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Original Paper

Postpartal Neural Plasticity of the Maternal Brain: Early Renormalization of Pregnancy-Related Decreases?

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Key Words
Pregnancy • Postpartum • SMRI • Neural plasticity

Abstract
Background/Aims: Human pregnancy goes along with decreasing gray matter volume in the brain of the mother. Whether these reductions remain for years or renormalize shortly after delivery is unclear. The present study used a longitudinal control group design to investigate postpartal neural plasticity. ***Methods:*** 24 healthy young women were assessed with cognitive and hormonal measures in late pregnancy and underwent a brain scan within the first two months after delivery (TP1). They were compared to 24 naturally cycling women. A follow-up cognitive and imaging measurement was performed three months after the first scan in both groups (TP2, 4-5 months postpartally in the mothers). ***Results:*** Compared to the control group, widespread gray matter volume increases from the first to second scan were observed in the new mothers (TP2 > TP1, whole-brain analysis). These were especially pronounced in frontal and cerebellar regions. The time by group interaction pattern of gray matter indicated a postpartal renormalization process, most likely following pregnancy-related decreases. Age was negatively correlated to postpartal gray matter increase in most of the regions. Despite pronounced changes in brain structure, the two groups did not reliably differ in cognitive performance. ***Conclusion:*** The results reveal the potential for plasticity in the adult female brain following pregnancy. They support the assumption that the volume reductions during pregnancy renormalize at least partly in the early postpartal phase. The course of renormalization seems to differ between participants of different ages. Future studies are needed to further investigate inter-individual variability and the time course of postpartal neural change.

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Introduction

The unique phase between late pregnancy and the first months postpartum goes along with multiple physiological, psychological and environmental changes for the mother. Several studies investigated cognitive and affective changes during that period in women [e.g., 1-5]. They demonstrated decreases in subjective memory performance in pregnant and postpartal women [6, 7], however, evidence for objective cognitive decline is inconsistent [4, 7]. Changes in affect, especially depressive symptoms, were described in a substantive proportion of pregnant and postpartal women [5, 8].

In parallel, there has been cumulative evidence for the hormonal sensitivity of the female adult brain [9-13]. Hormonal fluctuations across the menstrual cycle [11], contraceptive-intake [14] and hormone-replacement therapy [10] seem to go along with alterations in gray matter volume. Three longitudinal studies measured structural brain changes during or after pregnancy [15-17]. Hoekzema and colleagues assessed women before and about 2.5 months after delivery and compared the observed gray matter change to a control group of non-pregnant women measured in the same time distance. They showed strong decreases in gray matter volume from pre to post pregnancy in multiple brain regions, including anterior and posterior cingulate cortex, limbic structures and temporal and frontal cortices. Additionally, a subsample of formerly pregnant women was measured again two years after pregnancy. The brain regions affected by pregnancy did not differ in gray matter volume between the early (2.5 months) and late (2.5 years) postpartal measurement (for this comparison, no control group was investigated). The authors interpret these findings as evidence for long-lasting pregnancy-related neural decreases. Considerable pregnancy-related decreases in brain volume are also reported in a study by Oatridge & Holdcroft (2002), measuring women longitudinally during and in the first months after pregnancy. In contrast to the findings by Hoekzema et al. though - these brain changes renormalized during six month after delivery [17]. A possible renormalization of pregnancy-related volume decreases would also be in line with the findings of a third study by Kim and colleagues [16], measuring structural brain changes shortly after delivery. Gray matter volume increases were found in several brain regions (including frontal, parietal, limbic and cerebellar structures) in the first four months postpartum. A severe shortcoming of the latter study is the lack of a control group. Therefore it is unclear, whether the gray matter increases are evidence of a renormalization process (compatible with the results by Oatridge & Holdcroft [17]), or whether they represent additional gains above the normal condition (before pregnancy).

Taken together, there is congruent evidence for widespread and substantial decreases of gray matter volume during pregnancy [15, 17), but whether these decreases renormalize in the first months after delivery or persist for a longer period of time (up to years) is an open question.

The present study investigates neural plasticity following pregnancy using a longitudinal control group design. The two conflicting hypotheses about the renormalization of pregnancy-related brain changes lead to different predictions of gray matter volume change within the first postpartal months: the early renormalization account would be characterized by an increase in gray matter volume in women that have been pregnant, but not in the control group, in contrast the stability account would assume that pregnancy-related decreases are stable during the first postpartal period, accordingly it would predict the absence of a significant interaction effect in gray matter volume between the two groups.

Materials and Methods

Participants

Twenty-four healthy pregnant women were enrolled. We recruited women who had never been pregnant beyond 8 weeks before; therefore all of the women in the peripartal group were first-time mothers. A group of twenty-four healthy naturally cycling women that have also never been pregnant before was recruited as a control group. The mean age of women in the peripartal group was 28.38 (±3.41 (SD)) years and they had an average of 19.21 (±3.08) years of education. Women in the control group were on average 25.42 years (±2.95) old, had 17.66 (±2.72) years of education. There was a significant difference between the groups in age (mean difference 2.96 years, $t(46) = 3.22$, $p = 0.002$), but no significant difference in education level ($t(38) = 1.69$, $p = 0.10$). None of the women in the control group used hormonal contraceptives during six month prior to study participation and within the study phase. None of the participants had a history of neurological or psychiatric conditions. Informed consent was obtained from all individual participants included in the study. The study was conducted according to the Declaration of Helsinki, with approval from the Ethics Committee of the German Society for Psychology.

