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Review

The neuroanatomy of pregnancy and postpartum

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ABSTRACT

Pregnancy and giving birth are exceptional states in a woman's life for many reasons. While the effects of pregnancy and childbirth on the female body are obvious, less is known about their impact on the female brain, especially in humans. The scientific literature is still sparse but we have identified 12 longitudinal neuroimaging studies conducted in women whose brains were scanned before pregnancy, during pregnancy, and/or after giving birth. This review summarizes and discusses the reported neuroanatomical changes during pregnancy, postpartum, and beyond. Some studies suggest that pregnancy is mainly associated with tissue decreases, and a few studies suggest that this tissue loss is mostly permanent. In contrast, the majority of studies seems to indicate that the postpartum period is accompanied by substantial tissue increases throughout the entire brain. Future research is clearly warranted to replicate and extend the current findings, while addressing various limitations and shortcomings of existing studies.

1. Introduction

During pregnancy, the maternal placenta and the developing fetal endocrine system jointly orchestrate the multitude of endocrine changes needed to maintain and promote the pregnancy as well as to prepare a woman for childbirth, breastfeeding, and motherhood. Major endocrine players are sex hormones, such as estrogens and progesterone, which steadily rise throughout pregnancy and drastically drop at parturition (Hill et al., 2001; Rehbein et al., 2020; Skalkidou et al., 2012; Sundstrom-Poromaa et al., 2020). The powerful influence of estrogens and progesterone (amongst other hormones) on the structure of the brain has been vividly demonstrated during puberty, menopause, the menstrual cycle, or when administering hormonal interventions (Bramble et al., 2017; Kranz et al., 2020; Rehbein et al., 2020; Sundstrom-Poromaa et al., 2020). Thus, significant changes in the brain's physical makeup are also bound to occur during pregnancy and after giving birth. However, research in this field is still relatively sparse and the existing findings lack consistency. The aim of this review is to present and summarize the reported gross-anatomical changes in the female brain. To keep the article as focused and concise as possible, it is centered on changes in the human brain, during pregnancy and the postpartum period, that have been detected in longitudinal studies using structural neuroimaging. In other words, we have intentionally excluded animal studies, functional neuroimaging studies, cross-sectional studies as well as longitudinal studies where *all* data was collected after the end of the postpartum period, which is defined as the first six months after giving birth (Romano et al., 2010). Furthermore, for studies that included both healthy women and women with certain clinical conditions, only the outcomes pertaining to the healthy cohort were included in this review. As far as the actual retrieval of the publications is concerned, a search was conducted in PubMed, focusing on title and abstract, using "pregnancy" OR "postpartum" AND "brain" AND ["MRI or "brain imag*" or "gray matter" or "white matter"], AND NOT ["fetal brain" or "congenital"]. The resulting 1,188 articles were inspected and included if they fulfilled the aforementioned criteria. All search results retrieved by July 28, 2022 (NZST) were considered.

Altogether, we have identified 12 studies (Carmona et al., 2019; Hoekzema et al., 2017, 2020; Kim et al., 2010; Lisofsky et al., 2019; Luders et al., 2021a, 2021b, 2021c, 2018, 2020; Martinez-Garcia et al., 2021; Oatridge et al., 2002) that fulfill the aforementioned criteria. Out of the 12 studies, one included time points during pregnancy (Oatridge et al., 2002), five included time points before pregnancy (Carmona et al., 2019; Hoekzema et al., 2017, 2020; Martinez-Garcia et al., 2021; Oatridge et al., 2002), and all included one or more time points after giving birth. Hereafter, time points less than one month after giving birth will be referred to as "early postpartum", and time points between one month and six months after giving birth will be referred to as "late postpartum". Follow-up time points beyond the six-

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Table 1
Overview of the number of participants and time points of brain scanning.

	Study	N	Before	During	After Pregnancy			
					Early Postpartum		Late Postpartum	
					day(s)	< 1 month	> 1 month < 6 months	> 6 months
[1]	Oatridge et al. (2002)	9*	n = 2	n = 2, week 15 n = 4, week 20 n = 3, week 25 n = 4, week 30 n = 1, week 35 n = 9, week 37-42	-	-	n = 9, week 6 n = 8, week 24	n = 3, week 40 n = 3, week 52
[2]	Kim et al. (2010)	19	-	-	-	n = 19, week 2-4	n = 19, month 3-4	-
[3]	Hoekzema et al. (2017)◊◊	25	n = 25	-	-	-	n = 25, week 10	n = 11, years 2.3
[4]	Luders et al. (2018)◊	14	-	-	n = 14, day 1-2	-	n = 14, week 4-6	-
[5]	Lisofsky et al. (2019)	24	-	-	-	n = 24, month 2**	n = 24, month 4-5	-
[6]	Carmona et al. (2019)◊◊	25	n = 25	-	-	-	n = 25, week 10	
[7]	Luders et al. (2020)◊	14	-	-	n = 14, day 1-2	-	n = 14, week 4-6	-
[8]	Hoekzema et al. (2020)◊◊	25	n = 25	-	-	-	n = 25, week 10	n = 11, years 2.3
[9]	Luders et al. (2021a)◊	14	-	-	n = 14, day 1-2	-	n = 14, week 4-6	-
[10]	Luders et al. (2021b)◊	14	-	-	n = 14, day 1-2	-	n = 14, week 4-6	-
[11]	Martinez-Garcia et al. (2021)◊◊	25	n = 25	-	-	-	n = 25, week 10	n = 7, years 6
[12]	Luders et al. (2021c)◊	14	-	-	n = 14, day 1-2	-	n = 14, week 4-6	-

