Received: 20 January 2023 | Revised: 31 October 2023 | Accepted: 6 November 2023

DOI: 10.1002/hbm.26538

RESEARCH ARTICLE

WILEY

Previous pregnancies might mitigate cortical brain differences associated with surgical menopause

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Funding information
Horizon 2020 Framework Programme, Grant/Award Number: 883069; Instituto de Salud Carlos III, Grant/Award Numbers: CPII21/00016, PI22/01365; 'la Caixa' Foundation, Grant/Award Number: LCF/PR/HR19/52160001

Abstract

Surgical menopause causes a sharp drop in estrogen levels in middle-aged women, thus preventing the gradual physiological adaptation that is characteristic of the peri-menopause. Previous studies suggest that surgical menopause might increase the risk of dementia later in life. In addition, the transition to motherhood entails long-lasting endocrine and neuronal adaptations. We compared differences in whole-brain cortical volume between women who reached menopause by surgery and a group of women who reached spontaneous non-surgical menopause and determined whether these cortical differences were influenced by previous childbearing. Using surface-based neuroimaging techniques, we investigated cortical volume differences in 201 middle-aged women (134 women who experienced non-surgical menopause, 78 of whom were parous women; and 67 women who experienced surgical menopause, 39 of whom were parous women). We found significant atrophy in the frontal and temporal regions in women who experienced surgical menopause. Nulliparous women with surgical menopause showed significant lower cortical volume in the left temporal gyrus extending to the medial temporal lobe cortex, as well as in the precuneus bilaterally compared to parous women with surgical menopause; whereas our results revealed no significant differences between parous women with surgical menopause and both parous and nulliparous women who reached a non-surgical menopause. Furthermore, in the surgical menopause group, we found a negative correlation between cortical volume and age at first pregnancy in the temporal lobe. Our study suggests that the long-term brain remodeling of parity may mitigate the neural impact of the sudden drop in estrogen levels that characterizes surgical menopause.

KEYWORDS
cortical atrophy, menopause, neuroimaging, oophorectomy, parity

Alberto Fernández-Pena and Francisco J. Navas-Sánchez are first co-authorship.

1 | INTRODUCTION

Menopause is defined as the absence of a menstrual period for 1 year. It is a long natural process characterized by marked declines in ovarian hormone levels (Harlow et al., 2012). Although menopause affects about 50% of the world's population with a median age of over 50 years (Gold, 2011), it is a historically understudied life stage with important implications for mental and physical health (Monteleone et al., 2018).

Most women reach spontaneous menopause over a 4–8-year period known as perimenopause (Harlow et al., 2012). This period involves a gradual withdrawal of ovarian hormones, especially estrogens (Burger et al., 2002), thus, presumably, enabling the brain to adapt to the new hormonal milieu. However, there is also a smaller percentage of women who reach menopause by medical intervention, such as bilateral oophorectomy. Bilateral salpingo-oophorectomy (BO), the surgical removal of both ovaries and fallopian tubes, is undertaken as a prophylactic procedure, and it is often accompanied by hysterectomy (Parker et al., 2009). In 2003, around 19,000 women aged less than 60 years underwent BO in the United Kingdom (Clarke et al., 2006).

Premenopausal surgical menopause causes an abrupt drop in ovarian hormone levels, preventing the gradual physiological adaptation that characterizes perimenopause, such as energetic metabolism, blood flow changes, or structural white and gray matter changes (Mosconi et al., 2021). Studies suggest that surgical menopause has a more severe effect on cognitive functions than non-surgical menopause (NSM) (Georgakis et al., 2016). Previous data have shown that BO in premenopausal stages is associated with accelerated aging, increased cognitive impairment, and increased risk of dementia and Alzheimer's disease (AD) later in life (Rocca et al., 2007; Uldbjerg et al., 2022). Interestingly, these alterations are not observed when women undergo oophorectomy after they have reached menopause, suggesting that the gradual adaptation period during perimenopause exerts a protective effect on psychological wellbeing (Kurita et al., 2016).

Recent neuroimaging studies have reported that the menopausal transition could be associated with structural brain changes whose effect on total brain volume goes beyond those of aging (Ambikairajah et al., 2021). Changes in gray matter volume in subcortical medial temporal lobe structures and cortical regions have been reported in postmenopausal women (Goto et al., 2011; Mosconi et al., 2021; Storsve et al., 2014). These changes are associated with menopausal symptoms, such as cognitive impairment, which is caused by changes in the levels of different sex hormones, especially decreased estradiol levels (Kim et al., 2018) and could be related to the risk of AD (Mosconi et al., 2018). Previous region of interest (ROI) studies found marked atrophy of the amygdala and hippocampus in women who experienced surgical menopause compared to women who reached NSM (Gervais et al., 2022; Zeydan et al., 2019). The authors suggested that atrophy of the amygdala and hippocampus could potentially serve as a biomarker indicating an elevated risk of dementia in women who underwent surgical menopause. However, the impact of premenopausal surgical menopause on the outer cerebral cortex, which is also rich in estrogen receptors, remains unexplored.

