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Parental status and markers of brain and cellular age: A 3D convolutional network and classification study

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ABSTRACT

Recent research shows prominent effects of pregnancy and the parenthood transition on structural brain characteristics in humans. Here, we present a comprehensive study of how parental status and number of children born/fathered links to markers of brain and cellular ageing in 36,323 UK Biobank participants (age range 44.57–82.06 years; 52% female). To assess global effects of parenting on the brain, we trained a 3D convolutional neural network on T1-weighted magnetic resonance images, and estimated brain age in a held-out test set. To investigate regional specificity, we extracted cortical and subcortical volumes using FreeSurfer, and ran hierarchical clustering to group regional volumes based on covariance. Leukocyte telomere length (LTL) derived from DNA was used as a marker of cellular ageing. We employed linear regression models to assess relationships between number of children, brain age, regional brain volumes, and LTL, and included interaction terms to probe sex differences in associations. Lastly, we used the brain measures and LTL as features in binary classification models, to determine if markers of brain and cellular ageing could predict parental status. The results showed associations between a greater number of children born/fathered and younger brain age in both females and males, with stronger effects observed in females. Volume-based analyses showed maternal effects in striatal and limbic regions, which were not evident in fathers. We found no evidence for associations between number of children and LTL. Classification of parental status showed an Area under the ROC Curve (AUC) of 0.57 for the brain age model, while the models using regional brain volumes and LTL as predictors showed AUCs of 0.52. Our findings align with previous population-based studies of middle- and older-aged parents, revealing subtle but significant associations between parental experience and neuroimaging-based surrogate markers of brain health. The findings further corroborate results from longitudinal cohort studies following parents across pregnancy and postpartum, potentially indicating that the parenthood transition is associated with long-term influences on brain health.

1. Introduction

The transition to parenthood is a unique and transformative life phase, marked by cognitive, physiological, and emotional changes for parents (Orchard et al., 2023). Throughout pregnancy and postpartum, mothers undergo significant hormonal fluctuations and neural

adaptations that facilitate maternal behaviours and bonding with the newborn (Barba-Müller et al., 2019; Servin-Barthet et al., 2023). These processes have been linked to structural alterations in several cortical and subcortical brain regions, including the hippocampus, amygdala, and prefrontal cortex (Martínez-García et al., 2021a; Servin-Barthet et al., 2023).

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In contrast, fathers experience indirect prenatal and postpartum hormonal changes and engage in paternal care, which might also induce neuroplasticity and influence their cognitive functioning (Feldman et al., 2019). In first-time fathers, hippocampal volume increases across the parenthood transition have been linked to prenatal oxytocin levels and postpartum testosterone levels (Saxbe et al., 2023). Associations between caregiving behaviour, modified brain activation, and oxytocin levels have been reported in both mothers and fathers (Abraham et al., 2014), and some studies show brain changes in fathers that partly mirror those observed in mothers, albeit of a smaller magnitude (Martínez-García et al., 2023; Paternina-Die et al., 2020).

While research on brain changes throughout pregnancy and postpartum has increased over the past decade, less is known about potential long-term influences on brain health in midlife and older age. Our previous studies have shown population-level associations between number of childbirths and brain age (de Lange et al., 2020a, 2019; Voldsbekk et al., 2021) as well as cognition (Lindseth et al., 2023) in middle- and older- aged females, and some studies indicate detectable effects in both mothers and fathers (Ning et al., 2020; Orchard et al., 2020). In light of recent evidence of long-lasting effects of pregnancy on the brain (Martínez-García et al., 2021b; Puri et al., 2023), these findings might point to an impact of pregnancy and parenting on brain ageing trajectories decades after childbirth.

The potential for enduring neural alterations motivates an examination of the possible effects of parenting on cellular ageing. Telomeres, the protective end caps of our chromosomes, diminish in length as cells age (Chakravarti et al., 2021), making leukocyte telomere length (LTL) a notable indicator of biological ageing and overall health status (Codd et al., 2022; Samani and van der Harst, 2008). While pregnancy incites significant transformations in maternal brain structure, it also represents a phase of intense energy expenditure, especially for birthing mothers (Thurber et al., 2019). The inherent metabolic demands, as resources are channelled towards reproductive effort, might compromise cellular maintenance and regenerative processes, leading to accelerated biological ageing (Jasienska, 2009, 2020; Poganik et al., 2023; Shirazi et al., 2020). However, the postpartum period also involves a restoration towards the pre-pregnancy state (Poganik et al., 2023), with increased bodily defences against cellular harm (Giller et al., 2020). This recovery suggests that the course of pregnancy also involves rejuvenation mechanisms, which may offer protective health benefits over time (Michaeli et al., 2015; Ross et al., 2020). Yet, existing research examining the association between parity and LTL presents varied results (Houminer-Klepar et al., 2023), with some studies noting negative correlations (Kresovich et al., 2018; Pollack et al., 2018; Ryan et al., 2018), others positive (Barha et al., 2016), and several observing no discernible relationship (Lane-Cordova et al., 2017; Michaeli et al., 2022). To our knowledge, studies on LTL and parental status in males are largely missing. However, LTL has been linked to factors that are central to parenting, including caregiving, perceived stress, and social support (Rentscher et al., 2020).

In this study, we used deep learning and linear regression models to investigate how parental status and number of children were linked to markers of brain and cellular ageing in 36,323 UK Biobank participants (age range 44.57–82.06 years; 52% female). Building on our previous maternal brain studies in overlapping samples (de Lange et al., 2020a, 2019; Voldsbekk et al., 2021), we here broadened the scope to include both males and females for a comparative analysis. We further utilised deep learning for more accurate age prediction, and incorporated markers of cellular ageing alongside global and regional brain measures.

To assess global effects of parenting on the brain, we estimated brain age using a state-of-the-art prediction model based on a Simple Fully Convolutional Network (SFCN) architecture (Gong et al., 2021; Leonardsen et al., 2022; Peng et al., 2021). SFCN-based age prediction is known for its superior accuracy (Dörfel et al., 2023; Leonardsen et al., 2022), and offers a robust approach for deriving age predictions from raw or minimally processed Magnetic Resonance Imaging (MRI) data.

