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Research Article

Cerebral Morphometric Markers and Molecular Profiles in Pregnant Women: A Cross-Sectional Study

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Abstract

Pregnancy induces a range of hormonal and physiological changes and also affect the brain. Yet the specific cerebral morphometric markers and their associated molecular profiles throughout pregnancy remain poorly understood. In this study, we investigated the cerebral morphometric changes in 23 pregnant women using T1-weighted MRI scans, with pregnancy progression quantified by post-menstrual age (PMA). We performed a whole-brain regression analysis to examine how gray matter volume (GMV) was influenced by PMA, and further explored the molecular profiles of these changes by integrating GMV findings with the JuSpace toolbox. Our analysis revealed that with PMA increased, there was a significant reduction in the left medial frontal gyrus (MFG) GMV, suggesting structural brain changes associated with pregnancy progression. Spatial correlation analyses did not reveal any significant associations between neurotransmitter distribution and the observed GMV changes. Gene enrichment analysis pointed to an important molecular shift: protein binding was the most significantly enriched term during pregnancy. This suggests that molecular mechanisms related to protein binding may play a crucial role in the neurobiological adaptations observed during pregnancy. In conclusion, our findings provide new insights into how pregnancy is associated with alterations in both brain structure and molecular profiles. The decreased GMV in the left MFG and the changes in molecular functions contribute to our understanding of the neural and biological mechanisms underlying pregnancy. These findings offer a foundation for future research into maternal brain health and the long-term effects of pregnancy on brain structure and function.

Keywords

Pregnancy, Left Medial Frontal Gyrus, Neurotransmitter, Gene Enrichment

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1. Introduction

1.1. Pregnancy and Brain Insults

Pregnancy is a transformational period in women's life, accompanied by atypical neurobiological changes. Almost all body systems are affected during pregnancy, even involving physiological changes for a long time after deliver [1, 2]. Studies have demonstrated that pregnancy causes a decline in women's general cognitive function, memory, executive function, and other cognitive abilities, all of which are linked to changes in brain structure during this period [3]. Any brain regions that change in volume during pregnancy exhibit a pattern of reduction [4], with significant decreases in gray matter volume (GMV) persisting for at least two years post-pregnancy [5]. Researchers have found that pregnancy can lead to changes in the frontal lobe, especially the middle frontal gyrus (MFG) [5, 6]. Structural changes are associated with functional alterations, and a decrease in MFG GMV is thought to contribute to emotional disorders such as depression [7] and anxiety [8], which may indicate the impact of pregnancy on the emotional well-being of pregnant women.

1.2. Pregnancy and Neurotransmitter Changes

The maternal brain plays a pivotal role in the fundamental physiological changes during pregnancy, involving the network organization and molecular mechanisms within the neuroendocrine system. These changes may contribute to emotional disorders such as depression as the mother adapts to new roles [9]. Serotonin (5-HT), a crucial neurotransmitter, is implicated in various psychiatric disorders, including depression, anxiety, panic attacks, and obsessive-compulsive disorder [10, 11]. Additionally, the metabotropic glutamate receptor 5 (mGluR5) is significantly linked to the pathophysiology of anxiety and has been suggested as a potential therapeutic target for this condition [12]. Animal studies have shown that serotonin levels in the brains of female rats during the third trimester are below normal, which may significantly contribute to the prevalence of emotional disorders in pregnant women [13]. Therefore, changes in neurotransmitter levels during pregnancy are critical for brain regulation and essential for understanding the neuropsychiatric issues related to pregnancy.

1.3. Genetic Changes in Pregnancy

Compared to the pre-pregnancy period, the proportion of cell types and gene expression in healthy women undergoes extensive systemic changes [14]. During pregnancy, many hormone levels fluctuate significantly, including sex steroids and estrogen, to support the pregnancy [15, 16]. Pregnancy affects not only the woman but also the fetus, with substances transported via the placenta influencing the mother's brain. Placental secretory molecules play a crucial role in initiating physiological processes such as labor and lactation. Two types of placental genes—imprinted genes and placenta-specific genes—are particularly important in their interaction with the maternal brain [17].

1.4. The Present Study

In this study, T1 MRI scans were used to explore the effects of pregnancy on brain structure. Additionally, we examined the molecular profiles of pregnancy by integrating morphometric data with open-source atlases of neurotransmitters and genes. This approach may help us hypothesize about the potential impact of these morphometric and molecular features on the emotional stability of pregnant women throughout their pregnancy.