Pregnancy leads to abrupt increases in estrogen levels (Taylor et al., 2019). During pregnancy, estrogen levels rise by up to 900% at their baseline level (Schock et al., 2016), and recent reports suggest an association between estrogen levels and brain adaptations during this highly neuroplastic period (Hoekzema et al., 2022). In addition, studies in middle-age women, as compared to nulliparous women, suggest that parous women have shorter menstrual cycles with lower estrogen levels in each cycle, as well as different brain aging trajectories (Barrett et al., 2014; Barth & de Lange, 2020; de Lange et al., 2020; Najmabadi et al., 2020). However, no previous studies have assessed whether the physiological adaptations that occur during postpartum might influence the effects of surgical menopause on the brain.

The aim of this work is two-fold. First, we aimed to study differences in whole-brain cortical volume between women who experienced surgical menopause and women who reached non-surgical menopause. Second, we wanted to determine whether previous pregnancies impact the brain differences associated with surgical menopause and non-surgical menopause. We performed a whole-brain vertex-wise study of cortical volume to test the main effect of surgical menopause, the main effect of parity, and the 'Surgical Menopause × Parity' interaction. Taking into account previous work, we hypothesized that in women who experienced surgical menopause—and therefore do not undergo a period of gradual adaptation to the drop in estrogen levels—cortical volume will be significantly decreased in regions that are rich in estrogen receptors, such as the temporal and prefrontal areas. We also hypothesized that the physiological adaptations produced after a previous pregnancy might protect against the brain differences associated with surgical menopause.

2 | METHODS

2.1 | Participants

This study used brain neuroimaging data from the UK Biobank (http://www.ukbiobank.ac.uk/) (Miller et al., 2016). We initially selected 284 women aged between 45 and 65 years with MRI data and took into account the number of children they had and whether they had experienced surgical menopause ($n = 96$) or had reached spontaneous non-surgical menopause ($n = 188$). Data were curated based on the following exclusion criteria: clinical history of a neurological condition (migraine, sleep disorders, myelopathy, epilepsy, dystonia, Bell's palsy, nerve injury, or neurodegenerative disease such as multiple sclerosis), primary malignant neoplasm (breast, lymph nodes, lung, or others), or secondary neoplasm. The final sample comprised 201 women, of whom 67 underwent premenopausal bilateral oophorectomy and hysterectomy surgery (39 were mothers). A sample of women who reached spontaneous non-surgical menopause was randomly selected (at a 2:1 ratio), and the groups were matched for age, parity, and number of live children ($n = 134$; 78 of them were

mothers). All the women in the surgical menopause group undergone bilateral oophorectomy combined with hysterectomy.

Detailed demographic and clinical data are provided in Table 1, and the participant's code is provided in Appendix S1. Application of the UK Biobank was approved by the Research Ethics Committee (reference 11/NW/0382). All participants provided their written informed consent to participate.

2.2 | Clinical assessment

Clinical status was assessed based on tests available in the UK Biobank database. For the current study, we used the clinical data shown in Table 1. Most of the participants had undergone psychological assessment for cognitive status (matching test, reaction time, numerical memory test, fluid intelligence, and paired associates learning test [PAL]) and psychiatric evaluation for mental health conditions (depression, anxiety, and others). None of the participants had a history of neurological disease. Some patients had isolated neoplasms (i.e., without secondary tumors), although these were not classified as malignant in the UK Biobank database. The social assessment was based on self-reported instruments to assess miserableness, loneliness, happiness, and satisfaction with family, friends, and health.

2.3 | MRI data: acquisition parameters

MRI data were acquired from all participants at three imaging centers (Cheadle, Newcastle, and Reading) using an identical 3T Siemens Skyra MRI scanner (software VD13) equipped with the standard Siemens 32-channel head coil. In Appendix S1, we provide the bar plots with the number of subjects and percentages for each group.

The images were acquired based on T1-weighted imaging data (3D MPRAGE, sagittal, $R = 2$, TI/TR = 880/2000 ms; voxel size = 1 × 1 × 1 mm; matrix size = 208 × 256 × 256) and T2-weighted FLAIR imaging data (3D SPACE, sagittal, $R = 2$, PF 7/8, fat sat, TI/TR = 1800/5000 ms, elliptical acquisition; voxel size = 1.05 × 1 × 1 mm; matrix size = 192 × 256 × 256).

All the images used in this study, which were labeled as usable by the UK Biobank, were defaced and registered between modalities (Alfaro-Almagro et al., 2018).

2.4 | MRI data processing

We conducted a cross-sectional surface vertex-wise analysis to account for group differences in whole-brain cortical volume. Briefly, we processed the structural T1- and T2-weighted images with the standard FreeSurfer pipeline (available at: http://www.surfer.nmr.mgh.harvard.edu, version 7.2.0) (Dale et al., 1999; Fischl et al., 1999), which constructs models of the cortical interfaces (white–gray matter and CSF–gray matter) in the native anatomical space. Cortical volume maps were then normalized to the standard fsaverage space and smoothed using a Gaussian filter with a full width at half-maximum of 10 mm.