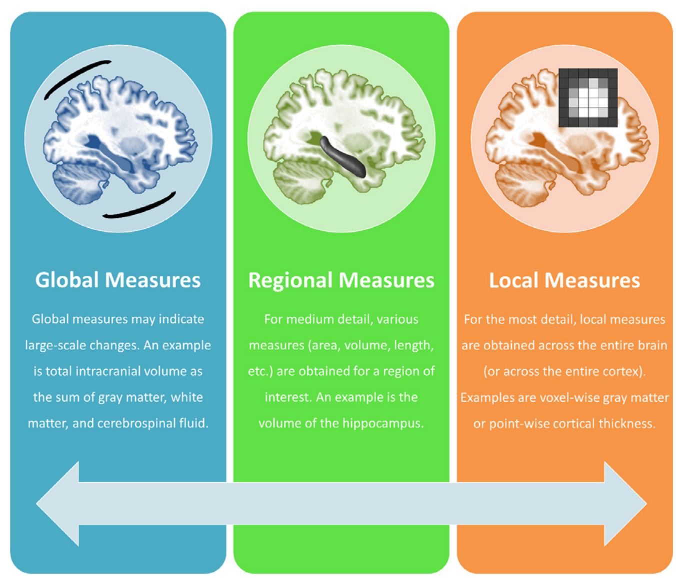
N is the total number of women included in the study; n is the number of women scanned at each time point.
*The study included 9 healthy women and 5 women with preeclampsia; the subsequent n refers to the 9 healthy women.
**The time point is described as "within 2 months following delivery", which could be either early or late postpartum, depending on the individual measures/group mean (unknown).
◊ same sample.
◊◊ same/overlapping sample.

month period after giving birth will be pointed out as such. This classification reflects the more rapid physiological changes occurring within the first few weeks after giving birth, which are followed by slower more gradual changes until maternal physiology reaches pre-pregnancy levels at around six months after giving birth (Romano et al., 2010). Table 1 summarizes the number of participants in each of the 12 studies, the number of time points, as well as the number of participants per time point. Note that the number of study samples is actually smaller than the number of studies as many samples overlap or are identical across studies (i.e., different analyses were conducted using the same dataset).

2. Applied methods

All 12 studies were based on structural magnetic resonance imaging (MRI), which is sufficiently sensitive to identify changes at the scale of a millimeter and as soon as after only a few weeks. While one study focused on brain size and ventricular size (Oatridge et al., 2002) and another on brain age[1] (Luders et al., 2018), the vast majority of studies (Carmona et al., 2019; Hoekzema et al., 2017, 2020; Kim et al., 2010; Lisofsky et al., 2019; Luders et al., 2021a, 2021b, 2021c, 2020; Martinez-Garcia et al., 2021) focused on attributes of gray matter (i.e., the brain's tissue that contains a mix of neuronal synapses, dendrites, and cell bodies, as well as glia cells). Two studies (Carmona et al., 2019; Hoekzema et al., 2017) additionally explored attributes of white matter (i.e., the brain tissue that contains the axons and glia cells).

There were substantial differences across studies in terms of the morphometric approach applied[2], which determined the spatial scale of the findings (Table 2), ranging from global, to regional, to local (Box 1). Global measures include total brain size, brain volume, and



Box 1. Degrees of Regional Specificity: Global, regional, and local measures.

intracranial volume (Carmona et al., 2019; Hoekzema et al., 2017; Luders et al., 2020; Oatridge et al., 2002), total gray and white matter volume (Hoekzema et al., 2017) and total gyral white matter thickness (Carmona et al., 2019), total cortical thickness, surface area, and gyrification as well as total sulcal depth, length, and width (Carmona et al., 2019), and brain age (Luders et al., 2018). Regional analyses were directed at the size or volume (or subvolumes) of so-called regions of interest (ROIs), such as the ventricles (Oatridge et al., 2002), pituitary gland (Hoekzema et al., 2017), striatum (Hoekzema et al., 2020), hippocampus (Luders et al., 2021a), auditory cortex (Luders et al., 2021b), amygdala (Luders et al., 2021c), as well as a composite of various regions (Martinez-Garcia et al., 2021). In contrast, local analyses led to the generation of detailed maps and were conducted across the

[1] Brain age was estimated based on the gray matter distribution throughout the entire brain using a relevance vector machine, as detailed elsewhere (Franke et al., 2010).

[2] There were also differences across studies with respect to the scanner, analysis software (software version, respectively), statistical tests, and covariates (see Supplemental Table 1).

Table 2
Study-specific spatial scales, measurements, and regions.

