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Morphologic brain changes induced by pregnancy.
A longitudinal magnetic resonance imaging study.

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To Andreas Müller
and our daughter Marlene

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SUMMARY

In humans, the survival of the young is dependent to a significant degree on the exertions of the mother, and the quality of her care will contribute significantly to the foundation of the infant's neurobiological, cognitive and socio-emotional development (Shonkoff et al., 2012). Furthermore, almost every women will experience pregnancy which is recognized to predispose the mother to a period of mental vulnerability (Brunton and Russell, 2008). Nevertheless, very little is known on how pregnancy affects the human brain.

It has been proven that less extreme endocrine changes render morphological brain modifications (Erickson et al., 2010; Woolley and McEwen, 1993, 1992) and several studies in mammals show adaptations in various brain systems in order to ensure pregnancy, delivery and postnatal care, suggesting in humans a brain plasticity inherent to reproduction itself (Brunton and Russell, 2008; Kinsley and Amory-Meyer, 2011; Swain et al., 2014). Although this question has been previously addressed assessing whole brain changes in size (Oatridge et al., 2002), the current findings are the first to explicitly show the precise morphologic brain changes associated with successful reproduction in human mothers.

The aim of this study is to examine whether pregnancy is associated with morphological brain changes in women. In this longitudinal case-control study, we obtained high-resolution brain magnetic resonance imaging (MRI) scans of 25 primiparous women and their male partners (n=19) before and after pregnancy. Longitudinal scans of 20 nulliparous control women and their male partners (n=17) were also acquired. A longitudinal voxel based morphometric analysis was applied to calculate changes in grey matter (GM) between the two different time-points and compare these changes between the groups of subjects (primiparous versus controls).

Group comparisons of these within-subject GM changes indicate a symmetrical pattern of highly significant GM volumetric reductions in the women who underwent pregnancy in comparison to the nulliparous control women. The comparison between the male samples does not yield significant differences.

These GM volume reductions associated with pregnancy are observed in the posterior midline (posterior cingulate and precuneus), the medial frontal cortex (medial prefrontal cortex and anterior cingulate), bilateral lateral prefrontal cortex (clusters in the ventrolateral and dorsolateral prefrontal cortex) and bilateral temporal cortex (bilateral superior temporal sulcus extending to surrounding lateral temporal sections as well as medial temporal structures such as the fusiform gyrus). All p values are below 0.05 familywise-error corrected.

The changes are remarkably consistent across subjects and the women can significantly be classified as having undergone pregnancy or not, based on the distribution of GM changes across the brain.

The current findings are the first to demonstrate that pregnancy is related to specific morphological brain changes in humans, providing primary insights into the way a woman's brain is modified during pregnancy.

The results are discussed in the light of studies assessing the implicated brain areas and the potential neurobiological mechanisms underlying these GM volume reductions. Although the mechanism and physiological meaning of these findings are speculative at the present time, these findings provide primary clues regarding the neural basis of motherhood, perinatal mental health and brain plasticity in general.

LIST OF ABREVIATIONS

ACC	Anterior cingulate cortex
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
BOLD	Blood oxygenation-level dependent
DF	Degrees of freedom
DHA	Docosahexaenoic acid
DMN	Default mode network
EC	Empathic concern scale
F_CTR	Female control group
F_EXP	Female experimental group
F_EXPnat	Female experimental group who became pregnant naturally
F_EXPtrt	Female experimental group who became pregnant with a fertility treatment
fMRI	Functional magnetic resonance imaging
FS	Fantasy scale
FWE	Familywise-error
FWHM	Full width at half maximum
GM	Grey matter
HPA	Hypothalamic-pituitary-adrenal
IRI	Interpersonal Reactivity Index
LCPUFA	Long-chain polyunsaturated fatty acids
M_CTR	Male control group
M_EXP	Male experimental group
mPFC	Medial prefrontal cortex

mPOA	Medial preoptic area
MR	Magnetic resonance
MRI	Magnetic resonance imaging
MTLs	Medial temporal lobes
NAA	*N*-acetyl aspartate
PC	Precuneus
PCC	Posterior cingulate cortex
PD	Personal distress scale
PT	Perspective taking scale
ROI	Region of interest
rs-fcMRI	Resting state functional connectivity MRI
SD	Standard deviation
SPM	Statistical parametric mapping
TAVEC	*Test de Aprendizaje Verbal España Complutense*
ToM	Theory of mind
VBM	Voxel based morphometry
WAIS	Wechsler Adult Intelligence Scale
WM	White matter
MBCh-pregnancy	Morphological brain changes related to pregnancy