2.5 | Statistical analysis

We ran a general linear model (GLM) including two discrete factors (with two levels each) and two continuous covariates. More specifically, the factor labelled 'SM' classifies the subjects depending on whether they had a non-surgical menopause (NSM) or surgical menopause (SM). The factor labelled 'Parity' has two levels: Parous and Nulliparous. We also included the two nuisance covariates: 'Age' at the MRI session, and the estimated 'Total Intracranial Volume' (ICV), for each subject, modeled independently for each group assuming potential between-group differences in the intercept and in the slopes.

We used permutation analysis of linear models (PALM) (Winkler et al., 2014) to determine the statistical inference with the threshold-free cluster enhancement (TFCE) method (Smith & Nichols, 2009). The number of random and synchronized non-parametric permutations for the statistical inference was set at 10,000. Resulting *p*-values were adjusted with a Bonferroni correction, considering both hemispheres and the number of hypotheses tested (in this case: the main effect of the surgical menopause, the main effect of parity, and the 'SM × Parity' interaction, as well as the six pairwise comparisons between the different levels of the factors: NSM parous vs. NSM nulliparous; NSM parous vs. SM parous; NSM nulliparous vs. SM nulliparous; SM parous vs. SM nulliparous; NSM parous vs. SM nulliparous; NSM nulliparous vs. SM parous). We tested one side of the distribution tails; *p* values <.025 were considered significant to adjust for the two-tailed analysis.

As a complementary analysis, we tested the potential influence of HRT. To do so, we performed a new GLM with the participants who underwent premenopausal surgery, with two factors ('HRT' and 'Parity') and two covariates ('Age' and 'ICV'). In this analysis, we tested the main effects of each factor and the potential between-factor interaction.

Finally, as a post hoc exploratory analysis, we decided to assess a ROI-based study in the group of parous women who experienced surgical menopause. We tested the potential correlation between cortical volume and a series of covariates as proxies of endogenous estrogen exposure (maternal age at the first pregnancy, and number of full-term pregnancies) as in other previous studies (Fox et al., 2013; Heys et al., 2011; Smith et al., 1999). We hypothesized that a higher endogenous estrogen exposure (associated with advanced maternal age or a lower number of full-term pregnancies) could be linked to a reduction in cortical volume among parous women who have undergone surgical menopause.

To perform this analysis, we obtained the mean cortical volume of each parous women who experienced surgical menopause for each significant cluster obtained from the hypothesis contrast 'SM parous versus SM nulliparous'. We performed a hypothesis-driven one-tailed partial correlation analysis (controlling for age and ICV).

TABLE 1 Demographic, clinical, and psycho-sociological data were included in the analyses.

	Non-surgical menopause, NSM (*n* = 134)								Surgical menopause, SM (*n* = 67)								Group main effect	Parity main effect	Group × parity' interaction
	Parous (*n* = 78)				Nulliparous (*n* = 56)				Parous (*n* = 39)				Nulliparous (*n* = 28)						
	N	Mean	SD	Sum	N	Mean	SD	Sum	N	Mean	SD	Sum	N	Mean	SD	Sum	*p*-value	*p*-value	*p*-value
Age (years)		57.69	3.38			58.25	4.29			57.51	3.87			58.14	4.31		0.808[a]	0.314[a]	0.951[a]
N live births		2.37	0.81			0.00	0.00			2.21	0.89			0.00	0.00		0.391[a]	**0.0000**[a]	0.391[a]
Age of menarche (years)	76	13.34	1.65		53	12.85	1.50		39	13.23	1.56		28	12.46	2.19		0.336[a]	0.015[a]	0.596[a]
Age onset menopause (years)	76	50.38	4.01		54	50.39	4.01		39	45.64	4.63		28	44.36	6.21		**0.0000**[a]	0.354[a]	0.348[a]
Menopause duration (years)	76	7.28	4.57		54	7.93	5.03		39	11.87	6.05		28	13.79	7.04		**0.0000**[a]	0.121[a]	0.443[a]
Reproductive span (years)	74	37.03	4.82		51	37.37	4.41		39	32.41	4.99		28	31.89	6.63		**0.0000**[a]	0.912[a]	0.579[a]
Had HRT				0				0				25 (64%)				18 (64%)	**0.0000**[b]	0.992[b]	
Years of HRT	0	0.00	0.000		0	0.00	0.000		24	6.29	9.83		18	14.16	12.44			0.008[a]	
Mental health																			
Mental disorder				3 (3.9%)								1 (2.6%)				2 (7.1%)	0.369[b]	0.662[b]	
Depression				2 (2.6%)								1 (2.6%)				2 (7.1%)			
Anxiety				1 (1.3%)				0				0				0			
Affective bipolar disorder				0				0				0				0			
Dementia				0				0				0				0			
Neoplasm				10 (12.8%)				6 (10.7%)				20 (51.2%)				12 (42.8%)	**0.0000**[b]	0.490[b]	
Ovarian/uterus				1 (1.3%)				2 (3.6%)				16 (41%)				9 (32.2%)			
Other				9 (11.5%)				4 (7.1%)				4 (10.2%)				3 (10.6%)			
Cognitive assessment																			
Pairs matching assessment	73	.18	.48		56	.30	.69		39	.64	1.04		28	.21	.63		0.068[a]	0.169[a]	0.008[a]
Reaction time	72	585.75	96.94		55	564.53	93.42		37	609.00	108.06		28	592.07	113.97		0.103[a]	0.220[a]	0.890[a]
Numeric memory assessment	52	6.79	1.04		38	7.00	1.04		20	6.15	1.87		21	7.05	1.02		0.461[a]	0.086[a]	0.090[a]
Fluid intelligence Score	72	6.83	1.96		56	6.80	1.77		37	6.41	1.99		28	6.39	2.13		0.161[a]	0.943[a]	0.977[a]
Paried associates learning test	50	8.06	1.98		39	7.90	2.19		20	6.05	2.87		20	6.00	3.01		**0.00003**[a]	0.815[a]	0.901[a]
Education																	0.832[b]	0.494[b]	
College or university degree				43 (55.1%)				30 (53.6%)				19 (48.7%)				14 (50%)			
Other degree				35 (44.9%)				26 (46.4%)				20 (51.3%)				14 (50%)			