Study		Spatial Scale(s)	Measurement(s)	Brain Region(s) of Interest
[1]	Oatridge et al. (2002)	global	total brain size	whole brain
		regional	ROI size	ventricles
[2]	Kim et al. (2010)	local	voxel-wise gray matter volume	whole brain
[3]	Hoekzema et al. (2017)	global	total brain volume, gray matter volume, white matter volume	whole brain
		regional	ROI volume	pituitary gland
		local	voxel-wise gray matter volume	whole brain
			point-wise cortical thickness, cortical surface area	whole cortex
[4]	Luders et al. (2018)	global	brain age	whole brain
[5]	Lisofsky et al. (2019)	local	voxel-wise gray matter volume	whole brain
[6]	Carmona et al. (2019)	global	total cortical thickness, cortical surface area, cortical gyrification, sulcal depth, sulcal length, sulcal width, gyral white matter thickness	whole cortex
[7]	Luders et al. (2020)	global	total intracranial volume	whole brain
		local	voxel-wise gray matter volume	whole brain
[8]	Hoekzema et al. (2020)	regional	ROI volume	ventral + dorsal striatum
[9]	Luders et al. (2021a)	regional	ROI gray matter volume	whole hippocampus + subsections
[10]	Luders et al. (2021b)	regional	ROI gray matter volume	primary, secondary, and higher auditory cortex + subsections
[11]	Martinez-Garcia et al. (2021)	regional	ROI gray matter volume	fusiform gyrus, inferior / middle / medial frontal, inferior orbitofrontal, superior temporal, hippocampus, precuneus
		local	voxel-wise gray matter volume	whole brain
[12]	Luders et al. (2021c)	regional	ROI gray matter volume	whole amygdala + subsections

ROI = Region of Interest.

Table 3
Study-specific findings: effects during pregnancy.

Study		Direction of the effect(s) and brain region(s)
[1]	Oatridge et al. (2002)	↓ global decrease in brain size
		↑ regional increase in ventricle size (combined measure: both lateral ventricles + 3rd ventricle)
[3]	Hoekzema et al. (2017)	↓ global decrease in total brain volume and total gray matter volume
		↓ local decrease in voxel-wise gray matter volume across the brain (for cluster locations, see Table 4)
		↓ local decrease in point-wise cortical thickness across the brain (see Table 4)
		↓ local decrease in point-wise cortical surface area across the brain (see Table 4)
		→ no global change in total white matter volume
		→ no regional change in the volume of the pituitary gland
		→ no local change in voxel-wise white matter volume
[6]	Carmona et al. (2019)	↓ decrease in global cortical thickness, surface area, gyrification, sulcal depth, sulcal length
		↑ increase in global sulcal width
		→ no change in global gyral white matter thickness
[8]	Hoekzema et al. (2020)	↓ regional decrease in the volume of the right and left (trend-level only) ventral striatum
		→ no regional change in the volume of the dorsal striatum

Changes summarized here are to be understood as "significant" changes.

whole brain, such as when examining voxel-wise gray or white matter volume (Hoekzema et al., 2017; Kim et al., 2010; Lisofsky et al., 2019; Luders et al., 2020), or across the whole cortex, such as when examining point-wise cortical thickness, gyrification, or surface area (Hoekzema et al., 2017; Martinez-Garcia et al., 2021).

3. Study outcomes

3.1. Changes during pregnancy

To establish changes occurring *during* pregnancy, brain measures were taken before pregnancy and compared to measures taken during pregnancy and/or after giving birth. Out of the 12 studies conducted, five included time points before pregnancy (Carmona et al., 2019; Hoekzema et al., 2017, 2020; Martinez-Garcia et al., 2021; Oatridge et al., 2002), albeit one of those (Martinez-Garcia et al., 2021) was an extension of a previous study (Hoekzema et al., 2017), with an extra time point added at six years after giving birth. Thus, it does not provide any additional insights beyond the initial study with respect to changes *during* pregnancy. As summarized in Table 3 and Fig. 1, the remaining four studies reported that pregnancy is accompanied by increases in total sulcal width (Carmona et al., 2019) and in the size of the ventricles (Oatridge et al., 2002). Furthermore, there are decreases in total brain size (Oatridge et al., 2002), decreases in total cortical thickness, cortical surface area, gyrification, sulcal depth, and sulcal length (Carmona et al., 2019), decreases in the volume of the ventral striatum (Hoekzema et al., 2020), as well as decreases in voxel-wise gray matter volume, point-wise cortical thickness, and point-wise cortical surface area across the brain (Hoekzema et al., 2017); for specific cluster locations, please refer to Table 4. These described changes are all compatible with tissue loss during pregnancy.

3.2. Changes after giving birth

To establish changes *after* giving birth, there are differences across studies with respect to the initial / follow-up time point(s), with four main experimental approaches: (I) Brain measures were obtained towards the end of pregnancy / around giving birth and compared to measures taken during late postpartum (Oatridge et al., 2002)[3]. (II) Brain measures were obtained within days after giving birth (very early postpartum) and compared to measures taken during late postpartum (Luders et al., 2021a, 2021b, 2021c, 2018, 2020). The idea here is that, by conducting the initial brain scan shortly after giving birth, the derived brain measures will still be representative of the pregnant brain.

[3] This study also had a pre-pregnancy time point (see **Table 1** and Section 3.1).

