynamic.

196 Pregnancy represents a period of enhanced neuroplasticity of which several underlying mecha-
197 nisms could confer long-lasting effects on the brain. Fluctuations in hormones including estradiol,
198 progesterone, prolactin, oxytocin, and cortisol are known to influence brain plasticity (*Galea et al.,*
199 *2014; Simerly, 2002; Barha and Galea, 2010*), and levels of estradiol - a potent regulator of neu-
200 roplasticity (*Barha and Galea, 2010*) - rise up to 300-fold during pregnancy (*Schock et al., 2016*)
201 and fall 100–1000 fold postnatally (*Nott et al., 1976*). Hormonal modulations are closely linked
202 to pregnancy-related immune adaptations such as the proliferation of Treg cells (*Kieffer et al.,*
203 *2017*), which promotes an anti-inflammatory immune environment and contribute to the observed
204 improvement in symptoms of autoimmune disease during pregnancy (*Whitacre et al., 1999; Na-*
205 *tri et al., 2019*). In contrast, the transition to menopause marks a period of decline in ovarian
206 hormone levels and can foster a pro-inflammatory phenotype involving increased risk for autoim-
207 mune activity and neuronal injury. Beneficial immune adaptations in pregnancy could potentially
208 have long-lasting effects, improving the response to menopause-related inflammation, and sub-

209 sequently leading to more favorable brain aging trajectories in multiparous women (*Mishra and*
210 *Brinton, 2018; Fox et al., 2018; Barth and de Lange, 2020*). Another mechanism through which preg-
211 nancy may have long-lasting effects on maternal physiology is fetal microchimerism - the presence
212 of fetal cells in the maternal body (*Boddy et al., 2015*). In mice, fetal cells have been found in sev-
213 eral brain regions including the hippocampus, where they mature into neurons and integrate into
214 the existing circuitry (*Zeng et al., 2010*). Further evidence for beneficial effects of childbirths on the
215 aging brain stems from studies showing that telomeres are significantly elongated in parous rela-
216 tive to nulliparous women (*Barha et al., 2016*), indicating that parity may slow the pace of cellular
217 aging. However, parity has also been linked to Alzheimer's-like brain pathology including neurofib-
218 rillary tangle and neuritic plaque (*Beeri et al., 2009; Chan et al., 2012*), as well as increased risk
219 of Alzheimer's disease (*Beeri et al., 2009; Colucci et al., 2006*), with a higher risk in grand-parous
220 women (> 5 childbirths) (*Jang et al., 2018*). Although our previous study showed some evidence of
221 a moderate non-linear trend between number of childbirths and global brain aging (*de Lange et al.,*
222 *2019*), this effect was not replicated in the current study. More research is needed to determine
223 whether positive effects of pregnancies are less pronounced in grand-parous women, as findings
224 could be biased by low power due to the relatively few women with five or more childbirths, as
225 well as confounding factors such as socioeconomic status or stress levels (*Zeng et al., 2016*).

226 In conclusion, the current study replicates preceding findings showing less apparent brain ag-
227 ing in multiparous women (*de Lange et al., 2019*), and highlights brain regions that may be par-
228 ticularly influenced by previous childbirths. While prospective longitudinal studies are needed to
229 fully understand any enduring effects of pregnancy, our novel use of regional brain-age predic-
230 tion - which captures deviations from normative aging - demonstrates that parity relates to region-
231 specific brain aging patterns evident decades after a woman's last childbirth.

232 Methods and Materials

233 Sample characteristics:

234 The sample was drawn from the UK Biobank (www.ukbiobank.ac.uk), and included an initial sample
 235 of 21,928 women. 1885 participants with known brain disorders were excluded based on ICD10
 236 diagnose (chapter V and VI, field F; *mental and behavioral disorders* and G; *diseases of the nervous*
 237 *system*, except G5 (<http://biobank.ndph.ox.ac.uk/showcase/field.cgi?id=41270>). 220 participants were
 238 excluded based on MRI outliers (see *MRI data acquisition and processing*) and 9 had missing data
 239 on number of previous childbirths, yielding a total of 19,787 participants that were included in the
 240 analyses. Sample demographics are provided in Table 11.

Table 11. Sample demographics. GCSE = General Certificate of Secondary Education, NVQ = National Vocational Qualification.

Age	
Mean \pm SD	63.59 \pm 7.38
Range [years]	45.13 - 82.27
Number of childbirths (live)	
Mean \pm SD	1.72 \pm 1.16
Range	0 - 9
N in each group:	
0 = 4297 1 = 2459 2 = 8770	
3 = 3334 4 = 729 5 = 142	
6 = 43 7 = 7 8 = 5 9 = 1	
Age at first birth (N = 15,446)	
Mean \pm SD	27.08 \pm 5.01
Range	14 - 47
Years since last birth (N = 13,023)	
Mean \pm SD	33.37 \pm 9.32
Range	6.77 - 60.34
Menopausal status (N = 19,781)	
Yes	6117
No	10737
Not sure, had hystorectomy	1912
Not sure, other reason	1015
Ethnic background	
% White	97.06
% Black	0.69
% Mixed	0.54
% Asian	0.75
% Chinese	0.37
% Other	0.55
% Do not know	0.03
Education	
% University/college degree	44.71
% A levels or equivalent	14.09
% O levels/GCSE or equivalent	24.91
% NVQ or equivalent	3.17
% Professional qualification	5.65
% None of the above	5.91
Assessment location (imaging)	
Newcastle	5139
Cheadle	11906
Reading	2742