Unlike our previous studies using gradient boosted decision trees (de Lange et al., 2019; Voldsbekk et al., 2021), this method circumvents the requirement for detailed anatomical feature extraction and the reliance on pre-defined brain atlases. Whilst deviations in brain age represent conceptually interpretable metrics, the deep-learning process of condensing high-dimensional brain scans into a single estimate limits the interpretation of regional effects. To provide complementary information on regional specificity, we extracted brain volumes using FreeSurfer, and performed hierarchical clustering to group the volumes based on covariance. LTL was measured as the ratio of telomere repeat copy number relative to that of a single copy gene (Cawthon, 2009; Codd et al., 2022; Welsh et al., 2017). We used linear regression models to measure the relationships between number of children, brain age, regional brain clusters, and LTL, assessing sex differences by including interactions terms in the models. Lastly, we employed extreme gradient boosting (XGBoost (Chen and Guestrin, 2016)) classification models to determine the predictive value of brain measures and LTL for parental status, offering complementary insights to effects captured by the linear regression models.

In summary, the study aimed to: (i) investigate relationships between number of children and brain age in both males and females; (ii) assess regional effects using brain volume measures; (iii) test for associations between number of children and LTL; and (iv) explore the capacity of brain age, regional brain volumes, and LTL to predict parental status.

2. Methods and materials

2.1. Sample characteristics

The sample was drawn from the UK Biobank (UKB) cohort (www.ukb.iobank.ac.uk), and included participants with T1-weighted MRI data, as well as complete data on demographic factors and number of children fathered (UKB data field 2405) / number of live births (UKB data field 2743) for males and females, respectively. Sex of participants refers to binary data on biological sex acquired from the NHS registry at recruitment, but in some cases updated by the participant (see <https://biobank.ndph.ox.ac.uk/showcase/field.cgi?id=31>). In line with our previous studies (de Lange et al., 2019; Leonardsen et al., 2022; Schindler et al., 2022; Voldsbekk et al., 2021), participants with relevant ICD10 diagnoses (UKB data field 41202, Chapter V: Mental and behavioural disorders and Chapter VI: Diseases of the nervous system) were excluded (n=2211) in order to probe normal variation in a healthy population-based sample. In addition, participants with > 10 childbirths were excluded to avoid extreme cases (de Lange et al., 2019), yielding a final sample of 36,323 participants (male = 17,329 female = 18,994). Sample demographics are provided in Table 1.

2.2. MRI data processing

A detailed overview of the UKB data acquisition and protocols is available in (Alfaro-Almagro et al., 2018) and (Miller et al., 2016). To preprocess the MRI data prior to SFCN modelling, images were skull-stripped and rotated using the FastSurferCNN from FastSurfer version 2.0.3 (Henschel et al., 2020) before a central crop of dimensions (224, 192, 224) was extracted, ensuring that the images were in approximately the same stereotaxic space and contained minimal non-brain tissue. For the regional features, raw T1-weighted MRI data for all participants were previously processed using a harmonised analysis pipeline as described in (Kaufmann et al., 2019). The data used for cortical and subcortical brain volumes corresponded to the data used in our previous UK Biobank studies on parity in females (de Lange et al., 2020a, 2019), and included 68 cortical features (34 per hemisphere) and 17 subcortical features (8 per hemisphere plus the brain stem) derived using the Desikan-Killiany atlas (Desikan et al., 2006) and automated subcortical segmentation in FreeSurfer version 5.3 (Fischl et al., 2002). Linear models were used to residualise the data with respect to scanning

Table 1

Sample demographics. Mean standard deviation (SD) and ranges for age, number of live child- births / children fathered, Townsend (TS) deprivation index (Townsend, 1987; Townsend et al., 1988), and % in each group for education. GCSE = General Certificate of Secondary Education, NVQ = National Vocational Qualification. Please refer to table notes for UKB data fields for each variable.

		Male	Female
N		17,329	18,994
Age	Mean \pm SD	64.74 \pm 7.65	63.57 \pm 7.39
	Range [years]	44.57–81.77	45.13–82.06
N children	Mean \pm SD	1.77 \pm 1.20	1.72 \pm 1.16
	Range	0–10	0–9
	Group count (n)		
	0	3606	4120
	1	2077	2363
Education	2	7859	7732
	3	2996	2934
	4–10*	980	886
	% University/college degree	49.59	45.77
	% A levels or equivalent	11.92	14.33
	% O levels/GCSE or equivalent	17.08	21.07
	% NVQ or equivalent	11.40	7.16
Ethnic background	% Professional qualification	3.94	5.72
	% None of the above	6.08	5.95
	% White	97.01	97.17
	% Black	0.58	0.67
	% Mixed	0.33	0.52
	% Asian	1.43	0.73
	% Chinese	0.24	0.37
TS deprivation index	% Other	0.42	0.54
	Mean \pm SD	–2.00 \pm 2.66	–1.91 \pm 2.69
	Range	–6.26–9.74	–6.26–10.10

* N children grouped as 4–10

Males: 4 = 741, 5 = 159, 6 = 50, 7 = 17, 8 = 9, 9 = 1, 10 = 3.

Females: 4 = 692, 5 = 138, 6 = 44, 7 = 7, 8 = 4, 9 = 1.

N children: <https://biobank.ndph.ox.ac.uk/showcase/field.cgi?id=2734> and <https://biobank.ndph.ox.ac.uk/showcase/field.cgi?id=2405>

Education: <https://biobank.ndph.ox.ac.uk/showcase/field.cgi?id=6138>

TS deprivation index: <https://biobank.ndph.ox.ac.uk/showcase/field.cgi?id=22189>

site and intracranial volume (Voevodskaya et al., 2014).

2.3. Brain age prediction

To create the brain age model, we extended the PAC2019-winning SFCN architecture (Gong et al., 2021; Peng et al., 2021). In summary, we used a backbone consisting of 5 repeated blocks with a 3×3×3 convolution, batch normalization, max pooling, and a rectified linear unit (ReLU) activation. Following this, a final convolutional block consisting of a 1×1×1 convolution, batch normalization, and ReLU was used. In addition, we made slight modifications to enhance the expressiveness of the latent space produced by the later layers. Specifically, we employed a max-pooling layer to reduce spatial dimensions before a multitask prediction head (Ruder, 2017). This head had six output neurons, corresponding to the variables age, sex, handedness, BMI, neuroticism, and fluid intelligence. Although only the age prediction was retained for subsequent analyses, the model was trained to minimise loss across all six outputs. Training with multiple prediction targets is known to enhance the model's representation robustness (Maurer et al., 2016), potentially enhancing the accuracy and stability of our age prediction.

The dataset was split into training and test sets in a sex-balanced manner to ensure equal representation of males and females in both datasets. Specifically, for each sex, we performed a 50/50 split using the *train_test_split* function from *sklearn.model_selection*, randomly selecting half of the individuals for inclusion in the training set, and the other half

for the test set. The sex-specific datafiles were merged, and the model was then trained on 50% of the full sample (n = 18,161) including a validation sample of 15%, and applied to the test set of 18,162 participants (see Table 2). Brain age gap (BAG) values were calculated by subtracting chronological age from predicted age, providing an estimation of each participant's brain age relative to their chronological age.