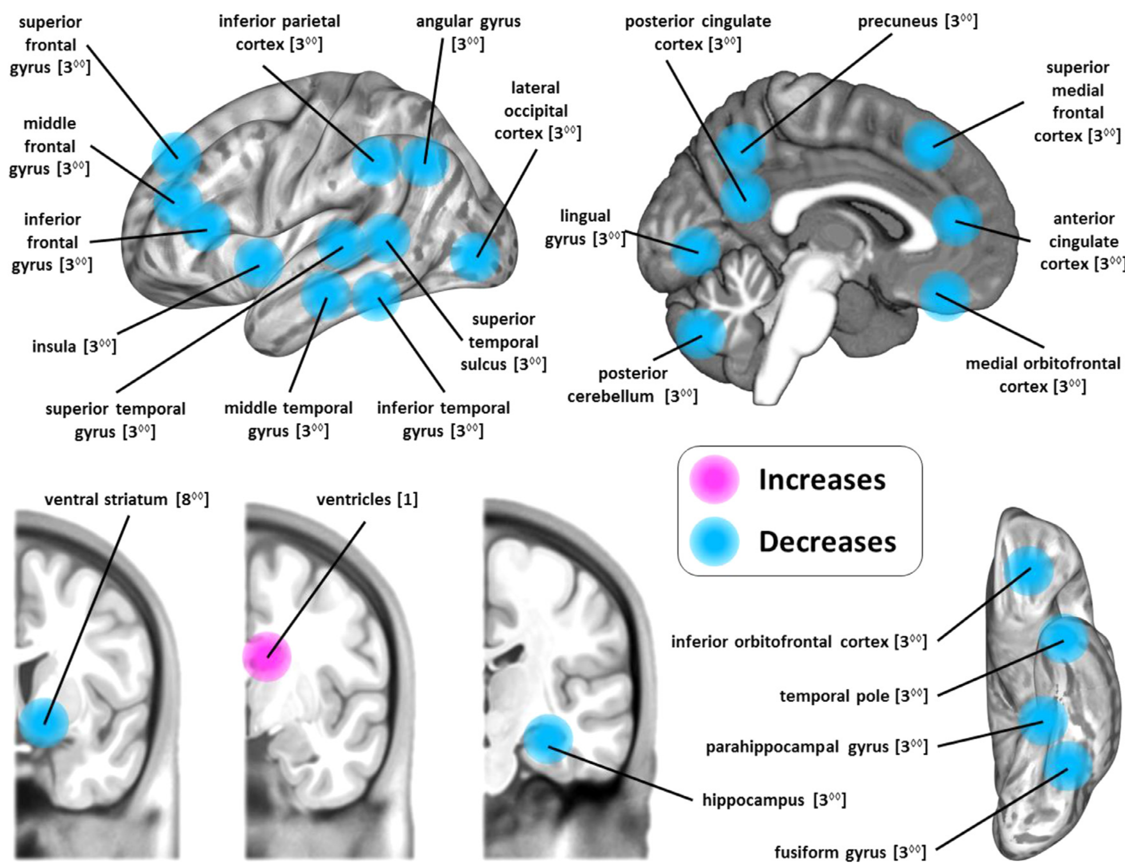


Fig. 1. Changes During Pregnancy. Significant local / regional increases (pink) and decreases (blue) when comparing post-pregnancy measures to pre-pregnancy measures (for global changes, see Table 3). Circles are approximations and displayed in the left hemisphere of the brain, regardless of whether the effect occurred in the left, right, or both hemispheres. For exact locations, please refer to the original publications indicated by the numbers in parentheses and Table 1; for information on laterality, see Table 4. The double-diamond symbol indicates if findings are based on the same / overlapping sample. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

(III) Brain measures were obtained weeks after giving birth (Kim et al., 2010) which is early postpartum or "within two months following delivery" (Lisofsky et al., 2019) which is either early or late postpartum, and compared to measures taken at late postpartum. (IV) Brain measures were obtained during late postpartum and compared to measures beyond the postpartum period, such as at 2.3 years (Hoekzema et al., 2017, 2020)[4] or at 6 years after giving birth (Martinez-Garcia et al., 2021)[4]. While those latter studies only moderately illuminate the postpartum period itself, they may inform about the permanence of any effects induced by pregnancy, giving birth, and/or the postpartum period as further discussed in Section 4.2.

As summarized in Table 5 and Fig. 2, all eight studies that followed experimental approaches I, II, and III were in good agreement with each other in terms of the observed "positive" changes after giving birth, specifically *decreases* in brain age (Luders et al., 2018) and in regional ventricle size (Oatridge et al., 2002), as well as *increases* in global brain size (Oatridge et al., 2002), regional volumes and subvolumes of the hippocampus, amygdala, and auditory cortex (Luders et al., 2021a, 2021b, 2021c), and in voxel-wise gray matter volume across the brain (Kim et al., 2010; Lisofsky et al., 2019; Luders et al., 2020); for specific cluster locations, please refer to Table 6**.** Together, these studies suggest that there is a widespread tissue growth during the first weeks and months after giving birth.

[4] These studies also had a pre-pregnancy time point (see **Table 1** and Section 3.1).

As summarized in Table 7, a different picture emerged from the three studies that followed experimental approach IV: As far as the time period between late postpartum and 2.3 years later is concerned, the first study reported no change in the volume of the striatum (Hoekzema et al., 2020), and the second study observed a decrease in the volume of the pituitary gland and an increase of voxel-wise gray matter volume within the hippocampus (Hoekzema et al., 2017). The third study (Martinez-Garcia et al., 2021) was primarily focused on comparing the 6-year measures to pre-pregnancy measures, and detailed statistical information on the time period between late postpartum and 6 years is missing. Descriptively, the graphs indicate decreases in all clusters of interest (except for the hippocampus) in mothers, but seemingly identical declines were also apparent in non-mothers scanned over the same time period, so those might just reflect natural age-related declines.