Design and Procedure

The study included two measurement occasions, both including a cognitive and neuroimaging assessments. For the women in the peripartal group, the cognitive session of the first measurement time point was scheduled during the last month of pregnancy, based on the expected date of delivery. During the cognitive session, the women provided three saliva samples and completed a number of questionnaires. Due to the restriction on scanning pregnant women, we scheduled the first MR imaging assessment within two months following delivery (TP1). On that occasion, the participants in the peripartal group filled out additional questionnaires and again provided three saliva samples. The same cognitive tasks, questionnaires and imaging sequences were used at the second measurement occasion, three months after the first MR-scan (TP2). Again, three saliva samples were collected during the cognitive session. The neuroimaging and cognitive test sessions at the second measurement occasion were either administered on two separate days, or within one day, following the same order for all participants. For the control group, the neuroimaging and cognitive sessions of both measurement occasions were scheduled on one or two days within the early follicular phase of their menstrual cycle (1 - 10 days after onset of menses) before and after an interval of three months. The procedures during the cognitive and neuroimaging session were the same for both groups. With few exceptions, all measurement sessions started before noon (8-12.00 am).

Hormonal assessment

Saliva samples were collected at each measurement occasion (for the peripartal group three times: 1) At the cognitive session of the first measurement time point in the last month of pregnancy (mean week of pregnancy: 37) 2) At the neuroimaging session of the first measurement time point within two months following delivery 3) At the second measurement time point, 4-5 months following delivery. For the control group saliva samples were taken on the two measurement time points three months apart.

Saliva samples were collected using SaliCaps collection devices (IBL-International, Hamburg, Germany), which are validated for sampling of steroid hormones. To account for the pulsative secretion of estrogen, we collected three samples spread over each testing session and pooled them afterwards, to minimize the effect of short-term fluctuations in hormone concentration. Immediately after collection, saliva samples were frozen and stored at -25°C. The estrogen and progesterone concentrations were determined by a commercial company (IBL-International, using IBL Saliva Imunoassay -17ß-Estradiol Saliva ELISA kit and IBL Saliva Progesterone LUMIA Competitive Chemiluminescence Immunoassay Kit). The hormonal data were log-transformed before analysis.

Cognitive tasks and questionnaires

Cognitive performance was assessed by a cognitive test battery including a number of memory tasks: episodic verbal memory (word-list recall [18], word-non-word cued recall [19] and face-name cued recall [19]) as well as working memory (dual-2-back) [20] and object location memory [18]. In addition, tasks measuring spatial abilities were applied: mental rotation [21], navigation [22], spatial orientation [23] and perspective-taking [24]. Executive functioning was assessed with a task-switching paradigm [25].

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All tasks except for the Guilford-Zimmerman spatial orientation task [23] were computer-based. Details on the tasks can be found in the corresponding reference articles. Task performance was analyzed in a multilevel model (R package lme4, [26]). G*roup* (as between-subject predictor), *Time* (as within-subject predictor) and *Age* (as a covariate of no interest) were included as predictors in the analyses. To test for main effects or interactions, the model was run twice, once with and once without the effect (main effect/interaction) of interest. The two models were than compared in their predictive value by means of the anova function in R. The threshold for statistical significance was $p<0.05$. Paired and independent t-tests were performed afterwards to identify the direction of effect (e.g., increase or decrease in performance).

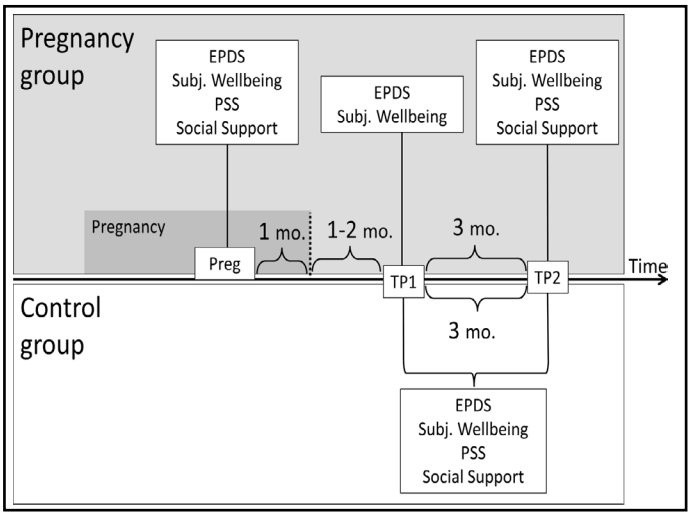

Fig. 1. Questionnaires administered at the different measurement occasions. EPDS = Edinburgh postnatal depression scale; Subj wellbeing = Subjective wellbeing; PSS = Perceived Stress Scale; Preg = Measurement during late pregnancy; TP = Time point

To assess depressive symptoms, stress, social support, and wellbeing in the women, the following questionnaires were applied on both measurement occasions: Edinburgh postnatal depression scale (EPDS) [27], perceived stress scale (PSS-10 item) [28], social support questionnaire (F-SoZu K14) [29] and a questionnaire in which participant rated 40 positive and negative mood words (e.g., happy, hostile) on an eight point Likert scale, depending on how they felt at the moment. The difference in ratings of positive and negative items was used as a measure of subjective wellbeing. For the group of pregnant women, the EPDS and the subjective wellbeing questionnaire were applied both during the cognitive session at the end of pregnancy and during the neuroimaging session shortly after delivery. All other questionnaires were administered during the cognitive session (see Fig. 1 for details on the questionnaires administered at each measurement occasion).

The variables were compared between the groups by means of rank-sum tests. The threshold for statistical significance was $p<0.05$.