3. Hierarchical clustering of regional volumes

To investigate associations between number of children and regional patterns of brain volume in the full sample (n = 36,326; see Table 1), we used hierarchical clustering in Scikit-learn version 0.22.2 (Pedregosa et al., 2011) (<https://scikit-learn.org/stable/modules/clustering>) to group the MRI features based on the Spearman rank-order correlation. Averages of the right and left hemisphere volumes were first calculated for each feature. The Ward method was employed to minimise the total within-cluster variance at each step of the clustering process. To assess the optimal number of clusters, a dendrogram and an elbow plot were generated using the Ward linkage criteria, illustrating the progression of cluster dissimilarity as a function of total cluster number. For each identified cluster, the volume measures were first standardised (subtracting the mean and dividing by the standard deviation (SD)). Next, a mean value was calculated across all the features contained in each of the clusters, providing a summary measure per cluster for each participant.

3.1. Leukocyte telomere length (LTL)

LTL measurements were derived from DNA obtained at the UK Biobank baseline assessment (prior to the MRI assessment; see Littlejohns et al., 2020) for an overview of data collection timelines and procedures), using a rigorously validated qPCR assay (Welsh et al., 2017). The values were reported as the T/S ratio; the proportion of telomere repeat count to a single-copy gene. The values were log-transformed and Z-standardised (UKB data field 22192) following technical quality adjustments as described previously (Codd et al., 2022). LTL measures were available for 34,382 of the participants in our sample.

3.2. Statistical analyses

Separate linear regression models were used to assess the relationships between number of children and the dependent variables (DV) brain age, regional volumes, and LTL:

$$[DV = \beta_0 + \beta_1 \times \text{N children} + \beta_2 \times \text{Age} + \epsilon]$$

where β_0 represents the intercept, β_1 is the coefficient for the effect of number of children on the outcome variable (DV), β_2 models the effect of age as a covariate, and ϵ is the error term. Number of children was measured as a discrete numerical variable representing the total count of children an individual reported (ranging from 0 to 10).

To test for differences between males and females, interaction terms were included in the models:

$$[DV = \beta_0 + \beta_1 \times \text{N children} + \beta_2 \times \text{Sex} + \beta_3 \times (\text{N children} \times \text{Sex}) + \beta_4 \times \text{Age} + \epsilon]$$

where β_2 models the effect of sex, and β_3 represents the interaction term of interest (N children \times Sex). Age was used as a covariate in all models, and *p*-values were adjusted for multiple testing using false discovery rate (FDR) correction with the Benjamini-Hochberg method (Benjamini and Hochberg, 1995; Korthauer et al., 2019), with 0.05 used as the threshold for statistical significance.

To predict parental status (children versus no children) based on brain age, regional volumes and LTL, we used XGBoost binary classification models (version 1.7.1; <https://xgboost.readthedocs.io/en/stable/python/index.html>) in Python 3.9.7. To keep samples consistent across the classification models with different input features, we only included participants who were allocated to the brain age test set (see

Table 2
Distributions for age and number of children in the CNN training and test sets.

		Training set		Test set	
		Male	Female	Male	Female
N		8664	9497	8665	9497
Age	Mean \pm SD	64.80 \pm 7.62	63.58 \pm 7.38	64.68 \pm 7.69	63.55 \pm 7.41
	Range [years]	44.57–81.77	45.13–82.06	45.46–81.29	46.12–81.49
N children	Mean \pm SD	1.77 \pm 1.20	1.72 \pm 1.17	1.76 \pm 1.19	1.71 \pm 1.15
	Range	0–10	0–9	0–10	0–8
	Group count (n)				
	0	1776	2069	1830	2051
	1	1065	1200	1012	1163
	2	3848	4174	3884	4249
3	1492	1593	1442	1609	
4–10*	483	461	497	425	

* N children grouped as 4–10:

Male training set: 4 = 364, 5 = 72, 6 = 27, 7 = 10, 8 = 7, 9 = 1, 10 = 2.

Female training set: 4 = 354, 5 = 77, 6 = 24, 7 = 3, 8 = 2, 9 = 1.

Male test set: 4 = 377, 5 = 87, 6 = 23, 7 = 7, 8 = 2, 9 = 0, 10 = 1.

Female test set: 4 = 338, 5 = 61, 6 = 20, 7 = 4, 8 = 2, 9 = 0, 10 = 0.

Table 2) in addition to having data on LTL. This resulted in groups of 7029 parous females, 1932 nulliparous females, 6469 males with children fathered, and 1733 males without children fathered. Three separate classification models were run, using each set of input features per model (brain age, clusters of regional brain volumes, and LTL values, respectively). The models were run for males and females together, with follow-up models stratified by sex for comparison purposes. To account for differences in group size, class weights were assigned during model training (*scale_pos_weight* argument in XGBoost). The weights were calculated using the relative sizes of each group. Model hyperparameters (max depth, learning rate, n estimators, lambda, alpha) were tuned using grid search with 5-fold stratified cross-validation.

3.3. Sensitivity analyses

To test if the results were consistent when using a different summary measure of regional volumes, we performed a principal component analysis (PCA) for each of the clusters identified in Section 2.4, and used the first component as an alternative to the cluster mean values in supplementary analyses. In addition, we repeated the regression models testing for relationships between number of children, brain age, regional volumes, and LTL, while adjusting for potential confounders including hypertension, body mass index (BMI), smoking status, alcohol intake, ethnic background, education, and Townsend deprivation index (Beck et al., 2022; Bountziouka et al., 2022; de Lange et al., 2020b, 2021; Goff, 2019; Rehkopf et al., 2016; Topiwala et al., 2022; Xu et al., 2020) in subsamples of participants with available data ($n = 14,280$ for brain age, 28,476 for regional volumes, and 26,927 for LTL). Lastly, we performed the linear regression models in a subsample excluding participants with ≥ 5 childbirths ($n = 433$ for the full sample; 207 for the brain age test sample; see Tables 1 and 2), to ensure that the results were not driven by outliers.

4. Results

4.1. Associations between brain age and number of children

The SFCN model showed high prediction accuracy, with a mean absolute error (MAE) of 2.96 and a correlation of 0.866 [0.857, 0.875] between predicted and true age in the validation set ($p < 0.001$). The MAE was 3.01 in the test set, with a correlation of 0.867 [0.863, 0.871] between predicted and true age ($p < 0.001$). The model performance

Table 3

Associations between brain age gap (BAG) and number of children. The table shows the association observed in the full sample, the interaction term (n children sex) with female coded as 0 (reference group), and associations from follow-up regression models run separately in males and females. Age was included as a covariate in the models. SE = standard error.