4. Discussion

At this point, there seem to be only a dozen studies (Carmona et al., 2019; Hoekzema et al., 2017, 2020; Kim et al., 2010; Lisofsky et al., 2019; Luders et al., 2021a, 2021b, 2021c, 2018, 2020; Martinez-Garcia et al., 2021; Oatridge et al., 2002) that examined structural changes in the female brain as related to pregnancy and childbirth. The relative sparseness of research in this particular field could be a result of various issues, such as difficulties enrolling women who plan to become pregnant, or the lack of enthusiasm of new or prospective mothers to undergo voluntary brain scanning, or the strict regulations that have been historically imposed on neuroimaging during pregnancy.

Table 4
Significance clusters: local effects during pregnancy.

Study		Measurement	Significant clusters – decreases*,**	Hemisphere
[3]	Hoekzema et al. (2017)	Voxel-wise Gray Matter Volume	Superior Temporal Sulcus, Inferior / Middle / Superior Temporal Gyrus, Fusiform, Angular Gyrus, Hippocampus, Parahippocampal Gyrus, Precuneus, Posterior Cingulate Cortex Superior Medial Frontal Cortex, Anterior Cingulate Cortex, Medial Orbitofrontal Cortex, Inferior / Middle / Superior Frontal Cortex, Inferior Orbitofrontal Cortex	Left + Right
			Insula	Left
			Temporal Pole	Right
			Posterior Cerebellum	Left + Right
[3]	Hoekzema et al. (2017)	Point-wise Cortical Thickness	Middle Temporal Gyrus	Right
			Superior Temporal Sulcus	Left
			Posterior Cingulate Cortex	Right
			Fusiform Gyrus	Left + Right
			Lingual Gyrus	Left
			Inferior Parietal Cortex	Left
			Lateral Occipital Cortex	Right
[3]	Hoekzema et al. (2017)	Point-wise Cortical Surface Area	Inferior Frontal Gyrus	Left + Right
			Middle Temporal Gyrus	Left + Right
			Superior Temporal Sulcus	Right
			Posterior Cingulate Cortex	Right
			Orbitofrontal Cortex	Right
			Middle Frontal Gyrus	Right
			Fusiform Gyrus	Left + Right
			Inferior Temporal Gyrus	Right
			Lingual Gyrus	Left + Right
			Inferior Parietal Gyrus	Left + Right

* no increases reported.
** some clusters merged for simplification.

Table 5
Study-specific findings: effects after giving birth (around birth / early postpartum vs. late postpartum).

Study		Direction of the effect(s) and brain region(s)
[1]	Oatridge et al. (2002)	↑ global increase in brain size ↓ regional decrease in ventricle size (combined measure: both lateral ventricles + 3rd ventricle)
[2]	Kim et al. (2010)	↑ local increase in voxel-wise gray matter volume across the brain (for cluster locations, see Table 5)
[4]	Luders et al. (2018)	↓ decrease in brain age
[5]	Lisofsky et al. (2019)	↑ local increase in voxel-wise gray matter volume across the brain (see Table 5)
[7]	Luders et al. (2020)	↑ local increase in voxel-wise gray matter volume across the brain (see Table 5) → no global change in total intracranial volume
[9]	Luders et al. (2021a)	↑ regional increase in the volume of the right hippocampus as a whole (trend-level only) and subvolumes: right cornu ammonis area 2, right cornu ammonis area 3, and right subiculum → no regional change in cornu ammonis area 1 and the dentate gyrus
[10]	Luders et al. (2021b)	↑ regional increase in the (sub)volumes of the primary, secondary, and higher auditory cortex: left + right Te1 = Te1.0, Te1.1, and Te1.2; left + right Te2 = Te2.1 and Te2.2; and left + right Te3
[12]	Luders et al. (2021c)	↑ regional increase in subvolumes of the amygdala: right + left superficial subarea and right centromedian subarea (trend-level only) → no regional change in the volume of the amygdala as a whole or its laterobasal subarea

Changes summarized here are to be understood as significant changes.

Challenges surrounding prospective studies will continue to exist, and there might not be much that can be done about the (understandable) reluctance of new mothers to subject themselves to a neuroimaging study. However, change is already happening in the field with respect to the third aspect, where restrictions on brain scanning during pregnancy are becoming more and more lenient. That is, an increasing number of studies suggest that MRI does not have adverse effects for the fetus, at least when no Gadolinium-based contrast agents are used (Bouyssi-Kobar et al., 2015; Chan et al., 2015; Chartier et al., 2019; Choi et al., 2015; Kok et al., 2004; Ray et al., 2016; Zvi et al., 2020). Professional entities, such as the Canadian Association of Radiologists, the American College of Obstetricians and Gynecologists, or the American College of Radiology, have concluded that no specific recommendations are necessary for the use of MRI for medical imaging during pregnancy (ACOG Committee, 2017; Jabehdar Maralani et al., 2021). Thus, in the future, we can probably expect to see more imaging studies that collect data at different time points over the course of pregnancy.

4.1. Changes during pregnancy

The four existing studies seem to indicate that pregnancy is accompanied by “negative” effects, such as decreases in brain size, striatal volume, gray matter tissue, cortical thickness, surface area, gyrification, sulcal depth and sulcal length, as well as increases in ventricular volume

Table 6
Significance clusters: local effects after pregnancy (early postpartum vs. late postpartum).