2. Methods

2.1. Participants and Data Acquisition

This study included 23 pregnant women, and the basic clinical information of the participants is provided in Table 1. All data were collected in the Department of Radiology at Tongji Medical College, Huazhong University of Science and Technology. T1 MRI scans were performed using a 3T scanner (Signa HDxt; General Electric Medical Systems) with the following parameters: repetition time/echo time (TR/TE), 600 ms/20 ms; flip angle, 90°; slice thickness, 6 mm; field of view (FOV), 240 mm; matrix size, 256 × 256 pixels; and acquisition time, 3-5 minutes. This study was approved by the Ethics Review Committee at Beijing University of Technology.

Table 1. *Basic clinical information for all subjects.*

Participant ID	Age	Scan PMA (weeks)	Scan status	TIV (mm^3)
sub001	35	33.86	2 days after Postpartum	1439.6
sub002	31	38.43	Prenatal	1471.7
sub003	36	29.29	Prenatal	1317.8
sub004	24	37.71	2 days after Postpartum	1304.5

Participant ID	Age	Scan PMA (weeks)	Scan status	TIV (mm^3)
sub005	30	34.00	Prenatal	1406.5
sub006	30	26.29	Prenatal	1281.3
sub007	27	27.57	Prenatal	1328.2
sub008	29	35.29	Prenatal	1305.3
sub009	31	32.14	Prenatal	1551.0
sub010	23	37.00	1 day after Cesarean section	1418.5
sub011	23	29.14	2 days after Cesarean section	1217.7
sub012	35	26.57	Prenatal	1107.5
sub013	31	39.00	Prenatal	1481.2
sub014	33	15.43	Prenatal	1307.0
sub015	33	14.71	Prenatal	1183.2
sub016	41	34.43	Prenatal	1492.5
sub017	30	31.00	Prenatal	1202.4
sub018	30	35.86	4 days after Cesarean section	1176.0
sub019	34	30.71	1 day after Cesarean section	1332.2
sub020	23	28.71	Prenatal	1445.1
sub021	27	39.29	1 day after Postpartum	1502.6
sub022	33	33.71	2 days after Postpartum	1408.0
sub023	34	36.43	3 days after Postpartum	1391.4

Note: We do not expect changes in the brain structure to affect the results of the experiment for up to four days after birth, and the woman after birth is considered to be pregnant, and the post-menstrual age (PMA) at the time of the scan is the PMA at the time of birth. TIV: Total intracranial volume.

2.2. Data Preprocessing and Statistical Analysis

MRI images were preprocessed using CAT12, which included skull stripping, registration, standardized segmentation, and smoothing with an 8 mm Gaussian kernel at Full Width at Half Maximum [18]. Additionally, total intracranial volume (TIV) and gray matter volume (GMV) were calculated. In group analyses, a whole-brain regression was performed to assess the relationship between GMV and post-menstrual age (PMA), adjusting for age and TIV as covariates. Results were evaluated using a voxel-wise threshold of $p < 0.005$ (uncorrected) and a cluster significance threshold of $p < 0.05$, corrected for family-wise error (FWE) based on Gaussian random field theory, as implemented in SPM. It is important to note that the T map utilized in conjunction with the JuSpace neurotransmitter atlases was not thresholded.

JuSpace (https://github.com/juryxy/JuSpace) allows for spatial correlation analyses between cross-modal neuroimaging data [19, 20]. To determine the neurochemical basis underlying the morphological alterations as pregnancy progresses, we calculated the spatial correlation of the SPM T maps derived from whole-brain regression of GMV against PMA and JuSpace maps of serotonin receptor (including 5-HT1a_1, 5-HT1a_2, 5-HT1b_1, 5-HT1b_2, 5-HT2a_1, 5-HT2a_2, 5-HT4); cannabinoid type I receptor (CB1); dopamine receptor (including D1, D2_1, D2_2); dopamine synthesis capacity receptor (FDOPA); gamma-aminobutyric acid receptor (including GABAa_1, GABAa_2); mu opioid receptor (including MOR_1, MOR_2); metabotropic glutamate receptor (including mGluR5_1, mGluR5_2, mGluR5_3); dopamine transporter (DAT); noradrenaline transporter (NAT); serotonin transporter (including SERT_1, SERT_2, SERT_3); vesicular acetylcholine transporter (including VAChT_1, VAChT_2, VAChT_3). Pearson correlation coefficients between the SPM T maps and these 27 neurotransmitter maps were calculated.