241 **MRI data acquisition and processing:**

242 A detailed overview of the UK Biobank data acquisition and protocols is available in papers by *Alfaro-*
243 *Almagro et al. (2018)* and *Miller et al. (2016)*. Raw T1-weighted MRI data for all participants were
244 processed using a harmonized analysis pipeline, including automated surface-based morphome-
245 try and subcortical segmentation. Volumes of cortical and subcortical brain regions were extracted
246 based on the Desikan-Killiany atlas (*Desikan et al., 2006*) and automatic subcortical segmentation
247 in FreeSurfer (*Fischl et al., 2002*), yielding a set of 68 cortical features (34 per hemisphere) and 17
248 subcortical features (8 per hemisphere + the brain stem). The MRI data were residualized with re-
249 spect to scanning site, data quality and motion using Euler numbers (*Rosen et al., 2018*) extracted
250 from FreeSurfer, intracranial volume (*Voevodskaya et al., 2014*), and ethnic background using lin-
251 ear models. To remove bad quality data likely due to subject motion participants with Euler num-
252 bers of standard deviation (SD) ± 4 were identified and excluded ($n = 192$). In addition, participants
253 with SD ± 4 on the global MRI measures mean cortical or subcortical gray matter volume were ex-
254 cluded ($n = 13$ and $n = 22$, respectively), yielding a total of 19,796 participants with T1-weighted MRI
255 data. Only participants who had data on number of previous childbirths in addition to MRI were
256 included, and the final sample used in all subsequent analyses (unless otherwise stated) counted
257 19,787 participants.

258 **Global and regional brain age prediction:**

259 Brain age prediction was used to estimate global and regional brain age based on the MRI data.
260 In line with recent brain-age studies (*de Lange et al., 2020a, 2019; Kaufmann et al., 2019*), the XG-
261 *Boost regressor model*, which is based on a decision-tree ensemble algorithm, was used to run the
262 brain age prediction (<https://xgboost.readthedocs.io/en/latest/python>). XGboost includes advanced
263 regularization to reduce overfitting (*Chen and Guestrin, 2016*), and uses a gradient boosting frame-
264 work where the final model is based on a collection of individual models ([https://github.com/dmlc/](https://github.com/dmlc/xgboost)
265 [xgboost](https://github.com/dmlc/xgboost)). Randomized search with ten folds and ten iterations was run to optimize parameters,
266 using all imaging features as input. Scanned parameters ranges were set to *maximum depth*: [2,
267 10, 1], *number of estimators*: [60, 220, 40], and *learning rate*: [0.1, 0.01, 0.05]. The optimized pa-
268 rameters *maximum depth* = 6, *number of estimators* = 140, and *learning rate* = 0.1 were used for all
269 subsequent models.

270 To replicate our findings described in *de Lange et al. (2019)*, we trained a global brain-age pre-
271 diction model using the part of the current sample that overlapped with the previous study ($N =$
272 10,907), and applied it to the newly added participants ($N = 8880$), before testing the association be-
273 tween number of previous childbirths and global brain age in the group of new participants. Note
274 that the training set of 10,907 participants overlapping with the previous study showed a lower N
275 relative to the sample in *de Lange et al. (2019)* due to correction for the variables listed in *sample*
276 *characteristics*.

277 The full sample (19,787) was utilized to investigate regional brain aging. Averages of the right
278 and left hemisphere measures were first calculated for each feature, and hierarchical clustering
279 was performed on the Spearman rank-order correlation using Scikit-learn version 0.22.2 (<https://scikit-learn.org/stable/modules/clustering.html#clustering>). All features were grouped according to
280 their associated cluster ID, and separate prediction models were run with ten-fold cross valida-
281 tion, providing cluster-specific brain age gap estimations (predicted age – chronological age) for
282 each individual. To investigate model prediction accuracy, R^2 , RMSE, and MAE were calculated for
283 each model, and correlation analyses were run for predicted versus chronological age. The same
284 procedure was followed for subclusters and region-specific brain age predictions.
285

286 **Associations between previous childbirths and regional brain aging:**

287 To investigate associations between number of previous childbirths and brain aging, separate re-
288 gression analyses were run using cluster-specific brain age gap estimates as the dependent vari-
289 able, and *number of childbirths* as independent variable. Chronological age was included as a co-

290 variate, adjusting for age-bias in the brain age predictions as well as age-dependence in number
291 of childbirths (*Le et al., 2018; de Lange and Cole, 2020*). *P*-values were corrected for multiple com-
292 parisons using false discovery rate (FDR) correction (*Benjamini and Hochberg, 1995*). To directly
293 compare the associations, *Z* tests for correlated samples (*Zimmerman, 2012*) were run using

$$Z = (\beta_{m1} - \beta_{m2}) / \sqrt{\sigma_{m1}^2 + \sigma_{m2}^2 - 2\rho\sigma_{m1}\sigma_{m2}} \quad (1)$$

294 where "m1" and "m2" represent model 1 and 2, the β terms represent the beta value from the
295 regression fits, the σ terms represent their errors, and ρ represents the correlation between the
296 two sets of associations. The statistical analyses were conducted using Python 3.7.0.

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