TABLE 1 (Continued)

	Non-surgical menopause, NSM ($n = 134$)						Surgical menopause, SM ($n = 67$)						Group main effect	Parity main effect	Group × parity' interaction
	Parous ($n = 78$)			Nulliparous ($n = 56$)			Parous ($n = 39$)			Nulliparous ($n = 28$)					
	N	Mean	SD	Sum	Mean	SD	Sum	N	Mean	SD	Sum	N	*p*-value	*p*-value	*p*-value
Psyco-social factors (self-reported)															
Lonelyness	77			9 (11.5%)	54		11 (19.6%)	39			5 (12.8%)	28	6 (21.4%)	0.833[b]	0.098[b]
Happyness	78			76 (97.4%)	56		53 (94.7%)	39			38 (97.5%)	28	27 (96.4%)	0.288[b]	0.046[b]
Health satisfaction	78			73 (93.6%)	56		47 (83.9%)	39			37 (94.9%)	28	24 (85.7%)	0.177[b]	0.068[b]
Family satisfaction	78			71 (91.0%)	55		32 (85.7%)	39			30 (92.3%)	28	26 (92.9%)	0.755[b]	0.404[b]
Friendship satisfaction	76			73 (93.6%)	56		54 (96.4%)	39			38 (97.4%)	27	26 (92.9%)	0.391[b]	0.782[b]

Notes: For psychosocial factors, we included the sum and the percentages of subjects who answered "yes" to the self-reported loneliness tests; the sum and the percentages of the subjects who answered that they felt "moderately happy", "very happy", and "extremely happy" in the satisfaction with health, happiness, family, and friendship tests.

Abbreviations: HRT, hormone replacement therapy; n.s., non-significant; N, sample size available; SD, standard deviation.

[a]Univariate test.

[b]Chi-square.

2.6 | Multiple comparisons correction

Finally, once the *p*-values were adjusted, we controlled for type I errors in a list of rejected hypotheses based on the false discovery rate (FDR) (Benjamini & Hochberg, 1995) for each statistical model run independently.

3 | RESULTS

3.1 | Demographic and clinical outcomes

Table 1 shows the descriptive and group comparisons of demographic, clinical, and psychosocial variables. Surgery associated with neoplasm was more frequent in women who experienced surgical menopause. As for psychological testing, we observed between-group differences in the PAL test, which is highly sensitive to medial temporal lobe dysfunction and is a valuable tool for the early detection of AD (de Rover et al., 2011). However, only 64% of participants performed this test. No between-group differences were observed in educational level or psychosocial factors.

3.2 | Vertex-wise analysis: main effects and pairwise comparisons

Vertex-wise analyses revealed that women who had experienced surgical menopause presented decreased cortical volume in the right and left prefrontal lobes, right temporal lobe (including the entorhinal and parahippocampal cortices), right inferior parietal lobe, right medial prefrontal cortex, and left isthmus cingulate (Figure 1a; see Appendix S1, the tables for the exact coordinates and anatomical localization of the clusters). We also observed a significant 'Surgical Menopause × Parity' interaction in the precuneus bilaterally (Figure 1b). No significant main effect of Parity was detected.