	β	SE	p-val	adj.p-val
BAG ~ n children (full test sample)	-0.125	0.021	<0.001	<0.001
BAG ~ n children \times sex (full test sample)	0.110	0.042	0.009	0.011
BAG ~ n children (female test sample)	-0.184	0.029	<0.001	<0.001
BAG ~ n children (male test sample)	-0.065	0.031	0.039	0.041

exceeds that of gradient-boosted decision trees used in our previous parity studies including female UKB participants (MAE > 4) (de Lange et al., 2019; Voldsbeek et al., 2021), and is comparable to recently published SFCN-based models (Dörfel et al., 2023; Leonardsen et al., 2022) considering expected variations in performance metrics across studies due to differences in age range and sample size (de Lange et al., 2022). As shown in Table 3, a greater number of children was linked to a younger brain age relative to chronological age, with significant sex interactions indicating more prominent effects in females. Fig. 1 illustrates the mean brain age values for groups of participants based on number of children. Supplementary Information (SI) Fig. 1 shows the mean values plotted in the groups with 4 and ≥ 5 children separately.

4.2. Associations between regional brain volumes and number of children

Based on an inspection of the hierarchical relationship between regional volume measures (Fig. 2), the progression of cluster dissimilarity (SI Fig. 2), and the features contained in each cluster, a threshold of 2, yielding six clusters, was selected for an optimal balance between regional detail and reduced multicollinearity. The regions contained in each of the clusters are provided in Table 4.

As shown in Table 5, clusters 1, 3, 5, and 6 showed significant positive associations with number of children, and significant interactions with sex (Table 6). Follow-up regression models run separately for males and females are provided in Table 7, with the most prominent associations observed for clusters 5 and 6 in females. Fig. 3 illustrates the standardised cluster mean values plotted for males and females, categorised based on number of children. Fig. 4 shows the brain regions in clusters 5 and 6. Clusters 1 and 3 are provided in SI Fig. 3.

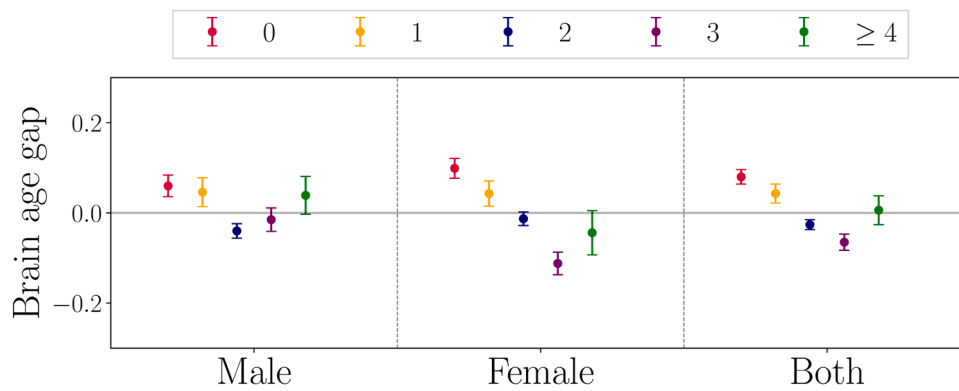


Fig. 1. Standardised brain age gap mean values plotted for groups of participants categorised based on number of children (colour coded in the legend), providing an illustration of the results provided in Table 3. Negative values indicate younger brain age relative to chronological age. For N in each group in the test set, see Table 2. Note that the grouping of participants with ≥ 4 children is for illustration purposes only (no grouping is used in the regression analyses). Please see SI Fig. 1 for mean values plotted in the group with 4 and those with ≥ 5 separately. To align with the inclusion of age as a covariate in the statistical analyses, the BAG values in the plot are residualised for age using linear regression models ($BAG \sim Age$).

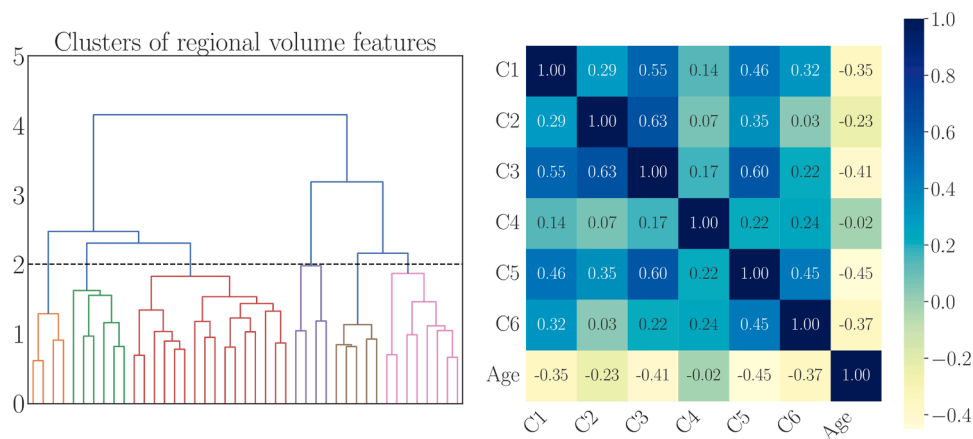


Fig. 2. Left: Dendrogram based on hierarchical clustering on the Spearman rank-order correlations of regional volume features. The x-axis represents individual features. The y-axis represents the dissimilarity between clusters, with higher y-values indicating less co-linearity between clusters. The colours show the six clusters identified and used in the subsequent analyses. The imaging features contained in each of the clusters are provided in Table 4. Right: Pearson's correlations between clusters 1–6 and age.

Table 4

List of features contained in each cluster. All feature names represent regional volumes extracted using the Desikan-Killiany atlas (Desikan et al., 2006) and automated subcortical segmentation in FreeSurfer version 5.3 (Fischl et al., 2002).

Cluster 1	Cluster 2	Cluster 3	Cluster 4	Cluster 5	Cluster 6
Cuneus	Caudal anterior cingulate	Isthmuscingulate	Entorhinal	Bankssts	Parahippocampal
Lateral occipital	Caudal middlefrontal	Lateral orbitofrontal	Temporalpole	Fusiform	Cerebellum cortex
Lingual	Paracentral	Medial orbitofrontal	Caudate	Inferior parietal	Thalamus
Pericalcarine	Posterior cingulate	Parsopercularis	Pallidum	Inferior temporal	Putamen
	Rostral anterior cingulate	Parsorbitalis		Middle temporal	Brain stem
	Frontalpole	Parstriangularis			Hippocampus
		Postcentral			Amygdala
		Precentral			Accumbens
		Precuneus			
		Rostral middlefrontal			
		Superior frontal			
		Superior parietal			
		Superior temporal			
		Supramarginal			
		Transversetemporal			
		Insula			

Table 5

Associations between number of children and mean volume for each cluster (β) for the full sample (both males and females), adjusted for age. SE = standard error.