MRI data acquisition

MRIs were acquired using a 3T Magnetom Tim Trio MRI scanner system (Siemens Medical Systems, Erlangen, Germany) using a 12-channel radiofrequency head coil. High-resolution anatomical images were collected using a T1-weighted 3D MPRAGE sequence (TR = 2500 ms, TE = 4.77 ms, TI = 1100 ms, acquisition matrix = 256×256×192, sagittal FOV = 256 mm, flip angle = 7°, voxel size = 1.0×1.0×1.0 mm^3).

MRI Data analysis

Anatomical data were processed by means of the cross-sectional stream of the VBM8 toolbox (http://dbm.neuro.uni-jena.de/vbm.html) with default parameters by Gaser and the SPM8 software package (http://www.fil.ion.ucl.ac.uk/spm). The VBM8 preprocessing involves bias correction, tissue classification and registration. The 'nonlinear only' modulation was applied in order to preserve the volume of a particular tissue within a voxel by multiplying voxel values in the segmented images by the Jacobian determinants derived from the spatial normalization step. In effect, the analysis of modulated data tests for regional differences in the absolute amount (volume) of gray matter. Images were smoothed with a full-width half-maximum kernel of 8 mm. The statistical analysis was carried out by means of whole-brain time by group interaction using ad flexible-factorial design. Age and total intracranial volume were entered as covariates of no interest. The resulting maps were thresholded with $p<0.05$ (FWE corrected) and a statistical extent threshold ($k>200$) combined with a non-stationary smoothness correction [30] were applied.

After performing the whole-brain analysis, the gray matter values for each participant in the statistically significant clusters were extracted by means of the toolbox rex (https://www.nitrc.org/projects/rex/) to describe the interaction pattern. Extracted gray matter volumes were used to correlate gray matter change with age.

To inspect whether the age difference between the groups influenced the results, we performed an analysis with a subsample of 17 participants per group. The subsamples were selected so that they did not differ in age (mean age PG (N = 17) = 26.47 (±1.84), mean age CG (N = 17) = 26.59 (±2.72), ($t(32) = -0.2$, $p = 0.88$). We performed exactly the same analysis as for the whole pooled group described above and tested similarly for a time by group interaction in the age-comparable subgroups. Because power was limited in this analysis due to smaller sample sizes and since we were mainly interested in the general (qualitative) pattern of results, we lowered the statistical cluster extent threshold to the expected voxels per cluster determined by SPM (which was in this case 19 voxels).

Results

Questionnaire data

The results of the questionnaire data are reported in Table 1. Groups did not differ in any of the measures (all $p>0.1$). The cognitive test session took place about 24 (±8.0) days before delivery in the peripartal group. The initial neuroimaging measurement took place about 37 (±12.8) days after delivery. The mean difference in terms of time interval between the two cognitive measurements was 160.8 (±23.7) days in the peripartal group and 95.0 (±19.7) days in the control group. The mean difference between the two imaging sessions was comparable for the two groups, with 97.6 (±13.3) days in the peripartal group and 91.5 (±13.9) days in the control group ($t(46) = 1.57$, $p = 0.12$). The measurements in the control group took place in the first week of their cycle (mean cycle day: 6.1 (±3.2)).

Hormonal data

Hormonal levels of both groups at all measurement occasions are reported in Table 2. Estrogen and progesterone were significantly elevated in the peripartal group during pregnancy compared to the control group (group comparisons were performed using independent t-tests, Estrogen: $t(45) = 14.63$; Progesterone: $t(45) = 25.01$, both $p<0.001$).There was no reliable difference between the groups at the second measurement time point (TP2, four to five months after delivery in the peripartal group) (Estrogen: $t(42) = 0.66$; Progesterone: $t(43) = 1.43$, both $p>0.1$). At the MR measurement time point shortly after delivery (TP1), estrogen levels were significantly lower in the peripartal group compared to the control group (TP1) ($t(44) = -5.41$, $p<0.001$). There was no group difference in the progesterone values at that time point ($t(45) = -0.93$, $p = 0.357$). Paired t-test within each group revealed the following: In the peripartal group, estrogen levels differed significantly between all three

Table 1. Results of questionnaires, values represent mean (standard deviation) and group comparisons using rank-sum tests. EPDS = Edinburgh postnatal depression scale; Subj wellbeing = Subjective wellbeing (positive affect – negative affect); PSS = Perceived Stress Scale; Preg = Measurement during late pregnancy

Variable	Peripartal group		Control group	z-value		p-value	
EPDS TP1	Preg	TP1	5.91 (4.55)	Preg	TP1	Preg	TP1
	5.91 (3.7)	5.57 (4.41)		0.35	0.31	0.72	0.76
EPDS TP2	4.82 (4.31)		3.38 (3.72)	-1.1		0.27	
Subj wellbeing TP1	Preg	TP1	3.45 (1.55)	Preg	TP1	Preg	TP1
	3.75 (1.54)	4.08 (0.99)		0.59	1.33	0.55	0.18
Subj wellbeing TP2	3.99 (1.56)		3.5 (1.76)	1.25		0.21	
PSS TP1	14.24 (4.39)		15.25 (6.52)	-0.48		0.63	
PSS TP2	13.68 (5.77)		11.81 (4.27)	-0.95		0.34	
Social support TP1	4.76 (0.22)		4.62 (0.47)	0.52		0.6	
Social support TP2	4.73 (0.27)		4.71 (0.29)	0.20		0.84	

Table 2. Salivary estrogen and progesterone levels for both groups and time points, values represent mean (standard deviation). Preg = Measurement during late pregnancy

Variable (pg/mL)	Peripartal group		Control group
Estrogen TP1	Preg 156.02 (59.9)	TP1 2.36 (2.0)	10.34 (9.5)
Estrogen TP2	13.13 (15.3)		8.63 (11.4)
Progesterone TP1	Preg 1909.6 (796.1)	TP1 67.75 (63.6)	66.87 (41.1)
Progesterone TP2	69.0 (32.2)		58.27 (41.4)

measurement time points (all $p<0.01$). Progesterone was significantly elevated at the first measurement during pregnancy (both $p<0.01$), but did not differ between the other two measurements following delivery ($t(22) = -1.6$, $p = 0.12$). The estrogen and progesterone values of the control groups did not differ between the two measurement time points (both $p>0.1$).