Correlation analyses was performed using gene expression matrix and SPM T map (using AAL 116 atlas). The gene expression data were obtained from the Allen atlas (http://human.brain-map.org/) and subsequently aligned to the Brainnetome atlas using the “abagen” toolkit (https://github.com/rmarkello/abagen). We selected the most

related genes with a threshold p < 0.00001.

3. Results

3.1. Effect of Pregnancy on Gray Matter Volume in the Brain

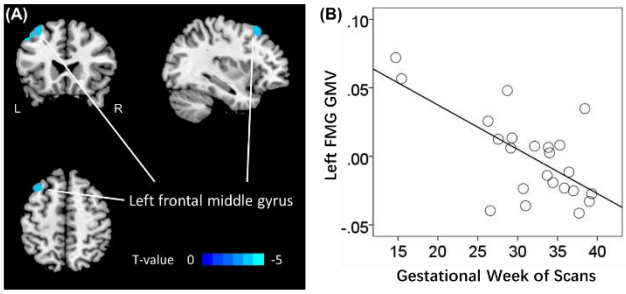

Figure 1. *Brain region showing GMV in correlation with PMA. (A) Left frontal middle gyrus (FMG) GMV showing negative correlation with PMA; (B) Scatter plot of correlation between PMA and the left MFG GMV. PMA: post-menstrual age, TIV: total intracranial volume, GMV: gray matter volume. Note that the residuals are plotted here with age and TIV accounted for in the regression.*

Whole-brain linear regression of the GMV against PMA reveal a cluster in the left frontal middle gyrus (MFG, x, y, z = -46, 26, 48; T = -5.86, 1390 mm^3; Figure 1A) showed a significant negative correlation with the PMA. The left MFG GMV was significantly correlated with gestational age (r = -0.796, p < 0.001; Figure 1B) in a linear regression with age and TIV as covariates.

Table 2. *Correlation between 27 neurotransmitters and T map of whole-brain regression of the GMV against PMA.*

Characteristic		Correlation
5-HT1a_1	r	-0.04
	p	0.717
5-HT1a_2	r	-0.03
	p	0.830
5-HT1b_1	r	-0.10
	p	0.447
5-HT1b_2	r	0.02
	p	0.780
5-HT2a_1	r	0.06
	p	0.486
5-HT2a_2	r	0.08
	p	0.529
5-HT4	r	0.30
	p	0.741
CB1	r	-0.05
	p	0.775
D1	r	-0.02
	p	0.829
D2_1	r	-0.07
	p	0.440
D2_2	r	-0.05
	p	0.586
DAT	r	-0.06
	p	0.553
FDOPA	r	-0.06
	p	0.506
GABAa_1	r	0.07
	p	0.433
GABAa_2	r	0.09
	p	0.521
MU_1	r	-0.05
	p	0.807
MU_2	r	-0.06
	p	0.819
NAT	r	0.02
	p	0.798
SERT_1	r	-0.06
	p	0.508
SERT_2	r	-0.04
	p	0.661
SERT_3	r	0.08
	p	0.373
VAChT_1	r	-0.07
	p	0.432
VAChT_2	r	-0.00
	p	0.990
VAChT_3	r	0.01
	p	0.943
mGluR5_1	r	-0.02
	p	0.918

Characteristic		Correlation
mGluR5_2	r	-0.01
	p	0.964
mGluR5_3	r	-0.12
	p	0.406

PMA: post-menstrual age, GMV: gray matter volume.

3.2. Neurotransmitters Associated with GMV Characteristic of Pregnancy

Cross-region spatial correlation analyses revealed no significant link between the GMV correlates of pregnancy progress and neurotransmitters (all p's > 0.373, Figure 2). The most closely were serotonergic 5HT1b_1 and mGluR5_3. Table 2 listed the statistics of all the 27 neurotransmitters.