Study		Measurement	Significant clusters – increases*,**	Hemisphere
[2]	Kim et al. (2010)	Voxel-wise Gray Matter Volume	Anterior Cingulate, Ventromedial Prefrontal Cortex	Left + Right
			Middle Frontal Gyrus (BA 9/10)	Left + Right
			Cerebellar VI	Left
			Middle Frontal Gyrus (BA 8)	Right
			Cerebellar Crus I/II	Left
			Nucleus Accumbens	Left
[5]	Lisofsky et al. (2019)	Voxel-wise Gray Matter Volume	Postcentral Gyrus	Right
			Medial Precentral Gyrus	Right
			Thalamus	Left + Right
			Central Operculum	Left
			Frontal Operculum	Left
			Inferior Frontal Gyrus	Left
			Precuneus	Right
			Middle occipital gyrus	Right
			Caudate	Left
[7]	Luders et al. (2020)	Voxel-wise Gray Matter Volume	Inferior / Superior Parietal Lobe, Precuneus, Medial Frontal Gyrus, Postcentral Gyrus, Cingulate Gyrus	Left + Right
			Inferior / Middle Frontal Gyrus, Precentral Gyrus	Left
			Thalamus	Right
			Hypothalamus, Substantia Nigra, Caudate Body, Caudate Head, Mammillary Body	Left + Right
			Amygdala, Putamen, Medial / Lateral Globus Pallidus, Anterior Cingulate, Parahippocampal Gyrus, Insula	Right
			Middle / Superior Frontal Gyrus, Precentral Gyrus	Right
			Superior Temporal Gyrus, Insula	Left
			Brainstem (Pons, Medulla)	Left
			Cerebellum (Anterior Lobe)	Right
			Cerebellum (Posterior Lobe)	Right + Left

* no decreases reported.
** some clusters merged for simplification.

Table 7
Study-specific findings: effects after giving birth (late postpartum vs. 2.3 and 6 years).

Study		Direction of the effect(s) and brain region(s)
[3]	Hoekzema et al. (2017)	↓ regional decrease in the volume of the pituitary gland ↑ local increase in voxel-wise gray matter volume within the left hippocampus [global change in total brain volume, gray matter volume, white matter volume not examined] [local change in point-wise cortical thickness and surface area not examined] [local change in voxel-wise white matter volume not examined]
[8]	Hoekzema et al. (2020)	→ no regional change in the volume of the ventral or dorsal striatum
[11]	Martinez-Garcia et al. (2021)	[regional / local analyses conducted but statistical information not available on 10 weeks postpartum vs. 6 years]

Changes summarized here are to be understood as significant changes.

and sulcal width (Carmona et al., 2019; Hoekzema et al., 2017, 2020; Oatridge et al., 2002). Nevertheless, findings should be interpreted with some caution: Importantly, the first study (Oatridge et al., 2002) only measured two women before pregnancy, which limits any conclusions due to the small sample size. However, it is noteworthy that this study also included measures during pregnancy and indeed, at least descriptively, brain size decreased and ventricle size increased across the weeks of gestation in some women. As far as the other three studies are concerned (Carmona et al., 2019; Hoekzema et al., 2017, 2020), all of them are based on the same sample and sometimes based on the same measures. Moreover, in all three studies the earliest post-pregnancy measurements were only obtained at week 10 after childbirth (i.e., at late postpartum). Thus, it is actually impossible to unscramble which of the reported effects are due to pregnancy, childbirth, or the postpartum period – which itself is marked by significant changes in brain structure (see Section 3.2 and Section 4.2).

Therefore, our current knowledge of structural brain changes during pregnancy is still extremely limited. The issue may be further complicated as in the latter three studies (Carmona et al., 2019; Hoekzema et al., 2017, 2020) "the radio frequency head coil was replaced for some time with another head coil" (Hoekzema et al., 2017). Changes related to the image acquisition equipment are usually beyond the control of the research team. Nevertheless, they constitute a problem, especially in longitudinal studies (Panman et al., 2019). The authors of the aforementioned studies conducted some additional analyses in order to mitigate the setback, but replication studies using stable scanner environments are required. Altogether, at this point, it seems sensible to abstain from drawing any final conclusions with respect to the presence, direction, and magnitude of structural brain changes during pregnancy.

4.2. Changes after giving birth

While the six studies following experimental approaches I and II have captured very early postpartum changes, including those that may be associated with the hormonal plunge during the first few days post-