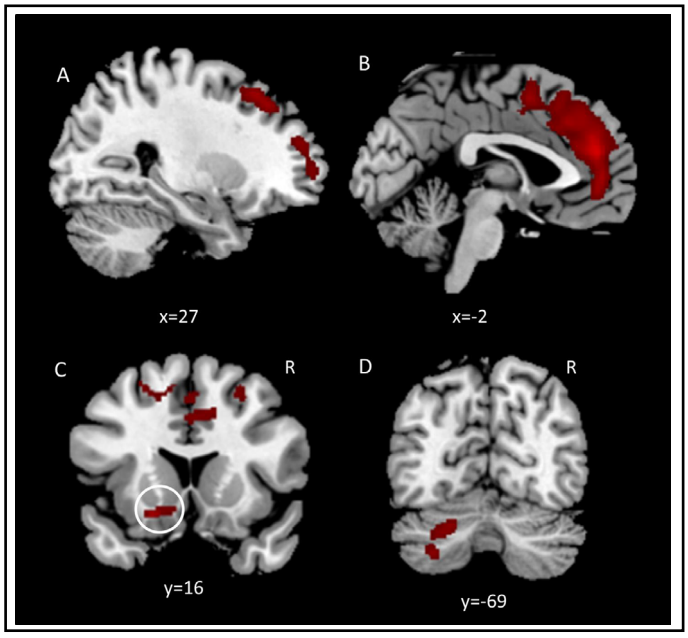

Fig. 2. Clusters showing significant time by group interaction in a whole brain VBM contrasts (p<0.05 (FWE corrected), k > 200, corrected for non-stationary smoothness). Panel A: Right middle frontal gyrus BA 8 (Cluster 5), BA 9/10 (Cluster 2); Panel B: Anterior cingulate cortex (ACC (Cluster 1); Panel C: Nucleus accumbens (Cluster 7, Panel C); Panel D: Cerebellar crus I/II and cerebellar VI (Cluster 4, Cluster 6)

Cognitive data

Multilevel analyses including *Age*, *Time* and *Group* as well as a T*ime by Group Interaction* as predictors revealed a significant main effect of *Time* for the following tasks: Dual-2-back, word-non-word cued recall, face-name cued recall, mental rotation, spatial navigation (tunnel task), perspective taking (all $p<0.05$). In each of these tasks, participants improved their performance from first to second measurement occasion, which is most likely due to a retest effect. There was no significant main effect of *Group* or *Time by Group Interaction* in any of the cognitive tasks.

Structural MR data

A whole-brain VBM interaction analysis revealed several regions showing a significant time by group interaction (Fig. 2; Table 3). Significant clusters were observed in the following regions: The anterior cingulate cortex (ACC)/ventromedial prefrontal cortex (vmPFC), the left and right middle frontal gyrus (BA 8 and BA 9/10), the cerebellum (VI and crus I/II), and the nucleus accumbens.

With exception for one cluster in cerebellar crus I/II, all clusters showed a similar interaction pattern (interaction plots for all seven clusters are shown Fig. 3): Strong group differences were present at TP1, with smaller volumes in the peripartal group. At TP2,

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Table 3. Clusters showing significant group by time interaction ($p < 0.05$ (FWE corrected) cluster threshold $k > 200$, corrected for non-stationary smoothness). ACC = Anterior cingulate cortex, vmPFC = ventromedial prefrontal cortex

Cluster	Region	Hemisphere	MNI Coordinate (x, y, z)	Volume (voxels)
1	ACC/vmPFC	-	-5,47,19	6733
2	Middle frontal gyrus (BA 9/10)	R	36,47,24	1462
3		L	-27,39,30	162
4	Cerebellar VI	L	-21,-72,-29	543
5	Middle frontal gyrus (BA 8)	R	26,26,48	473
6	Cerebellar crus I/II	L	-32,-67,-45	157
7	Nucleus accumbens	L	-18,18,-14	156