Cluster	β	SE	p-val	adj.p-val
1	0.012	0.004	0.003	0.007
2	0.005	0.004	0.221	0.221
3	0.010	0.004	0.012	0.018
4	0.007	0.005	0.105	0.127
5	0.022	0.004	<0.001	<0.001
6	0.021	0.004	<0.001	<0.001

Table 6

Interactions between sex and number of children on mean volume for each cluster. β_{int} represents the coefficient for the interaction term, indicating sex differences in associations. Females were coded as 0 and used as reference group in the fit. SE = standard error.

Cluster	β_{int}	SE _{int}	p-val _{int}	adj.p-val _{int}
1	-0.023	0.008	0.007	0.010
2	-0.010	0.009	0.227	0.273
3	-0.024	0.008	0.004	0.008
4	-0.004	0.009	0.646	0.646
5	-0.028	0.008	<0.001	0.001
6	-0.045	0.008	<0.001	<0.001

Table 7

Associations between number of children and mean volume for each cluster, based on linear regression models run for females and males separately (adjusted for age). SE = standard error.

Cluster	Sex	β	SE	p-val	adj.p-val
1	Female	0.016	0.006	0.009	0.018
	Male	0.009	0.006	0.117	0.241
2	Female	0.002	0.006	0.724	0.724
	Male	0.009	0.006	0.161	0.241
3	Female	0.013	0.006	0.031	0.046
	Male	0.008	0.006	0.149	0.241
4	Female	0.006	0.006	0.339	0.407
	Male	0.008	0.006	0.216	0.259
5	Female	0.031	0.006	<0.001	<0.001
	Male	0.015	0.006	0.008	0.048
6	Female	0.038	0.006	<0.001	<0.001
	Male	0.007	0.006	0.259	0.259

4.3. Associations between leukocyte telomere length and number of children

As shown in Table 8, we found no evidence of associations between number of children and LTL, and no interactions with sex. Higher age was associated with shorter LTL ($\beta = -0.022$, SE = 0.001, $p = < 0.001$), and shorter LTL was associated with higher brain age gap ($\beta = -0.079$, SE = 0.008, $p = 0.001$). SI Fig. 5 shows the mean LTL values for groups of participants based on number of children.

4.4. Predicting parental status based on brain measures and leukocyte telomere length

As shown in Fig. 5, the average area under the receiver operating characteristic curve (AUC) was 0.57 for the model using brain age as input feature to classify parental status, while AUC was 0.52 for the models using mean cluster volumes and LTL as features. For context, a classification model without any predictive power would show an AUC of 0.50. Follow-up models stratified by sex showed similar results in males and females.

4.5. Sensitivity analyses

When using PCA components instead of mean volume measures for each cluster, the PCA components of clusters 1, 3, 4, 5, and 6 showed positive associations with number of children (SI Table 1). In line with the main results, interactions between number of children and sex were observed for clusters 1, 3, 5, and 6 (SI Tables 2 and 3). When including additional covariates (see Section 2.7), the relationships between number of children and brain age were consistent with the main results (SI Table 4). Mean volume in clusters 1, 3, 5 and 6 showed positive associations with number of children, but in contrast to the main results, cluster 1 volume did not show significant interactions with sex (SI Table 6), and the association between number of children and cluster 1 volume in the female subsample did not reach statistical significance (SI Table 7). The results did not change notably when excluding participants with ≥ 5 children, as shown in SI Tables 9–12.

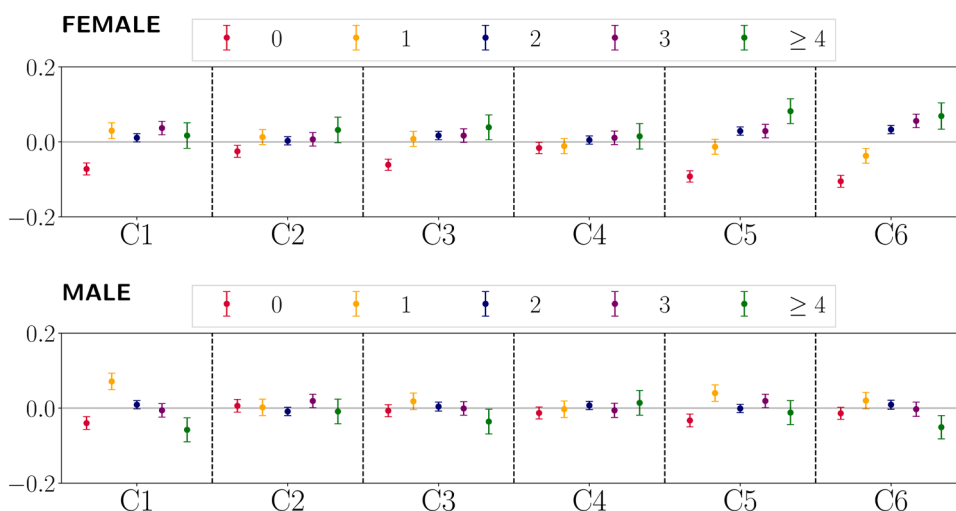


Fig. 3. Standardised cluster (C) mean values plotted for groups of participants categorised based on number of children (colour coded in the legend). Positive values indicate larger mean volumes. For N in each group in the test set, see Table 2. Note that the grouping of participants with ≥ 4 children is for illustration purposes only (no grouping is used in the regression analyses). Please see SI Fig. 4 for mean values plotted in the group with 4 and those with ≥ 5 separately. To align with the inclusion of age as a covariate in the statistical analyses, the cluster mean values in the plot are residualised for age using linear regression models (Cluster mean \sim Age).