Morphologic brain changes induced by pregnancy
A longitudinal magnetic resonance imaging study

INTRODUCTION

Preface: the pregnant brain

Parental care is by far the most obvious and pervasive example of altruism in the animal kingdom, and may well represent the original form of prosocial behavior from which all others are derived

James K. Rilling, 2013, p. 732

Parental care varies extensively between species. Parenting in fish and reptiles is exceptional while is common in birds and mammals. In birds, biparental care is the rule, but the awareness of the mental state of the offspring does not appear to be required as contrary to what we observe in most of the mammals (Rilling, 2013). The evolution of placental viviparity – the development of the embryo inside the body of the mother, eventually leading to live birth, as opposed to laying eggs – implicates an extended post-natal care that requires offspring recognition and a strong bonding relationship. The parent that is present at birth and that is equipped to provide initial feeding through lactation is the mother. Therefore, in mammals the females form their strongest bonds with their own offspring and their maternal behavior is a central social behavior that provides nutrition, warmth, protection, and close social stimuli for the young (Broad et al., 2006). In order to become maternal, the mother's organism, the brain included, undergoes various changes to meet the demands of the offspring. These adaptations,

which start with the pregnancy along the complex hormonal changes, continue in lactation as a result of close mother–offspring interactions (Bosch and Neumann, 2012; Kinsley, 2008).

Although pregnancy has been extensively studied, little is known about the effects of pregnancy in the female brain, especially in humans. The study presented here explores the structural brain changes that might occur in the women that undergo pregnancy. The effects of pregnancy in the female brain are measured with structural MRI comparing two time points: before the pregnancy and after it. It also explores changes in behavior measured by cognitive and empathy test in order to look for correlations between the physiological brain data and the psychological one.

Although the research presented here is centered in the effects of *pregnancy* on the human brain, at this initial-contextual section we will include the wider concept of *motherhood*. It would impoverish this section to make a strict differentiation of pregnancy vs. motherhood because the vast majority of the behavioral and neurological studies are focused on the latest. Also, an exact differentiation would be artificial, since clearly in humans the pregnancy already encompasses a motherly attitude and behavior: the pregnant woman changes her habits looking after the fetus and even starts a relationship with the unborn baby.

We would also like to address that the main object of our study is the *brain*, but since it is going to be correlated with cognitive data, we will start with a review of the *behavioral* changes that convey the reproductive experience. I also did not want to leave the behavioral perspective a side, as it might give light into the comprehension of the occurrences in the brain.

The introduction chapter follows the subsequent order:

1. I will first review the main behavioral changes accompanying this life-altering event in humans and in rodents, the animal model more utilized in this area.
2. In the next section, called "Vignettes of the behavior-hormone-brain constellation underpinning pregnancy and motherhood" I will establish some associations of the pregnant-maternal behavior with the endocrine system and the neuronal system as well. The aim of this section is to expose a theoretical framework of this work, were the neuroendocrine system and the behavior/mind-system affect each other constantly. Also, although the

endocrine changes during pregnancy go beyond the boundaries of this dissertation, I want to include a notion of their importance, at least with a couple of illustrations.

3. The next section presents the core of this study's fundaments by reviewing the neuronal changes related to pregnancy that have been found in mammals and in humans, to latter empathize the lack of well controlled studies that asses structural brain plasticity inherent to reproduction in humans. Here, I will also review the neuronal mechanism underlying the maternal behavior as found with functional magnetic resonance (fMRI) studies while mothers perceive theirs own child visual or auditory stimuli.
4. In order to introduce the MRI data acquisition and analysis of the study, here is a technical fragment describing the MRI neuroanatomical approaches in an elementary manner.
5. The contributions of this study are described and enumerated in a comparative scheme that includes previous studies assessing whole brain structural changes related to pregnancy.
6. The chapter is concluded by explaining the outline, objective and hypothesis of this study.