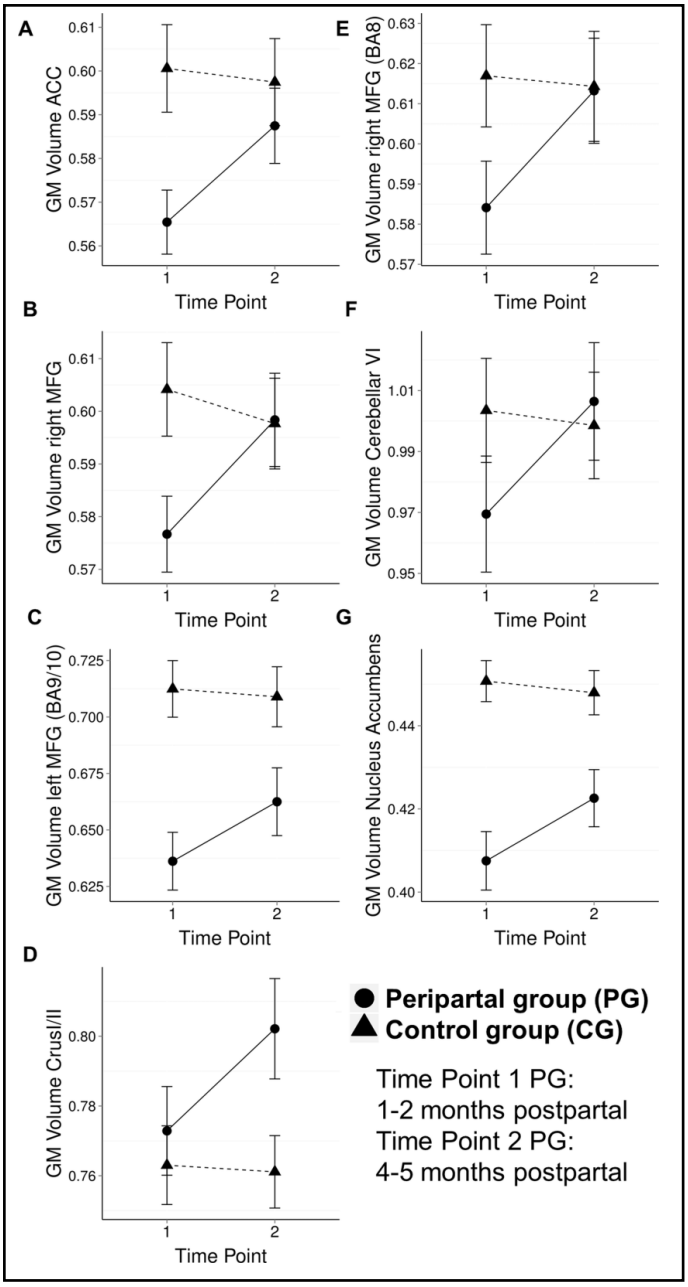

Fig. 3. Time by group interaction of gray matter (GM) volume in the significant clusters. Error bars represent standard error (SE). Panel A: Anterior cingulate cortex (ACC) Cluster 1; Panel B: Right middle frontal gyrus (BA 9/10) Cluster 2; Panel C: Left middle frontal gyrus (BA 9/10) Cluster 3; Panel D: Cerebellar crus I/II Cluster 4; Panel E: Right middle frontal gyrus (BA 8) Cluster5; Panel F: Cerebellar VI Cluster 6; Panel G: Nucleus accumbens Cluster 7

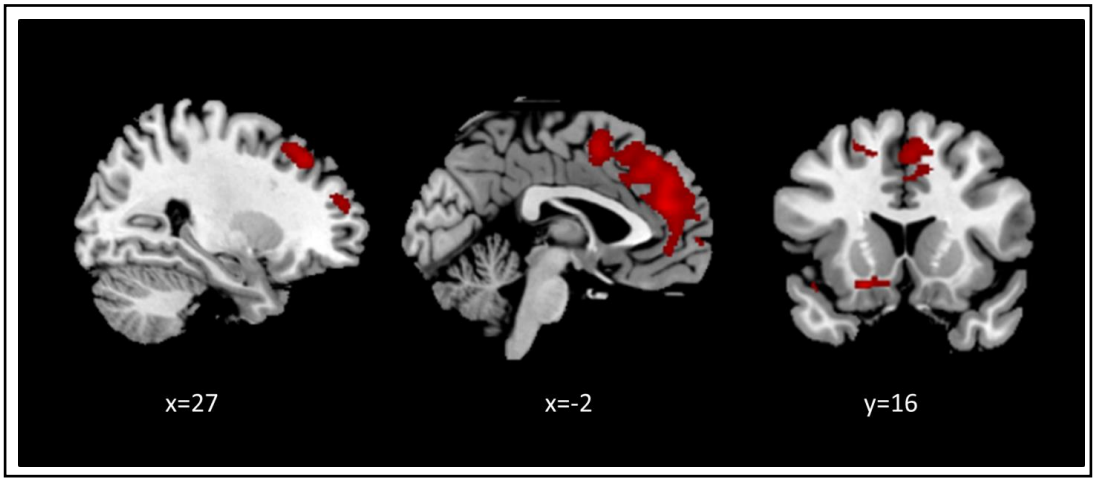

Fig. 4. Clusters showing significant time by group interaction in a whole brain VBM contrast with age-matched groups (p<0.05 (FWE corrected), k (expected voxels per cluster) > 19, corrected for non-stationary smoothness)

group differences in gray matter volume were reduced and for most regions non-significant, due to volume increases from TP1 to TP2 in the peripartal group, while there was no volume change in the control group. The only region showing a qualitatively different interaction pattern, the cerebellar crus I/II, is shown in panel D of Fig. 3. For this region, similar gray matter volume between the groups was observed at TP1. A gray matter increase in the peripartal group, but not in the control group leads to a difference in gray matter volume between the groups at TP2 with larger volumes in the peripartal group.

The whole-brain VBM interaction analysis of the age-comparable subsamples revealed a qualitatively similar result to the whole group (Fig. 4), with the exception that no cerebellar regions became significant in this analysis. All other clusters of the main analysis (Table 3, Fig. 2) were approximately the same in this subgroup analysis. The mean gray matter volume of all significant clusters in the subgroup analysis increased