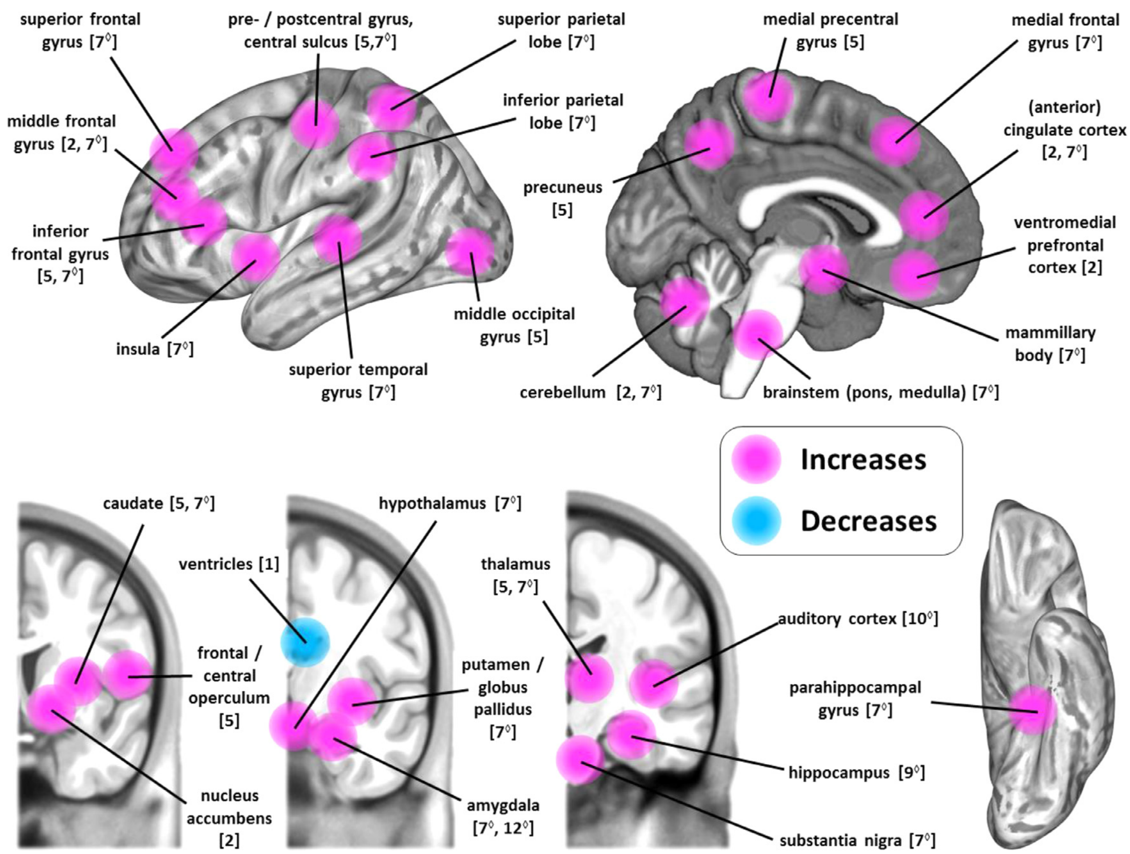


Fig. 2. Changes After Pregnancy (Postpartum Period). Significant local / regional increases (pink) and decreases (blue) when comparing late postpartum measures to early postpartum measures (for global changes, see Table 5). Circles are approximations and displayed in the left hemisphere of the brain, regardless of whether the effect occurred in the left, right, or both hemispheres. For exact locations, please refer to the original publications indicated by the numbers in parentheses and Table 1; for information on laterality, see Table 6. The single-diamond symbol indicates if findings are based on the same sample. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

partum (Hendrick et al., 1998; Hill et al., 2001; Rehbein et al., 2020; Sundstrom-Poromaa et al., 2020) and the rapid physiological changes occurring during the first weeks after giving birth (Romano et al., 2010), the two studies following experimental approach III have probably captured only the tail end of these early changes. Nevertheless, all eight studies (Kim et al., 2010; Lisofsky et al., 2019; Luders et al., 2021a, 2021b, 2021c, 2018, 2020; Oatridge et al., 2002) unanimously agreed that the postpartum period is marked by "positive" effects, in a way that brains seemed larger and younger, had smaller ventricles, and presented with locally / regionally increased brain tissue at the follow-up time point. Note though that some studies are based on identical samples (Luders et al., 2021a, 2021b, 2021c, 2018, 2020). Importantly, albeit a few of those eight studies reported a lack of significant change in some regions, none reported any "negative" effects. So, if indeed there were tissue reductions during pregnancy (see Section 4.1), female brains may actually recover from at least some of that tissue loss, and the observed effects could be understood as restorations. Moreover, if the tissue gain after pregnancy outweighs the tissue loss during pregnancy, the observed effects would point to actual tissue enhancements after giving birth.

The assumption of tissue *restorations* after giving birth seems to conflict with the outcomes of the three studies that followed experimental approach IV (Hoekzema et al., 2017, 2020; Martinez-Garcia et al., 2021) obtaining measures before pregnancy, at 10 weeks after giving birth, and then again after 2.3 years (or 6 years, respectively). More specifically, these studies reported that – with the exception of the left hippocampus (Hoekzema et al., 2017) – none of the gray matter regions marked by significant decreases during pregnancy, had any significant increases after pregnancy, neither during the postpartum period nor years later. Nevertheless, the first postpartum scan in those studies was obtained only at week 10 after giving birth, so would have missed any early postpartum restorations. Indeed, strong evidence for postpartum tissue restorations (as well as for a pregnancy-induced tissue loss) comes from the study by Oatridge et al. (2002) obtaining measures before and during pregnancy, at term, and during late postpartum. More specifically, the authors reported "a reduction in brain size during pregnancy that was maximal at term and that reversed by 6 months after delivery" (Oatridge et al., 2002).