The introduction is accompanied by several boxes including inquiring data adjacent to the main topic.

Behavioral changes due to reproductive experience

The female that makes the transition into maternity must adapt to new demands in order to ensure their offspring gestation, safety delivery and survival or they may lose a significant metabolic and genetic investment. Subsequently, she requires refocusing her behavior and activities. This adjustment is deeper and obvious after the birth but some modifications take place since the pregnancy.

In rodents

In laboratory, rodents such as rats and mice show that right after parturition the females display a range of behavioral adaptations in order to protect and promote the growth and survival of their pups. Some of these behavioral modifications are novel maternal activities like, nest building, placentophagia, various forms of nursing, sniffing, exploring and crouching over the young, retrieving them to the nest, and body/genital licking of pups (Bosch and Neumann, 2012; Neumann, 2003; Rosenblatt et al., 1994). Motherly behavior also shows an urge to find and be with their pups the vast majority of their time. This maternal motivation has been studied in a laboratory context and mothers eagerly retrieve pups from anxiety provoking areas, bar-press for contact with their pups (A. Lee et al., 2000) and find pup suckling more rewarding than cocaine (Ferris, 2005).

Additionally, female rats with reproductive experience display altered behaviors that are not directed to the offspring but that support the rearing task. There is an increase in food consumption in lactating females (Ota and Yokoyama, 1967) and a sharpening of some cognitive abilities, predominantly spatial memory, which might be important for hunting, finding and remembering the sources of water and food, and returning to the nest faster (Gatewood et al., 2005; Kinsley et al., 1999; Love et al., 2005; Macbeth et al., 2008). These improvements in spatial memory are clearly measured in the late post-partum and in the post-weaning periods, while they are not so evident during pregnancy and early postpartum period. These cognitive changes appear to persist for years showing somewhat permanent changes and suggesting that reproduction, with its related natural endocrine and postpartum sensory experiences, may facilitate lifelong learning and memory. Remarkably, Gatewood and colleagues

(2005) discovered that these enhancements in memory correlates negatively with markers of neurodegeneration and age-related cognitive loss in the hippocampus, suggesting that the reproductive experience might mitigate neural aging.

There is also an increase of the protective behavior in order to guard the offspring against a potentially dangerous intruder. The so-called "maternal aggression" is a combative, agonistic behavior distinguished from irritable, territorial, sex-related, fear-induced, predatory and inter-male aggression. At the laboratory this is generally exemplified by an augmented frequency of attacks towards an intruder rat in the home cage, but this enhanced aggressive behavior is also shown in situations where the protection of the litter is not directly involved, like in competing for a water source (Neumann, 2003). During the peripartum period, the intensity of maternal aggression grows as the pregnancy develops and reaches a peak during the beginning of the partum and around days 4 to 7 of lactation. This behavior doesn't persist consistently: at weaning it almost disappears and if the litter is removed the aggression subsides (Caughey et al., 2011; Rosenblatt et al., 1994).

Studies also indicate a reduction of the stress response circuits in lactating rats. The mothers show reduced anxiety in front of unfamiliar or even potentially dangerous situations (Macbeth and Luine, 2010). It has been suggested that the neurobiological mechanisms underlying this behavioral change, — a down regulation of the stress responsiveness via the inhibition of the brain corticotropin-realising hormone (CRH) system — may facilitate the protective behavior described above, as well as leaving the nest for scavenging confronting any threats she may encounter (Macbeth and Luine, 2010) as well as may protect the maternal brain against the intense hormonal changes that takes place at this time (Neumann, 2003). It is not clear if a reduction of the stress response also occurs during pregnancy; studies have conflicting results (Faturi et al., 2006; Macbeth et al., 2008; Neumann et al., 1998) and more investigations on this behavioral topic are required.