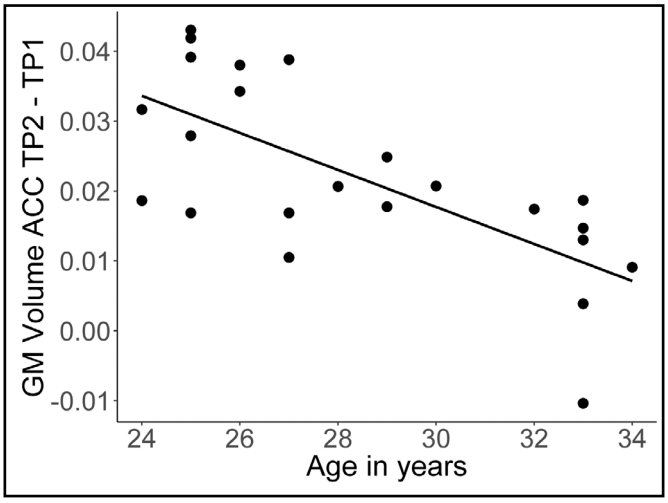

Fig. 5. Negative correlation of age and postpartal anterior cingulate cortex (ACC) gray matter (GM) difference scores in the peripartal group (r(22) = -.70 p<0.001)

Table 4. Correlation coefficient and p-value of change in gray matter volume for significant clusters in the VBM whole-brain time by group interaction and age. Bold: p < 0.007 (corrected for multiple comparisons), Italic: p < 0.05 (uncorrected); ACC = Anterior cingulate cortex, vmPFC = ventromedial prefrontal cortex

Cluster	r (p)
1 ACC/vmPFC	**-0.70 (< 0.001)**
2 Right middle frontal gyrus (BA 9/10)	**-0.57 (0.004)**
3 Left middle frontal gyrus (BA 9/10)	-0.39 (0.059)
4 Cerebellar VI	-0.10 (0.652)
5 Right middle frontal gyrus (BA 8)	**-0.63 (< 0.001)**
6 Cerebellar crus I/II	-0.01 (0.981)
7 Nucleus accumbens	*-0.53 (0.008)*

from TP1 to TP2 in the PG ($t(16) = -11.03$, $p<0.001$), but not in the CG ($t(16) = 1.09$, $p = 0.29$). The difference in volume was significant at TP1 ($t(32) = -2.44$, $p = 0.02$), but not at TP2 ($t(32) = 0.87$, $p = 0.39$).

Relationship between MR data and age

Except for the two cerebellar regions, gray matter increase in the peripartal group was negatively correlated with age in all regions derived from the VBM interaction analysis (correlation of gray matter increase in the ACC and age is shown in Fig. 5, Spearman correlation coefficients are given for all clusters in Table 4). The younger the participants in the peripartal group were, the stronger their gray matter increased from TP 1 to TP 2.

Discussion

The present study used a longitudinal control group design to investigate postpartal neural plasticity. We found that gray matter volume increased in large parts of the brain, especially in frontal and cerebellar regions, within the first months following pregnancy. The interaction pattern between group and time suggests that this is an expression of renormalization following pregnancy-related volume decreases. In contrast to the widespread and pronounced brain structural changes, group differences in cognitive variables were not statistically significant.

Our results support the assumption that pregnancy-related decreases in brain volume renormalize during the first months postpartum. The interaction pattern of the whole-brain VBM analysis indicates a renormalization of brain structure rather than additional gains in the new mothers. One to two months after delivery, mothers had significantly lower gray matter volume compared to women that have not been pregnant before. This discrepancy diminishes (and disappears in some of the regions) within the following three to four months, due to an increase in gray matter volume in the new mother's brains. Unfortunately, the two groups in the present investigation differ in age (the peripartal group was on average four years older than the control group). As a consequence, remaining group differences at the second measurement time point may be due to incomplete (or still ongoing) renormalization or age-differences between the groups.

Our results replicate and go beyond the previous investigation by Kim and colleagues [16], who described postpartal gray matter volume increases in several brain regions. Besides the improved design including a control group, our study used a more conservative significance level to identify brain regions showing the strongest interaction effects. When lowering the threshold to $p<0.05$ (FDR corrected) used by Kim et al., we observe significant time by group interactions in almost the entire brain, demonstrating the great extent of the postpartal neural rebuilding.

Our findings are in partial contradiction to the assumption of long-lasting pregnancy-related brain volume decreases suggested by Hoekzema et al. [15]. Some (but not all) significant clusters in our analysis are located in similar regions as the ones by Hoekzema et al. (e.g., ACC and mid-frontal cortex). The increases in gray matter volume observed within three months after delivery in the present study are in a similar range as the volume decreases Hoekzema et al. describe from pre- to post pregnancy (it should be noted though, that the measurement 2.5 months after delivery in the Hoekzema article was in-between our two postpartal measurements, therefore a direct comparison of the magnitude of change is difficult because it might be highly dependent on the exact postpartal period). The discrepancy between our findings – substantial volume increases in the early postpartal phase – and the ones reported by Hoekzema – stable volume reductions for years after delivery – clearly demonstrates the need to further study postpartal neural change in women.

Possible explanations for the inconsistency are environmental, physiological and behavioral factors causing brain changes in the first years of motherhood. Sleep deprivation, lifestyle changes related to motherhood or physical (e.g., hormonal) changes associated

with breastfeeding and weaning could be associated with decreases in brain volume. These factors could act on brain structure irrespective of and additive to a renormalization of brain volume shortly after delivery. Therefore, these processes have to be differentiated from the early renormalization process our results indicate. They might impact the brain of mothers independently of each other and follow different time courses. In addition it has to be taken into account that the renormalization process itself might depend on internal and external variables, and also differs between brain regions. Gray matter volume increases were strongly negatively correlated with age of the new mother, providing first evidence for inter-individual differences in the postpartal renormalization process. This association is in line with animal studies showing slower and less pronounced plastic changes in the brain structure of older compared to younger individuals [31]. Women in our sample were on average five years younger than the women investigated by Hoekzema et al. This age difference could add to the contradicting findings. The discrepant results highlight that research on pregnancy and postpartal neural change is still in its infancy. Future research should investigate the precise timing of postpartal gray matter increase, its inter-individual variability as well as preceding variables that could help to pinpoint the sources of postpartal neural plasticity.