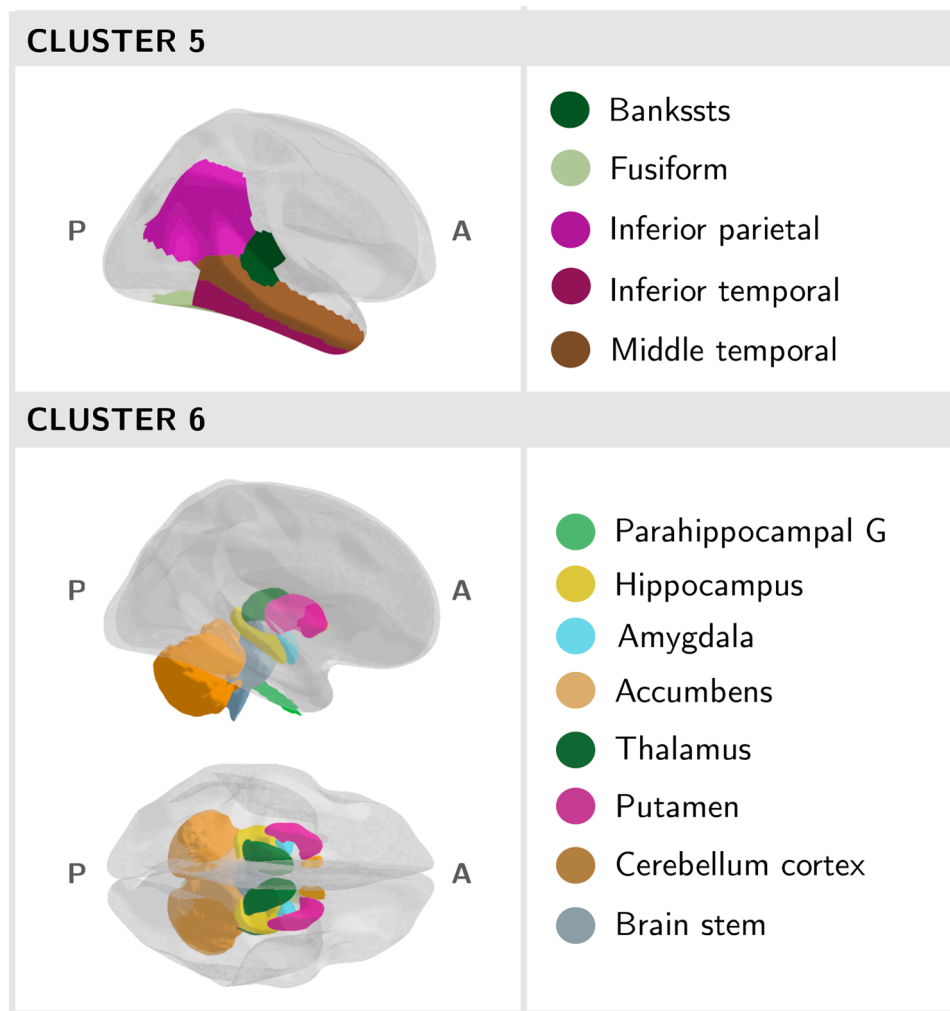


Fig. 4. Regional brain volumes contained in clusters 5 and 6, which showed the most prominent associations with number of children in females. A = anterior, G = gyrus, P = posterior. Figure created using the ggseg3d visualisation tool for brain atlases (Mowinckel and Vidal-Piñeiro, 2020).

Table 8

Associations between leukocyte telomere length (LTL) and number of children. The table shows the association observed in the full sample with LTL data available, the interaction term (n children sex) with female coded as 0 (reference group), and associations from follow-up regression models run separately in males and females. Age was included as a covariate in the models. SE = standard error.

	β	SE	p-val	adj.p-val
LTL ~ n children (full sample)	-0.007	0.005	0.110	0.140
LTL ~ n children \times sex (full sample)	0.001	0.009	0.952	0.952
LTL ~ n children (female sample)	-0.011	0.006	0.082	0.114
LTL ~ n children (male sample)	-0.001	0.006	0.826	0.890

5. Discussion

This study contributes to the growing body of research on the biological implications of parenthood, providing evidence of subtle yet significant associations between parental experience and brain characteristics in a large sample of middle-aged and older adults.

5.1. Associations between brain age and number of children

The results demonstrate population-level associations between a greater number of children born/fathered and younger brain age in both males and females, with more prominent effects observed in females.

The results align with our previous UK Biobank studies in mothers (de Lange et al., 2020a, 2019; Voldsbekk et al., 2021), and other cross-sectional studies that also include fathers (Ning et al., 2020; Orchard et al., 2020). While these associations might partly reflect inherent variations in individuals who tend to have more or fewer children, it is also plausible that they represent enduring influences of the parenthood transition on the brain.

This transition to parenthood notably affects brain structure in both mothers and fathers (Feldman et al., 2019; Martínez-García et al., 2023; Paternina-Die et al., 2020), and potential long-term effects may be attributed to a combination of biological factors and experience-dependent brain plasticity (Orchard et al., 2023). In birthing mothers, pregnancy and postpartum are characterised by significant changes in oestrogen, which is known to influence brain structure and function (Barth et al., 2015; Jett et al., 2022; Rehbein et al., 2021; Schelbaum et al., 2021; Barth et al., 2023). Alongside maternal immune alterations — a response evolved to support fetal development — these hormonal shifts could entail prolonged implications for brain health (Barth and de Lange, 2020; Duarte-Guterman et al., 2019; Galea et al., 2018; Mor et al., 2017). While hormonal changes are less drastic in fathers, subtle variations in hormones such as testosterone and oxytocin might also affect brain structure and function (Abraham and Feldman, 2022; Feldman et al., 2019; Kuo et al., 2012; Nishitani et al., 2017; Abraham et al., 2014). Testosterone has been shown to decrease in fathers during the transition to parenthood (Gettler et al., 2011; Saxbe