In humans

Human mothers also experience behavioral changes in the context of maternal care. Pregnant women take a series of measures in order to take care of their gestation. Along the medical care, the future mother usually avoids or reduces the consumption of

injurious substances and risky activities and improves specific nutrients to her diet. As the birth approaches, she gets preoccupied with creating a secure environment where cleaning and renovation projects are commonplace; a behavior popularly referred to as "building the nest" where main parental concerns are safety and the readjustment of the home in preparation of the newborn (Leckman et al., 1999). Right after parturition, mothers display novel behavior like holding, nursing, and feeding. "Women describe breast-feeding as a uniquely close, very physical, at times sensual experience and one that brings a particular unity between the mother and her infant" (Leckman and Herman, 2002, p. 28). Cleaning, grooming, and dressing the baby are also central behaviors that favor a closeness interaction between mother and infant and provide for frequent inspection of the infant's body and appearance.

Like in other mammals, human mothers are also highly attracted and very sensitive to the body odor of their progeny (Fleming et al., 1997). In the immediate newborn period, 90% of the women could recognize their own infant smell versus another newborn baby after 10 to 60 minutes exposure to their infants (Eidelman et al., 1987).

Parents usually spend a large amount of time just observing their baby. This is driven by both a sensation of being in love, as well as by a preoccupation for the infant's safety. "Parents may experience an anxious tension between the joyous reveries of being 'at one' with the child, and the intrusive worries that something terrible could happen and jeopardize the relationship" (Swain et al., 2007, p. 264). Hence, parents also manifest changes in thoughts and emotions (Buckwalter et al., 2001). The perinatal period is associated with intense parental preoccupations regarding the infant's safety and wellbeing, as well as concerning the parents' adequacy and capabilities (Leckman et al., 1999). It has also been described that mothers during the perinatal period reach a special psychological condition. This is characterized by a state of "heightened sensitivity" or "normal devotion" where she becomes preoccupied with her newborn to the exclusion of other interests –in a way that is normal and temporary– allowing her to adjust delicately and sensitively to the infant's needs at the very beginning (Winnicott, 1975, 1960).

Another characteristic of the perinatal period is a subjective appraisal of memory difficulties: pregnant women subjectively rate their own memory performance as less

effective (Crawley et al., 2003) and this coincides with the popular belief that pregnant women are more forgetful and inattentive. Many behavioral studies have considered this judgment, measuring whether pregnancy and postpartum affects the cognitive abilities of the mothers testing attentional processes and various types of memory: visual, verbal, explicit, implicit and working memory. The results are less conclusive than the studies with rodents —and it is interesting to note that in rodents has been found the opposite: an enhancement in memory— but there is a tendency to conclude that pregnancy implicates some subtle memory impairments, particularly in the third trimester, and so does the postpartum period (for review see Buckwalter et al., 2001; Henry and Rendell, 2007; Macbeth and Luine, 2010). These subtle diminishment does not happen in all kinds of memory measures; the ones who have a tendency to be disrupted are those that place relatively high demands on executive cognitive control (Henry and Rendell, 2007). With regard to the duration of such memory impairment, some studies indicate that they are transient and cognitive abilities rebound within a year postpartum, but some others report maintained memory deficits postpartum (Macbeth and Luine, 2010).

It is difficult to determine the reasons for such differences in the studies. Macbeth and Luine (2010) in their review mention some problems to be solved in order to better understand the effects of pregnancy on memory. They say the comparisons must take into account the time of testing relative to birth. In relation to the memory test used, they suggest a greater use of ethologically relevant tasks like recognition memory – tasks that would better aid mothers in caring the baby – with less emphasis on IQ-related memory tests. They also mention that in most of the studies the control group contains women who are not currently pregnant, but may have had an earlier pregnancy, and that given the potential long-term effects that pregnancy can produce on cognition, a control group consisting exclusively of women who have never been pregnant is critical. Because of this same reason, with regard to the experimental group it should also be taken into account the number of previous pregnancies and whether the pregnancies are/were primigravid or multigravid. They also mention the invaluable contribution of longitudinal studies that could measure the same subjects before, during and after the pregnancy.