One powerful explanatory factor for structural brain changes is hormonal variation,

which has been related to neural alterations in women [10, 11, 14]. Endocrine changes during postpartum represent renormalization processes (e.g., rebound of estrogen), as well as novel influences (e.g., prolactin release during lactation). Neural plasticity and hormonal levels during postpartum period might be related, but the nature of this relationship and potential underlying variables influencing hormonal as well as neural changes (such as age) have to be investigated in future studies with larger samples. In addition to hormonal influences, other physiological and psychological processes (e.g., mother-child interaction) as well as environmental effects (living in relationship, working conditions) are likely to influence the mother's brain and initiate growth of specific brain structures. These aspects should be investigated in further studies to disentangle the complex interplay of peripartal behavioural, hormonal and neural change.

In a previous study, we assessed differences in brain structure and cognition in a partially overlapping sample of peripartal and non-pregnant women [32]. In that study we used a cross-sectional approach comparing cognitive and neuroimaging measurements between the two groups. The left striatum showed the strongest volume differences between the peripartal and the control group. The short-term longitudinal approach of the present investigation however, allowed us to test for interaction effects and investigate within-subject change within the first months postpartum. Using this approach revealed additional brain regions that had potentially decreased during pregnancy. This indicates that regions showing the greatest differences between the two groups shortly after delivery are not necessarily identical to brain regions that show the strongest increases in the first months postpartum and vice versa (although the striatal region that showed cross-sectional differences also showed strong interaction effects over time after pregnancy).

The observed brain structural changes could underlie cognitive decreases during pregnancy, which have been described in some previous investigations [3, 33], but see for example [7]. However, we did not observe significant group by time interactions in the cognitive tasks. This disagreement with previously reported results may be due to selection effects within the peripartal group: As the peripartal women in the present study participated in several sessions, scheduled during late pregnancy and shortly after delivery, the sample was presumably positively selective with regard to health, stress and negative mood. Accordingly our participants might have had better general and actual health and lower stress and negative mood levels compared to the general population of pregnant women in western countries. These criteria could be related to cognitive functioning [e.g., 34]. Such a selection effect (and therefore mediator variables such as stress and negative mood) might also help to explain previous inconsistencies in findings of cognitive decreases during and after pregnancy.

We would like to outline particular advantages and disadvantages of the present investigation. A longitudinal control group design enabled us to compare within-person changes in brain structure in the peripartal group against a control group. We only included women that were pregnant for the first time and did not have any psychological or medical condition at recruitment; therefore the group was very homogeneous and well-controlled with regard to important variables. We also controlled for hormonal influences in the control group, by only including women that did not use hormonal contraceptives for the last six months and by keeping cycle phase at time of measurement constant.

Nevertheless, the precursors and causes of postpartal neural plasticity cannot be comprehensively understood based on the present study. It proved difficult to find women in their late twenties and early thirties that did not use hormonal contraceptives (or scanner-incompatible intrauterine devices) and never had been pregnant. As a consequence, women in the control group were on average younger than those in the peripartal group. Differences in gray matter volume could also be driven by the age difference and the effects of age may go beyond the effect we controlled for by including age as a covariate of no interest in the whole-brain VBM analysis. However, the directionality of the age effect (the peripartal group being older) would if anything been expected to weaken our finding of gray matter increases in the peripartal group. Moreover, our analysis on age-matched subsamples (N = 17 per group) revealed comparable results. Nevertheless, the results of the present study should be replicated with larger age-matched groups.

The present findings may not be generalizable to all first-time mothers (or pregnant women) in western countries, because our sample was small and presumably highly positive selective with regard to education, health and psychological well-being during and around pregnancy. This might have influenced the lack of group differences in cognitive performance. However, the neural findings, which are the key issue of the present investigation, should have been rather weakened by such a selection effect.

Conclusion

To summarize, the present study used a longitudinal control group design to investigate peripartal neural plasticity. We found widespread gray matter volume increases in the first months postpartally, which in general seem to reflect a renormalization pattern of brain structure after pregnancy-related decreases. At least for younger women, pregnancy-related volume decreases in a number of brain regions seem *not* to persist in full amount for years after delivery. Age was negatively correlated with postpartal gray matter increases in most brain regions. Despite the strong effects at the brain structural level, no cognitive differences between the groups were observed. These findings demonstrate the plasticity of the adult human brain as well as its ability to compensate for structural remodeling. Further studies are needed to investigate antecedents and consequences of postpartal brain changes.

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Disclosure Statement

The authors declare that they have no conflict of interests.