Pairwise comparisons between the different levels of each factor indicated reduced cortical gray matter volume in nulliparous women who experienced surgical menopause as compared with parous women who experienced surgical menopause in the left precuneus and right entorhinal and inferior temporal cortices. When comparing nulliparous women who experienced surgical menopause with mothers who reached NSM, we observed decreased volume bilaterally in the precuneus and occipital and prefrontal cortices in the former. The comparison between nulliparous women who experienced surgical menopause and parous women who reached NSM revealed volumetric reductions in the precuneus/cuneus, as well as in the medial prefrontal and inferior temporal cortices, extending towards the medial temporal lobe cortical region bilaterally (Figure 2; tables showing the location of the clusters in Appendix S1). No significant differences were observed between parous women who experienced surgical menopause and parous women who reached NSM or between parous women who experienced surgical menopause and

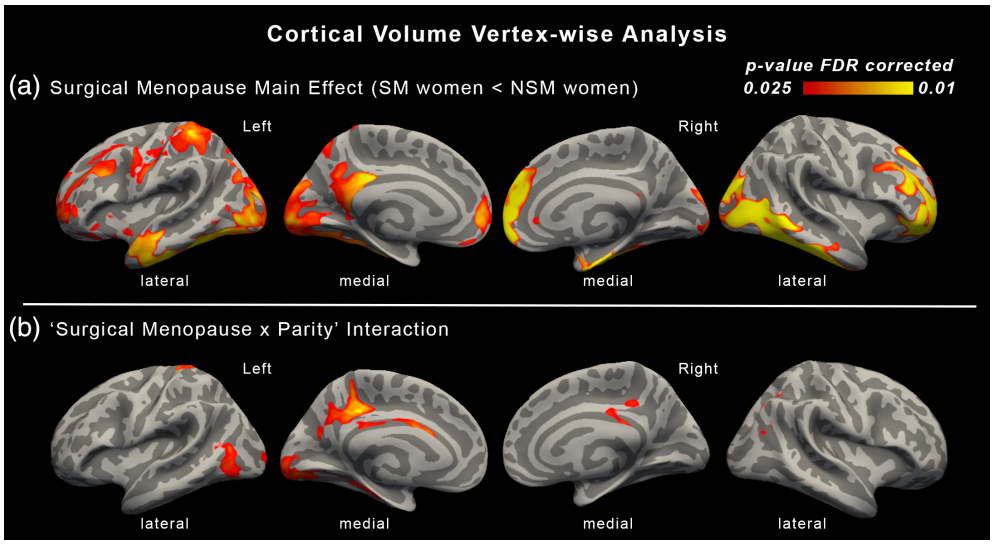

FIGURE 1 Vertex-wise whole-brain analysis. (a) Group differences in cortical brain volume between women who experienced surgical menopause (SM) and women who reached non-surgical menopause (NSM). (b) Significant 'Surgical Menopause × Parity' Interaction. All the reported *p*-values were adjusted using FDR correction.