With regard to the stress/anxiety levels during pregnancy and postpartum, these are very difficult to assess as they are highly correlated with social, physiological and

psychological factors that are independent from motherhood. Also, becoming a mother usually brings with it a variety of stressors regarding the health of the fetus/infant, personal health and appearance, increased demands on time and energy, the ability to adequately care for the baby and the ability to make this compatible with other areas of the mother's life (Lonstein, 2007). These external stressors that have a greater variability among subjects and are difficult to control, could be also modulating the mothers cognitive performances; this might be a reason why results concerning changes in memory and attention are not jet conclusive.

Nevertheless the complexity of the stressors that can come into play, a general decrease in stress reactivity occurs during pregnancy which may contribute the safeguarding of energy stores and prevent the fetus and the mother from an adverse over-exposure to glucocorticoids (Douglas, 2005; Macbeth and Luine, 2010). Weerth and Buitelaar (2005) review laboratory studies that have used tests designed to produce physiological (pain, discomfort), cognitive and psychological stress to study physiological stress reactivity in pregnant women assessing changes in blood pressure, heart rate and/or cortisol levels. In conclusion, these authors say that physiological stress reactivity becomes diminished during pregnancy, but it shows sufficient inter-individual variability to allow the study of links between responsivity patterns, psychosocial variables, fetal behavior, pregnancy outcome and offspring development (de Weerth and Buitelaar, 2005).

In relation to the postpartum, conclusions are somewhat unclear: some studies show that a similar hypo-reaction to stress happens during this period (Douglas, 2005), but a high number of women suffer a postpartum mood disorder that often involves elevated anxiety (see box 1 for "Concurrence of psychopathology in the perinatal period"). What is somehow clear, is that the physical contact with the baby (which is implicit in breastfeeding but can still be gotten without it) is an important contributor to positive mood and reduced anxiety in the mother (Groer et al., 2002; Lonstein, 2007). In other words: touching and caring the baby close to the mother's own body has a naturally anxiolytic effect in the mother.

In conclusion, several scientific studies in mammals and humans confirm what we know from our day-to-day experience: female behavior changes with pregnancy. Does a female brain change as well?

Box 1. Concurrence of psychopathology in the perinatal period

Beyond the elation, happiness and gratitude a mother can experience after giving birth, the early postpartum period is a time of disturbance in her physiology and psychology and therefore a vulnerable time. The etiology of postpartum mood disorders is very likely multifactorial: dramatic hormonal fluctuations that occur following childbirth (Neumann, 2003), lack of sleep, psychological factors (negative early experiences in the family of origin; difficulties in accepting the particular characteristics of the baby which does not match with the idealized-fantasized baby; etc.) (Brazelton and Cramer, 1993) and social factors (poor social support; poverty; stressful life events; single parenting) influences the increased incidence of mood disorders during this time (Barrett and Fleming, 2011; Marcus, 2009; Payne, 2007).

Postpartum mood disorders include a wide range from mild to severe distress that are usually designated as postpartum blues, minor depression, postpartum anxiety disorders (such as obsessive compulsive disorder, panic disorder and post-traumatic stress disorder), mayor postpartum depression and postpartum psychosis (Scrandis et al., 2007).

The first weeks after delivery are usually characterized by a postpartum reactivity sometimes known as “postpartum blues” or “baby blues”. This is a common non-pathological phenomenon affecting between the majority of women after giving birth (Scrandis et al., 2007). It appears within the first days after delivery and it is self-limited: resolves spontaneously with or without treatment usually within two weeks postpartum (Scrandis et al., 2007). The etiology is not conclusive but it may include a heightened liability of mood resulting from hormonal withdrawal and in relation to situational difficulties such as the establishment of breastfeeding (Scrandis et al., 2007). Symptoms include mood lability, tearfulness, despondency, anxiety, poor concentration and feeling overwhelmed (Payne, 2007; Scrandis et al., 2007).