References

1 Brett M, Baxendale S: Motherhood and memory: a review. Psychoneuroendocrinology 2001;26:339-362.
2 Cuttler C, Graf P, Pawluski JL, Galea LA: Everyday life memory deficits in pregnant women. Can J Exp Psychol 2011;65:27–37.
3 Glynn LM: Giving birth to a new brain: hormone exposures of pregnancy influence human memory. Psychoneuroendocrinology 2010;35:1148–1155.
4 Henry J D, Rendell PG: A review of the impact of pregnancy on memory function. J Clin Exp Neuropsychol 2007;29:793–803.
5 Workman JL, Barha CK, Galea LA: Endocrine substrates of cognitive and affective changes during pregnancy and postpartum. Behav Neurosci 2012;126:54–72.
6 Crawley R, Grant S, Hinshaw K: Cognitive Changes in Pregnancy: Mild Decline or Societal Stereotype? Appl Cogn Psychol2008;22:1142–1162.
7 Logan DM, Hill KR, Jones R, Holt-Lunstad J, Larson MJ: How do memory and attention change with pregnancy and childbirth? A controlled longitudinal examination of neuropsychological functioning in pregnant and postpartum women. J Clin Exp Neuropsychol 2014;36:528–539.
8 Schiller CE, Meltzer-Brody S, Rubinow DR: The role of reproductive hormones in postpartum depression. CNS Spectrums 2015;20:1–12.
9 Comasco E, Sundström-Poromaa I: Neuroimaging the Menstrual Cycle and Premenstrual Dysphoric Disorder. Curr Psychiatry Rep 2015;17:1-10.
10 Erickson K I, Colcombe S J, Raz N, Korol D L, Scalf P, Webb A, Cohen NJ. McAuley E, Kramer A F: Selective sparing of brain tissue in postmenopausal women receiving hormone replacement therapy. Neurobiol Aging 2005; 26: 1205–13. DOI:10.1016/j.neurobiolaging.2004.11.009
11 Lisofsky N, Mårtensson J, Eckert A, Lindenberger U, Gallinat J, Kühn S: Hippocampal volume and functional connectivity changes during the female menstrual cycle. Neuroimage 2015;118:154-162.
12 Peper JS, van den Heuvel M , Mandl RC, Hulshoff Pol HE, van Honk J: Sex steroids and connectivity in the human brain: a review of neuroimaging studies. Psychoneuroendocrinology 2011;36:1101-1113.
13 Pletzer B, Kronbichler M, Kerschbaum H: Differential effects of androgenic and anti-androgenic progestins on fusiform and frontal gray matter volume and face recognition performance. Brain Res 2015;1596:108–115.
14 Lisofsky N, Riediger M, Gallinat J, Lindenberger U, Kühn S: Hormonal contraceptive use is associated with neural and affective changes in healthy young women. Neuroimage 2016;134:597-606.
15 Hoekzema E, Barba-Müller E, Pozzobon C, Picado M, Lucco F, García-García D, Soliva JC, Tobeña A, Desco M, Crone EA, Ballesteros A, Carmona S, Villaroya O: Pregnancy leads to long-lasting changes in human brain structure. Nature Neurosci 2017;20:287-296.
16 Kim P, Leckman JF, Mayes L C, Feldman R, Wang X, Swain JE: The plasticity of human maternal brain: longitudinal changes in brain anatomy during the early postpartum period. Behav Neurosci 2019;124:695–700.
17 Oatridge A, Holdcroft A: Change in brain size during and after pregnancy: study in healthy women and women with preeclampsia. Am J Neuroradiol 2002;23:19–26.
18 Schmiedek F, Lövdén M, Lindenberger U: Hundred Days of Cognitive Training Enhance Broad Cognitive Abilities in Adulthood: Findings from the COGITO Study. Frontiers in Aging Neuroscience 2010;2:1–10.
19 Mårtensson J, Lövdén M: Do intensive studies of a foreign language improve associative memory performance? Frontiers in Psychology 2011;2:12.
20 Jaeggi SM, Studer-Luethi B, Buschkuehl M, Su YF, Jonides J, Perrig WJ: The relationship between n-back performance and matrix reasoning - implications for training and transfer. Intelligence 2010;38:625–635.
21 Vandenberg SG, Kuse AR: Mental rotations, a group test of three-dimensional spatial visualization. Percept Mot Skills 1978;47:599–604.
22 Gramann K, Müller HJ, Eick EM, Schönebeck B: Evidence of separable spatial representations in a virtual navigation task. J Exp Psychol Hum Percept Perform 2005;31:1199–1223.
23 Guilford JP, Zimmerman WS: The Guilford-Zimmerman Aptitude Survey. J Appl Psychol 1948;32:24-34.
24 Hegarty M: A dissociation between mental rotation and perspective-taking spatial abilities. Intelligence 2004;32:175–191.

25 King J A, Colla M, Brass M, Heuser I, von Cramon D: Inefficient cognitive control in adult ADHD: evidence from trial-by-trial Stroop test and cued task switching performance. Behav Brain Funct 2007;3:42.
26 Bates D, Maechler M, Bolker B, Walker S: Fitting Linear Mixed-Effects Models Using lme4. J Stat Softw 2015;67:1-48.
27 Cox J, Holden J, Sagovsky R: Detection of postnatal depression. Development of the 10-item Edinburgh Postnatal Depression Scale. Br J Psychiatry 1987;150:782–787.
28 Cohen S, Williamson GM: Perceived stress in a probability sample of the United States, in Spacapan S, Oskamp S (eds): The social psychology of health: Claremont Symposium on Applied Social Psychology. Newbury Park, CA, Sage, 1988, pp 31-67.
29 Fydrich T, Sommer G, Tydecks S, Brähler E: Fragebogen zur sozialen unterstützung (F-SozU): Normierung der Kurzform (K-14). Z Med Psychol 2009;18:43-48.
30 Hayasaka S, Nichols TE: Combining voxel intensity and cluster extent with permutation test framework. Neuroimage 2004;23:54–63.
31 Lövdén M, Wenger E, Mårtensson J, Lindenberger U, Bäckman L: Structural brain plasticity in adult learning and development. Neurosci Biobehav Rev 2013;37:2296–2310.
32 Lisofsky N, Wiener J, de Condappa O, Gallinat J, Lindenberger U, Kühn S: Differences in navigation performance and postpartal striatal volume associated with pregnancy in humans. Neurobiol Learn Mem 2016;134:400-407.
33 Sharp K, Brindle PM, Brown MW, Turner GM: Memory loss during pregnancy. Br J Obstet Gynaecol 1993;100:209–215.
34 McEwen BS, Sapolsky RM: Stress and cognitive function. Curr Opin Neurobiol 1995;5:205-216.