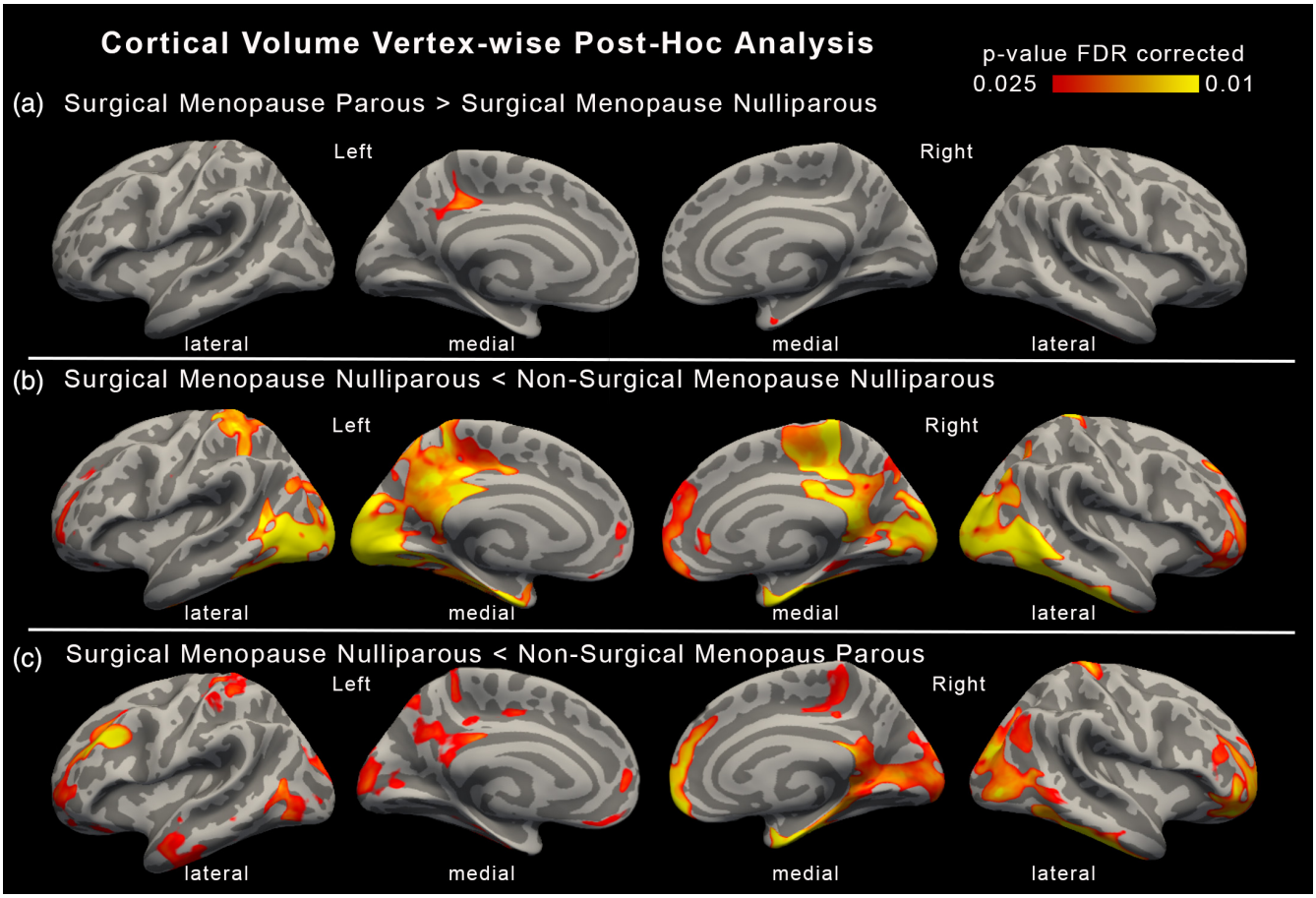

FIGURE 2 Between-group pairwise whole-brain analysis. (a) Group differences in cortical brain volume between parous women who experienced surgical menopause and parous women who reached non-surgical menopause (NSM). (b) Group differences between nulliparous women who experienced surgical menopause and nulliparous women who reached NSM. (c) Group differences between nulliparous women who experienced surgical menopause and parous women who reached NSM. All the significant regions were adjusted using the FDR correction.

nulliparous women who reached NSM. Finally, no significant differences were found between parous and nulliparous women who experienced NSM.

To ensure that the obtained results are not influenced by hormone replacement therapy (HRT), we conducted a complementary analysis exploring the potential effect of HRT. In this study, we did

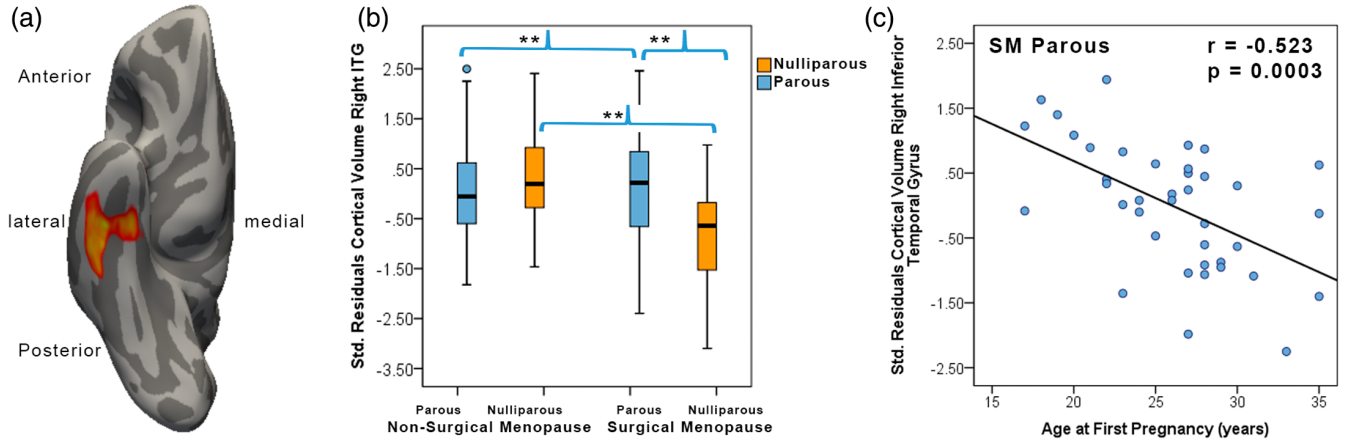

FIGURE 3 Post hoc region of interest analysis within the group of parous women who experienced surgical menopause. (a) Cluster located in the right inferior temporal gyrus (ITG) obtained from the pairwise group differences between parous women and nulliparous women who experienced surgical menopause. (b) Boxplot showing standardized residuals in the right ITG; significant between-group differences are marked with asterisks (**). (c) Significant partial correlation between standardized residuals of cortical volume and maternal age at first pregnancy in the right inferior temporal cortex.

not detect significant between-group differences in women who experienced surgical menopause.