The assumption of tissue *enhancement* (actual net gains) seems to be supported by the extent and locations of the increases (see Tables 5 and 6) in relation to the decreases (see Table 3 and 4). Additional support comes from large-scale cross-sectional studies (Aleknaviciute et al., 2022; de Lange et al., 2020, 2019; Voldsbekk et al., 2021), which revealed more gray matter and younger appearing brains in mothers compared to nulliparous women. Cross-sectional studies cannot solve the question of causality, but it is intriguing that the reported effects seem to be in agreement with the longitudinal findings indicating substantial tissue increases during the postpartum period (Kim et al., 2010; Lisofsky et al., 2019; Luders et al., 2021a, 2021b, 2021c, 2018, 2020; Oatridge et al., 2002). Last but least, the assumption of tissue enhancement appears to conflict with the outcomes of the three studies that followed experimental approach IV (Hoekzema et al., 2017, 2020; Martinez-Garcia et al., 2021). However, those studies may have missed any regional net gain, either because some of their follow-up analyses were restricted to clusters where the initial tissue loss occurred (Hoekzema et al., 2017, 2020; Martinez-Garcia et al., 2021) or because their analyses were directed at specific regions of interest to begin with (Hoekzema et al., 2020).

4.3. Status quo and implications for future research

The data providing the basis for the 12 studies considered in this review were collected – at least partly – on different scanners, with different field strengths, and different imaging protocols. Moreover, while the majority of studies focused on gray matter, measurement scales ranged from local, to regional, to global. However, even if studies operated on the same spatial scale (e.g., examining voxel-wise gray matter volume), analyses were conducted using different softwares (software versions, respectively), different statistical tests, and/or different covariates. Furthermore, there is likely[5] to be considerable variability across studies with respect to the exact duration of pregnancy, the age of the mother at term, whether it was a first-time pregnancy, the means of delivery, whether mothers were breastfeeding (and for how long), whether mothers gained or lost weight during and after pregnancy (and how much), whether mothers were sleep-deprived (and to what extend), or whether mothers were solo or cohabitating parents.

One would therefore expect a certain degree of inconsistency in terms of study outcomes, just as it would be the case in any other field of research. Thus, it is actually somewhat re-assuring that there is some agreement across the 12 studies. More specifically, while a small fraction of studies (Carmona et al., 2019; Hoekzema et al., 2017, 2020; Martinez-Garcia et al., 2021) suggests that pregnancy is associated with tissue decreases and that pregnancy-induced loss will persist even years after giving birth (with the exception of the left hippocampus), the majority of existing studies seems to indicate that giving birth is accompanied by substantial tissue increases on the global, regional, and local level (Kim et al., 2010; Lisofsky et al., 2019; Luders et al., 2021a, 2021b, 2021c, 2018, 2020; Oatridge et al., 2002). Without a doubt, the conducted studies provide an excellent foundation and also reference system to relate the outcomes of follow-up studies. However, future research is clearly warranted, not only to address the shortcomings discussed, but also to replicate the existing findings using larger samples[6] as well as to determine the consequences of these structural changes for maternal mood, cognition, and behavior during and after pregnancy.

Importantly, the brain is not a homogenous structure and, ideally, global measures should be accompanied by local / regional measures. As summarized elsewhere (Luders and Kurth, 2020), global measures appear to offer a solid starting point to explore whether there are any effects at all, but they may also fail to produce any significant effects if changes over time are restricted to small regions and/or if increases and decreases cancel each other out. As already evident based on the existing data, different brain regions seem to be affected differently, with some regions losing tissue during pregnancy and not gaining it back during the postpartum period; some regions losing but also gaining back; some regions losing, gaining back, and gaining something extra; some regions not losing at all but gaining something extra; and yet some other regions neither losing during pregnancy nor gaining during postpartum. In addition, any region-specific changes might manifest at different time points during and after pregnancy. So, it will be desirable to generate voxel-, cluster-, or region-specific trajectories – ideally across the entire brain – and use standardized time points before pregnancy, during pregnancy (if applicable), early postpartum, late postpartum, and follow-up (if applicable).

[5] Most studies did not provide any information on these variables.

[6] Currently, the number of women included at each time point ranges between 2 and 25.

Finally, the brain consists of three main tissue types, gray matter, white matter and cerebrospinal fluid, and most of the studies reviewed here (Carmona et al., 2019; Hoekzema et al., 2017, 2020; Kim et al., 2010; Lisofsky et al., 2019; Luders et al., 2021a, 2021b, 2021c, 2018, 2020; Martinez-Garcia et al., 2021) have analyzed features related to gray matter, either as direct measure (e.g., voxel-wise gray matter volume), as derivatives of gray matter (e.g., estimates of brain age), or as composite measures that include gray matter (e.g., total intracranial volume). Only one study (Oatridge et al., 2002) specifically focused on cerebrospinal fluid by measuring ventricular volume, and two studies (Carmona et al., 2019; Hoekzema et al., 2017) additionally explored attributes of white matter using T1-weighted images, which are suboptimal for white matter analyses (Hoekzema et al., 2017). Thus, future studies may consider complementing T1-weighted images with T2-weighted and/or diffusion-weighted images, especially given that significant white matter changes during pregnancy and/or in relation to pregnancy-related hormones have been reported in animals (Chan et al., 2015; Gregg, 2009, 2007). Similarly, future research might benefit from quantitative T1-mapping, T2-mapping, or susceptibility mapping, which may provide insights into the underlying processes by providing information on a range of cellular properties, including fluid or iron content, degree of myelination, and cellular density (just to name a few).

Data & Code Availability

Not applicable.

Ethics Statement

Not applicable.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2022.119646.

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