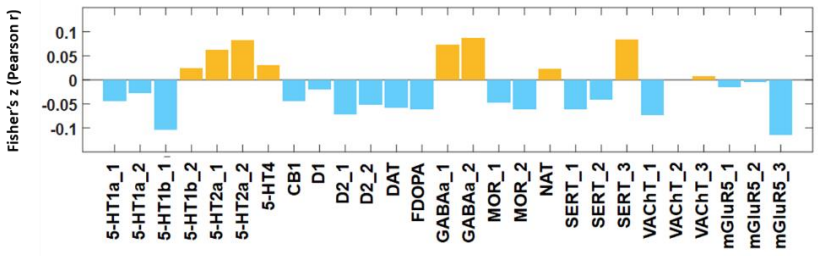

Figure 2. *Correlations between T values of whole-brain regression of the GMV against PMA and neurotransmitter distribution maps, orange/blue each represents positive/negative Pearson's. Abbreviations: 5-HT,5-hydroxytryptamine (serotonin); CB1, cannabinoid type 1; D, dopamine receptor; DAT, dopamine transporter; FDOPA, fluorodopa, an analog of L-DOPA to assess the nigrostriatal dopamine system; GABAa, gamma-aminobutyric acid a; MOR, mu opioid receptor; NAT, noradrenaline transporter; SERT, serotonin transporter; VAChT, vesicular acetylcholine transporter; mGluR5, metabotropic glutamate type 5. PMA: post-menstrual age, GMV: gray matter volume.*

3.3. Gene Enrichment Associated with GMV Characteristic of Pregnancy

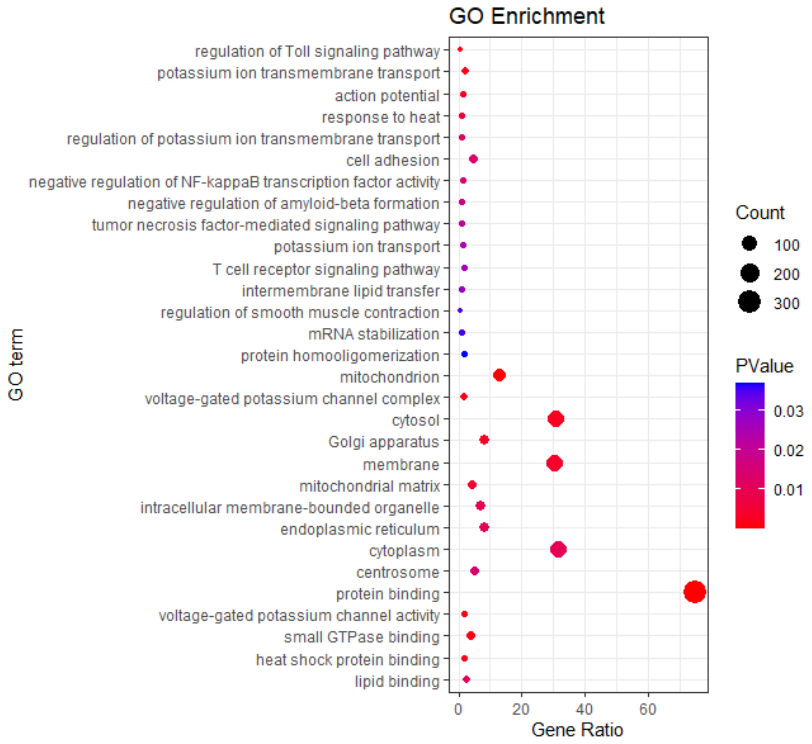

Figure 3. *Bubble map of gene enrichment. The horizontal coordinate is the ratio of the number of genes associated with the Go term to the total number of target genes in the target gene set, %. The ordinate lists Go terms for significant gene enrichment, with the first 15 terms representing a specific Biological Process (BP), and the 16th to 25th terms being Cellular Component (CC). Terms 26-30 stand for Molecular Function (MF).*

441 genes were selected for gene enrichment. Figure 3 shows the analysis results of gene ontology (Go). The most significantly enriched Go terms were mainly concentrated in protein binding, cytoplasmic matrix, cytoplasmic membrane and cytoplasm, among which the concentration ratio of protein binding was the highest, indicating that protein interaction functions were important during pregnancy progress.

4. Discussion

In this study, the left MFG GMV was negatively correlated with PMA. Meanwhile, spatial correlation analyses revealed that the cerebral morphometric features showed a near-significant correlation with 5-HT1b and mGluR5. Gene enrichment analyses identified that genes associated with cerebral morphometric features were primarily concentrated in protein binding, cytoplasmic matrix, cytoplasmic membrane, and cytoplasm. These may play roles in metabolism, signal transduction, and enzyme regulation mechanisms.

The human brain undergoes a series of changes during pregnancy, primarily characterized by a widespread reduction in gray matter volume (GMV) [2]. A longitudinal follow-up study revealed that the GMV of the frontal gyrus in women was higher before pregnancy than after [5]. Additionally, another study indicated that the brain regions most affected by pregnancy were concentrated in the frontal cortex and temporal lobes [6]. These findings align with the current work, which also observed a decrease in the left medial frontal gyrus (MFG) GMV during pregnancy, consistent with prior research. The medial frontal gyrus is associated with emotion regulation [21, 22] and plays a critical role in depression [23] and schizophrenia [24]. Although the maternal brain undergoes structural changes due to basic behavioral adaptation during pregnancy, this neural plasticity renders the maternal brain more susceptible to mental disorders, such as depression, anxiety, and puerperal psychosis [9, 25].