3.3 | Exploratory correlation analysis in parous women who experienced surgical menopause

No significant correlations were observed between cortical volume and the number of full-term pregnancies in the group of parous women who experienced surgical menopause in any cluster. However, we observed a significant relationship between cortical volume and maternal age at the first pregnancy in the cluster located in the right inferior temporal cortex that extended to the medial temporal lobe cortical region ($r = -0.523$; $p = .0003$), as well as a trend of correlation in the left precuneus ($r = -0.285$; $p = .039$) that did not survive FDR correction (Figure 3). The correlation observed in the temporal lobe remains significant even when the number of children is included as a control covariate, together with age and ICV ($r = -0.393$; $p = .007$).

In addition, correlation analyses were also conducted within the group of women who experienced non-surgical menopause. It is noteworthy that these analyses did not reveal any statistically significant correlations. This finding further underscores the specificity of the results observed in the group of women who underwent surgical menopause.

4 | DISCUSSION

We studied potential differences in whole-brain cortical volume between women who experienced surgical menopause and a group of women who reached NSM and determined whether these differences were influenced by the fact of having had at least one pregnancy. Taken together, our data suggest that gradual brain adaptations both from completing the menopausal transition and having a previous pregnancy, might be neuroprotective against the adverse effects of surgical menopause on brain structure, especially in the lateral and medial prefrontal cortices, temporal lobe, and precuneus. Furthermore, the timing of exposure to these hormone levels, such as earlier maternal age, could be essential in mitigating surgical menopause-related cortical volume changes in the temporal lobe.

Surgical menopause causes a sharp decline in ovarian hormone levels that hinders the gradual adaptation of brain estrogen receptors during perimenopause that is a necessary part of the new physiological stage (Scheller et al., 2018). Although this adaptation is accompanied by symptoms such as cognitive dysfunction (Brinton et al., 2015), the absence of the perimenopausal period and physiological adaptation processes are associated with accelerated aging, increased cognitive decline, and increased risk of dementia later in life (Georgakis et al., 2019). Our psychological data consistently showed that women who experienced surgical menopause differ significantly from women who achieved NSM on the PAL test. The absence of perimenopause could cause not only cognitive decline (Rocca et al., 2021), but also neurological changes such as smaller volume of medial temporal lobe structures (Gervais et al., 2022; Zeydan et al., 2019). Consistently, our whole-brain vertex-wise analysis detected a significant decrease in volume in the temporal cortex (including entorhinal and parahippocampal regions), cingulate isthmus, and occipital and prefrontal areas bilaterally. Brain regions affected by surgical menopause, especially the temporal lobes and prefrontal cortex, have a higher density of estrogen receptors in the cerebral cortex (Barth et al., 2015). Our results are probably related to the absence of a complete menopausal transition, which is characterized by a reorganization of sex hormone receptors in the brain (Brinton et al., 2015; Mosconi et al., 2021). It should be noted that our cognitive data, although consistent with previous studies, should be interpreted with

caution, as psychological test results were not available for all the participants in this study.

In our study, approximately 65% of women who experienced surgical menopause were receiving HRT, that is used to mitigate the effects of the drastic drop in hormone levels. We did not find a significant effect of HRT on cortical differences associated with surgical menopause. Future studies that collect HRT type and duration are needed as the current neuroimaging literature provides inconsistent results (Boyle et al., 2021; Gervais et al., 2022; Zeydan et al., 2019).

Our analysis revealed a significant interaction between parity and the effect of BO on the cerebral cortex, mainly in the temporal lobe and bilateral precuneus, suggesting that parity might mitigate brain atrophy caused by surgical menopause. These regions have been described in other studies as crucial areas of brain change during pregnancy and postpartum processes (Hoekzema et al., 2017). Reproductive history has been shown to influence endogenous estrogen exposure in women (Fox et al., 2013). Pregnancy leads to a sudden increase in estrogen levels, and some studies suggest beneficial effects associated with higher cumulative estrogen exposure over a woman's lifetime (Deems & Leuner, 2020; Jett et al., 2022; Schelbaum et al., 2021). Conversely, postpartum estrogen levels decrease and tend to be lower in women who have given birth (Barrett et al., 2014; Najmabadi et al., 2020; Windham et al., 2002). During perimenopause, estrogen levels gradually decline in the context of highly fluctuating menstrual cycles, and the brain adapts gradually to estrogen deficiency. Parity has been found to enhance the brain's responsiveness to lower doses of estrogen later in life, promoting proliferation and neuroplasticity. Additionally, the cumulative dose of estrogen a woman is exposed to throughout her life may influence the inflammatory response, resulting in reduced reactivity (Barha & Galea, 2011; Barth & de Lange, 2020; de Lange et al., 2019; Prestwood et al., 2004). Our findings support the hypothesis that parity may mitigate the impact of surgical menopause on brain structure in women. Specifically, we observed no significant differences in cortical volume between parous women who underwent premenopausal surgical menopause and parous or nulliparous women who experienced non-surgical menopause. In contrast, the absence of hormonal influences from a previous pregnancy and potential adverse psychological effects such as the loss of future childbearing possibilities may exacerbate cortical brain differences associated with surgical menopause. Therefore, in nulliparous women, the absence of previous compensatory adaptive mechanisms could be a significant factor contributing to higher cortical atrophy.