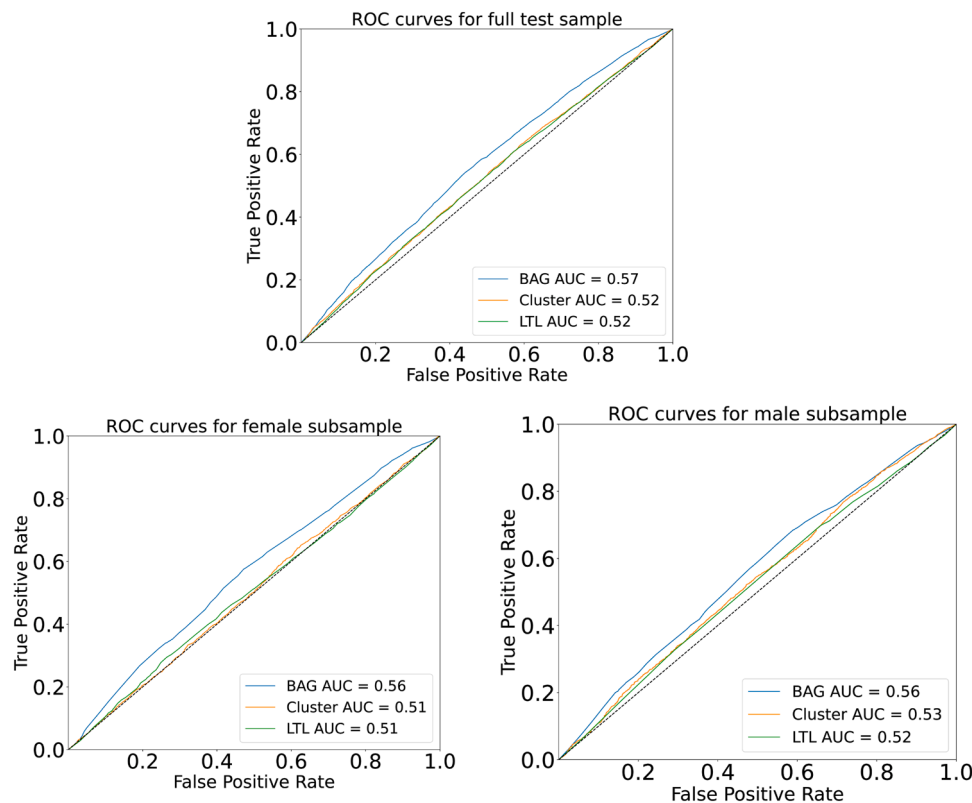


Fig. 5. Binary classification with parental status (children vs no children) as the label, performed using XGBoost (see Section 2.6). Average area under the receiver operating characteristic curve (AUC) for models using brain age gap (BAG), mean cluster values, and leukocyte telomere length (LTL) as input features. The bottom plots show the AUCs for models stratified by sex.

et al., 2017), correlating with higher degrees of positive paternal behaviour (Gray et al., 2017; Kuo et al., 2018).

Beyond biological factors, experience-dependent brain plasticity offers another avenue for understanding parental brain changes. Interacting with the baby during the postpartum period has been shown to reshape the brain's anatomy and functionality in both mothers and fathers (Abraham et al., 2014; Duarte-Guterman et al., 2023; Feldman et al., 2019; Kim et al., 2010; Parsons et al., 2017), and the continued learning and adaptation as the child grows may leave lasting imprints on neural circuits. From the onset of motherhood, women are required to remain constantly vigilant to their infants' needs and employ multi-tasking strategies for effective caregiving. Although research shows a generational increase in paternal involvement (Dex et al., 2005; Lamb, 2000; Norman et al., 2014), mothers are generally more likely to assume the primary caregiving role, encompassing responsibilities such as night-time child care, household duties, and the planning and organising of children's activities (Bourke-Taylor et al., 2013; Doucet, 2000). In addition to direct biological effects of pregnancy, this disproportionate involvement could partly explain the more prominent effects observed in mothers compared to fathers. However, given the UK Biobank age range, our results may not generalise to younger cohorts of parents. Future studies could aim to disentangle biological from experience-driven brain changes by measuring childcare involvement, and compare diverse parenting roles and arrangements including adoptive parents and parents in same-sex couples, as well as involvement in grandparenting.

While our results reveal linear associations between an increased number of children and younger brain age, distributions of mean brain age values across parenthood groups may point to non-linear effects (Fig. 1). These findings echo some observations in our previous work (de Lange et al., 2019; Voldsbekk et al., 2021), suggesting that protective effects of parenthood may diminish with a larger number of children.

However, we previously failed to replicate this pattern in a study including 8800 UK Biobank participants (de Lange et al., 2020a), highlighting the influence of less statistical precision in the smaller groups of this sample. While a moderate number of children might offer optimal benefits for brain health compared to none or many (Jang et al., 2018; Zeng et al., 2016; Lindseth et al., 2023), factors not considered in our analyses, such as stress levels, social support, and access to childcare, could also play a significant role. Future research incorporating a wider array of potentially confounding factors are needed to fully understand how parenthood influences brain ageing trajectories.

5.2. Associations between regional brain volumes and number of children

Volume-based analyses showed maternal effects in striatal and limbic regions, which were not evident in fathers. Given the richness of oestrogen receptors ($ER\alpha$ and $ER\beta$) in these brain regions (Barth et al., 2015), this finding might reflect long-term influences of altered oestrogen levels in females during pregnancy. In longitudinal cohort studies following parents across pregnancy and postpartum, subcortical volume changes have primarily been observed in mothers (Hoekzema et al., 2022, 2020, 2017), while cortical grey matter alterations have been found in both mothers and fathers (Hoekzema et al., 2017, 2020, 2022; Kim et al., 2014; Martínez-García et al., 2023; Paternina-Die et al., 2020, 2024) - with some studies reporting less pronounced effects in fathers (Martínez-García et al., 2023; Paternina-Die et al., 2020). While research indicates an interaction between hormonal changes and subcortical brain adaptations in first-time fathers (Saxbe et al., 2023), such effects may be subtle and potentially undetectable decades after transitioning to parenthood.

Maternal brain changes in temporal and subcortical regions, as well as cortical areas underpinning social behaviour, are consistently reported across pregnancy in human cohorts (Hoekzema et al., 2022,

2020, 2017; Martínez-García et al., 2021a; Orchard et al., 2023; Servin-Barthet et al., 2023) and animal studies (Ammari et al., 2023; Champagne et al., 2004; Duarte-Guterman et al., 2023, 2019; Pawluski et al., 2016; Puri et al., 2023; Robinson et al., 2011). Similarly, a single-case dense-sampling study found widespread reductions in grey matter volume and cortical thickness during gestation, with high-resolution imaging revealing specific volume reductions in the parahippocampal cortex (Pritschet et al., 2023). At the group level, such volume reductions have been associated with stronger mother-child responses and postpartum attachment (Hoekzema et al., 2020; Rocchetti et al., 2014). Together, these studies substantiate pregnancy as a period of unique neuroplasticity and development — often referred to as ‘matrescence’ — involving neural fine-tuning to adapt to the demands of motherhood (Barrière et al., 2021; Carmona et al., 2019; McCarthy, 2023; McCormack et al., 2023; Orchard et al., 2023; Pawluski et al., 2022; Puri et al., 2023). This remarkable period of brain remodelling may not only reflect the immediate needs of childrearing, but could also have long-term implications for maternal brain health.