The decrease in GMV may be related to processes such as synaptic pruning, neuronal connectivity, or cell proliferation. Studies have shown that during pregnancy and the perinatal period, rodent brain cells experience both proliferation and volume reduction [26]. The 5-HT1b receptor inhibits the release of several neurotransmitters, including serotonin, GABA, acetylcholine, and glutamate. Reduced activity of the 5-HT1b receptor may lead to increased impulsivity [27]. Another study also found that dysfunction of the 5-HT1b receptor can increase susceptibility to depression [11]. Similarly, mGluR5, a receptor involved in various mental disorders, plays a role in conditions such as anxiety, depression, and schizophrenia. Glutamate exerts excitatory effects by acting on ionotropic or metabolic glutamate receptors on the cell surface, and dysfunction of mGluR5 may contribute to anxiety, depression, and other psychiatric conditions [28]. Thus, the reduction of both 5-HT1b and mGluR5 in the brain may lead to emotional disorders such as depression and impulsivity, which could be significant factors contributing to the emotional instability observed in pregnant women.

In the Gene Ontology (GO) terms enrichment analysis, genes related to protein binding are highly enriched. This suggests dynamic adjustments in intracellular molecular interactions during pregnancy, such as the assembly of signal transmission complexes and regulation of enzyme activity [29, 30]. Throughout pregnancy, both protein expression and cellular metabolism become more active [31-33]. For instance, in rodent studies, levels of estradiol and progesterone have been found to increase during pregnancy in several brain regions, including the hypothalamus, preoptic area, hippocampus, frontal cortex, and cerebellum. Importantly, these changes in hormone expression are tissue-specific [34].

5. Limitations and Conclusion

Several limitations should be considered in this study. First, the MRI data were obtained from routine clinical scans, which were not originally intended for scientific research. As a result, the image slices were relatively thick (6 mm), which may have introduced errors. Second, this is a cross-sectional study rather than a longitudinal one, meaning it cannot capture the dynamic process of brain changes during pregnancy. Third, the lack of additional scale information limited the exploration of cognitive and affective factors. Moreover, all participants were considered healthy based on their medical history, potentially overlooking the influence of underlying health conditions on the findings.

Future research should utilize higher-resolution imaging techniques and implement longitudinal designs to better investigate the dynamic changes in brain structure during pregnancy and their relationship to emotional stability. Additionally, incorporating a wider range of health statuses in the study could provide valuable insights into how health conditions or individual differences influence brain changes during pregnancy, thus enriching our understanding of the neurobiological mechanisms associated with pregnancy.

In conclusion, this study revealed that the left MFG GMV decreased as pregnancy progressed. The altered cerebral morphometric features were associated with the serotonin and glutamate neurotransmitter systems, and gene expression during pregnancy was significantly enriched in processes related to protein binding.

Abbreviations

PMA	Post-menstrual Age
GMV	Gray Matter Volume
MFG	Medial Frontal Gyrus
TIV	Total Intracranial Volume
FOV	Field of View
5-HT	5-hydroxytryptamine (Serotonin)

CB1	Cannabinoid Type 1
D	Dopamine Receptor
DAT	Dopamine Transporter
FDOPA	Fluorodopa
GABAa	Gamma-Aminobutyric Acid a
MOR	Mu Opioid Receptor
NAT	Noradrenaline Transporter
SERT	Serotonin Transporter
VAChT	Vesicular Ace-tylcholine Transporter
mGluR5	Metabotropic Glutamate Type 5
BP	Biological Process
CC	Cellular Component
MF	Molecular Function

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Author Contributions

Yanan Su: Conceptualization, Formal Analysis, Methodology, Software, Visualization, Writing – original draft, Writing – review & editing

Xiaohang Ren: Data curation, Formal Analysis, Software, Validation, Writing – review & editing

Shufang Li: Data curation, Project administration, Resources, Validation, Writing – review & editing

Guangfei Li: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Methodology, Project administration, Validation, Visualization, Writing – review & editing

Ziyan Sun: Data curation, Project administration, Resources, Writing – review & editing

Conflicts of Interest

The authors declare that they have no competing interests.

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