Moreover, not only can the parity might dampen the brain differences related to surgical menopause, but the age at which the mother had her first pregnancy is also important for neuroplasticity and brain adaptation. In parous women who experienced surgical menopause, we found a negative association between maternal age at first pregnancy and cortical volume in the right temporal lobe and a trend toward this association in the precuneus. Therefore, after delivery, the slow, gradual reorganization of the brain, driven by estrogen levels (de Lange et al., 2019; Martínez-García et al., 2021; Puri et al., 2023), may mitigate the drastic differences caused by surgical menopause. This is consistent with the conjecture that advanced maternal age would preclude sufficiently long postpartum neural adaptation from coping with surgical menopause-related differences in brain structure. Based on previous studies, we put forward two hypotheses: either the time between delivery and surgical menopause is not long enough for the brain to reorganize, or, with an older mother, the capacity for neuroplasticity is lower. However, we would need longitudinal data to be able to contrast these hypotheses.

Finally, we found no significant correlations between the number of children and cortical volume in parous women in the surgical menopause group. Other recent works showed non-linear and linear relationships between brain structure and the number of children in a large sample of middle-aged women (Orchard et al., 2020). The absence of significant results in our analysis could be a consequence of the metric analyzed. Cortical volume includes both cortical thickness and cortical surface area, which may hide the effect detected in previous studies. Besides the above-mentioned limitations, we highlight that the lack of clinical data prevents us from appropriately testing the potential association between the brain differences observed and cognitive performance. Moreover, as there are no other studies on the effects of parity on the brains of women who have reached menopause through surgery, we believe that further studies are warranted to consolidate our results.

There are further limitations to be noted in this study. First of all, we acknowledge the importance that the present study is based on cross-sectional data and does not include hormonal determinations, which are indispensable for a comprehensive evaluation of the long-term impacts of estrogens on brain functioning. To adequately address this concern, longitudinal designs that incorporate measurements of sex steroid levels are needed. When accounting for the possible effect of HRT on the analyses, we did not have the possibility of matching women who had experienced surgical menopause with women who had reached non-surgical menopause with HRT. Furthermore, we lacked access to crucial information such as the timing, types, potential changes, and composition of the medication taken as part of HRT. These variables are undoubtedly significant factors that should be considered when assessing the effects of HRT. However, it is important to note that our study did not primarily focus on investigating the influence of HRT. Thus, since we did not obtain statistically significant results in our comparative analyses, we believe that the impact of HRT in our study is likely limited. Finally, another limitation of the chosen sample is the lack of information on the clinical history of possible aggressive cancer-related treatments, such as chemotherapy. We believe that having eliminated from the sample those patients who showed more than one tumor, or who presented a tumor classified as malignant, greatly decreases the probability of finding women in the sample who had undergone this type of treatment.

5 | CONCLUSIONS

Our study is the first to examine differences in whole-brain cortical volume associated with surgical menopause and the potential influence of parity on these differences. Our results showed that surgical menopause leads to decreased cortical brain volume in the prefrontal,

temporal, and midline cortical regions. However, at least one pregnancy before surgical menopause might mitigate the reported reductions in cortical volume. Our data also indicate that an early age at first pregnancy may be relevant in dampening brain changes related to surgical menopause.

ACKNOWLEDGEMENTS

This study has been funded by Instituto de Salud Carlos III through the project PI22/01365, co-funded by European Regional Development Fund "A way to make Europe". Susanna Carmona funded by Instituto de Salud Carlos III, co-funded by European Social Fund "Investing in your future (grant CPII21/00016)". The project leading to these results has received funding from "la Caixa" Foundation under the project code LCF/PR/HR19/52160001, from the European Research Council (ERC) under the "European Union's Horizon 2020" research and innovation programme (grant agreement no. 883069), and from the Centro Nacional de Investigaciones Cardiovasculares (CNIC). The CNIC is supported by the Ministerio de Ciencia, Innovación y Universidades and the Pro CNIC Foundation, and is a Severo Ochoa Center of Excellence (SEV-2015-050).

CONFLICT OF INTEREST STATEMENT

None of the authors have any conflicts of interest to disclose.

DATA AVAILABILITY STATEMENT

Data used in this work is available under a request.

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SUPPORTING INFORMATION

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How to cite this article: Fernández-Pena, A., Navas-Sánchez, F. J., de Blas, D. M., Marcos-Vidal, L., Desco, M., & Carmona, S. (2024). Previous pregnancies might mitigate cortical brain differences associated with surgical menopause. *Human Brain Mapping*, *45*(1), e26538. https://doi.org/10.1002/hbm.26538