5.3. Associations between leukocyte telomere length and number of children

Although some maternal brain volume reductions persist beyond the postpartum phase, studies also indicate a partial restoration in the postpartum period (Chechko et al., 2022; Hoekzema et al., 2022; Lisofsky et al., 2019; Luders et al., 2020; Nehls et al., 2024; Paternina-Die et al., 2024). This adaptive brain response may be accompanied by telomere length alterations, as some studies link reproductive effort to the pace of cellular ageing (Jasienska, 2009, 2020; Poganik et al., 2023; Ryan et al., 2018), as well as potential long-term health benefits via rejuvenation mechanisms postpartum (Giller et al., 2020; Michaeli et al., 2015; Ross et al., 2020). However, our results do not provide evidence of extended effects of pregnancy and parenting on LTL. This contrasts with one study showing shorter LTL in females with fewer children (Barha et al., 2016), and echoes the heterogeneity observed in existing research on parity and LTL (Houminer-Klepar et al., 2023). This variability in study outcomes highlights the complexities in deciphering relationships between reproductive effort and cellular ageing, which may also be influenced by factors such as resources, social support, and allomaternal care (Carroll et al., 2013; Kramer and Ellison, 2010; Meehan and Hawks, 2013; Rentscher et al., 2020). Moreover, LTL shows heritability of around 70% in adult samples (Broer et al., 2013) and might serve as a marker of reproductive success (Sudyka, 2019), emphasising the need for continued research to understand the dynamics between LTL and reproductive experiences.

5.4. Predicting parental status based on brain measures and leukocyte telomere length

The classification models achieved modest predictive performance, with no differences in predictive accuracy between males and females. The AUCs (0.52–0.57) indicate a degree of predictive ability beyond mere chance, yet underscore the subtle influence parenthood may have on markers of brain and cellular ageing. The brain age model yielded the highest AUC (0.57), highlighting its improved sensitivity for predicting parental status relative to regional volume measures. This enhanced performance may arise from the use of minimally processed brain images, encapsulating a wider spectrum of detailed brain characteristics and circumventing the constraints of pre-defined brain atlases.

While longitudinal studies on brain alterations in pregnancy have demonstrated highly accurate classification performance (Hoekzema et al., 2017), our study focused on middle-aged and older adults - many years after the parenthood transition. This temporal aspect might explain the modest predictive performance, as long-term effects of parenthood on biological ageing could be minor relative to the cumulative impact of other life course factors. Future research might consider

integrating a broader range of genetic, environmental, and lifestyle factors to model the multifaceted influences of parenthood on biological ageing processes more accurately.

5.5. Study limitations

To the best of our knowledge, this study is the first to evaluate the effects of parity on markers of both brain and cellular ageing in middle-aged and older males and females. While the sample size and advanced computational methods represent considerable strengths, the study also has noteworthy limitations.

Firstly, social and cultural factors play a significant role in shaping childcare engagements and parenting practices (Feldman and Masalha, 2010; LaForett and Mendez, 2020; Vincent and Maxwell, 2016), which in turn could influence the neural adaptations observed in parents. In societies where active paternal involvement is more common, fathers might experience more pronounced hormonal and neural changes compared to those in societies where childcare is predominantly the mother’s responsibility. Additionally, socioeconomic life context, access to parental leave, and the presence of supportive childcare systems can all significantly affect the extent and nature of parental engagement (Lanfranco and Valarino, 2014; Stahl et al., 2018; Williams et al., 2022). Although we adjusted for available covariates including education and social deprivation, our findings might not capture the diversity of experiences in different social and cultural settings (Boelsma et al., 2021; Slaughter-Acey et al., 2016). Further research with more diverse and representative samples (Subramaniapillai et al., 2023) is crucial to understand the full spectrum of parental brain and hormonal changes across various contexts.

Secondly, the UK Biobank cohort predominantly consists of white participants and is characterised by a ‘healthy volunteer’ bias (Fry et al., 2017), limiting the representativeness of our findings across broader and more diverse populations. There is also no recording of gender alongside biological sex, and data on sex is derived from the NHS registry at recruitment but in some cases updated by the participant. Information about such updates is not available, thus leading to some ambiguity regarding the precision of this data field (Ackley et al., 2023).

Finally, despite the superior accuracy of deep-learning-based age prediction, such models introduce significant opacity in decision-making processes. This challenge is potentially exacerbated by our multitask model, which leverages covariance structures between phenotypes—a process which is not directly observable or easily interpreted. To enhance the interpretability of our findings, we supplemented our analysis with atlas-based brain volume assessments to probe regional effects. Future studies might utilise techniques for explainability to generate interpretable model predictions (Leonardsen et al., 2023), facilitating the characterisation of distinct brain patterns and trajectories at the individual level. Such measures could be analysed alongside cognitive outcomes and age-related diseases, enhancing the interpretability of the observed relations between parenting and neuroimaging-based markers of brain health.

6. Conclusion

In summary, this study reveals subtle yet significant associations between parental experience and brain characteristics among middle-aged and older adults, with stronger effects in females compared to males. We found no significant relationships between number of children and markers of cellular ageing, potentially suggesting more prominent long-term influences of parenthood on brain age relative to cellular ageing processes. Our regional volume findings align with longitudinal studies on neuroplastic changes during pregnancy and postpartum, with subcortical effects observed primarily in females. These sex differences might be due to biological effects of pregnancy, discrepancies in childcare involvement and parenting-related brain plasticity, or a combination of these factors. Furthermore, our models

predicting parental status using brain measures and LTL achieved modest success, highlighting that the complexities of parenthood's effects on ageing processes are not easily captured by brain and cellular markers in a binary classification context. While our findings suggest enduring effects of pregnancy and parenthood on the brain, longitudinal studies following individuals from pre-conception through pregnancy and beyond are essential for confirming long-term implications for brain health. Future research is warranted to elucidate these nuanced relationships, offering deeper insights into how critical life events and environmental exposures shape our neurological health and ageing processes.

CRediT authorship contribution statement

Ann-Marie G. de Lange: Conceptualization, Methodology, Data processing and preparation, Formal analysis, Visualization, Writing – original draft, Project administration. **Esten H. Leonardsen:** Conceptualization, Methodology, Data processing and preparation, Formal analysis, Writing - review & editing. **Claudia Barth:** Conceptualization, Writing – original draft, Data processing and preparation, Writing, review and editing. **Louise S. Schindler:** Formal analysis, Writing – original draft, Writing - review & editing, Data processing and preparation. **Arielle Crestol:** Writing – review & editing, Data processing and preparation. **Madelene C. Holm:** Writing – review & editing. **Sivaniya Subramaniapillai:** Writing – review & editing. **Dónal Hill:** Conceptualization, Methodology, Formal analysis, Visualization, Writing - review & editing. **Dag Alnæs:** Writing – review & editing, Methodology. **Lars T. Westlye:** Conceptualization, Methodology, Writing - review & editing, Project administration.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work, Generative Pre-trained Transformer (GPT) 4 / OpenAI was used to check and improve grammar and language. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Declaration of Competing Interest

None.

Data Availability statement

The data that support the findings of this study are available through the UK Biobank data access procedures (<https://www.ukbiobank.ac.uk/researchers>).

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.psyneuen.2024.107040](https://doi.org/10.1016/j.psyneuen.2024.107040).

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