Postpartum depression, is less frequent than “baby blues” but is still a common clinical disorder affecting around 10% of the new mothers within the first six months after delivery (Friedman and Resnick, 2009). It is a disorder that meets the DSM-IV criteria for a major depressive episode (Wisner et al., 2002). The prognosis is good if the mother seeks professional treatment, but unfortunately it is estimated that nearly one-half of all cases go undetected and the detrimental consequences involves the mother-infant dyad (Marcus, 2009) (see box 7 for “Parent-infant interactions and its repercussion on the infant’s health”).

Postpartum psychosis is rare, occurring in approximately 0.1% of all deliveries, but the symptoms are severe and jeopardize the safety and wellbeing of the mother and the baby. The patient develops frank psychosis (hallucinations and delusional beliefs that can sustenance suicidal or infanticide ideation), cognitive impairment, and disorganized behavior. The overall prognosis is positive, mainly when symptoms emerge within the first month post-delivery (Sit et al., 2006).

Research initiatives like the one presented here, may enhance our ability to prevent or treat disorders affecting a substantial number of women by better understanding the etiology of peripartum mental disorders. Also, an effort in divulging accurate information about the pregnancy and the postpartum period (including the neuronal and endocrine changes that convey) could aid lower the social expectations of what being a mother should feel like, enhancing mothers experiencing emotional complaint to request assistance.

Vignettes of the behavior-hormone-brain constellation underpinning pregnancy and motherhood

Interplay of behavioral and hormonal factors

Pregnancy and parturition implies a profound endocrine adaptation (Pepe and Albrecht, 2009). This complex hormonal changes are beyond the boundaries of this dissertation, but a brief sketch is that, on one side, there is the activation of systems that sustain the reproductive processes which mainly involve progesterone, estrogens, prolactin, oxytocin and endogenous opioids (opioid-like peptides). And, on the other side, there is an inhibition of the hypothalamic-pituitary-adrenal (HPA) axis and a decline of testosterone levels. For reviews see Rilling (2013), Workman, Barha and Galea (2012), Saltzman and Maestripieri (2011) and Brunton and Russell (2008).

In some animals the commencement of maternal behavior is hormonally ascertain (Pedersen et al., 1982) but in some others, like in lactating females, several hours of contact with the pups is necessary for maternal behavior to be firmly established (Bridges, 2008). So, after parturition, maternal behavior appears to be regulated mostly by the mother-young interaction where different external factors affect such relationship (see boxes 2 and 3 for "Alloparental care" and "Breastfeeding and holding").

Box 2. Alloparental care

It is interesting to note that humans and certain animals can be motherly towards infants without ever being pregnant. Outside the context of pregnancy and parturition, and in the absence of lactation, exposure to the pups alone can be sufficient for alloparental care. Adult virgin female rats who are not exposed to pregnancy hormones will exhibit maternal behavior towards pups when exposed to pups consistently for 24 hours per day during several days (Seip and Morrell, 2008). Alloparenting can also happen in females that are taking care of their offspring and adopt a parental role towards other unrelated infants (Schubert et al., 2009) it can occur in males (Stiver and Alonzo, 2011) and there are also cases of interspecies nursing: .

Clearly, humans are an alloparental species. Even if mothers are usually the primary caregiver, also fathers, grandmothers, other related kin and unrelated professionals take care of the baby. Likewise, the adoption of infants is clearly successful outside the context of endocrine priming. Hence, as Rilling says in his review (2013, p. 733): "Given that many fathers, adoptive parents and step-parents form strong, loving bonds with their children, pregnancy-related hormones cannot be essential for such bonding."

Nevertheless, in the natural state, mothers are consistently exposed to specific hormones during pregnancy and parturition, and this exposure facilitates the mother-infant bond (Broad et al., 2006; Rilling, 2013; Scanlan et al., 2006). The hormonal priming during pregnancy has an impact in maternal behavior, as shown by several studies in rodents:

a) Terkel and Rosenblatt (1972) showed that blood transfused from a parturient female to a virgin female stimulated maternal behavior.
b) Pedersen and colleagues (1982) directed and investigation consisted of intracerebroventricular injections of several hormones and peptides to ovariectomized, estrogen-primed virgin rats. They found that prostaglandin, vasopressin and mainly oxytocin can rapidly induce a full maternal behavior (in front of pups but without a process of sensitization by means of consistent exposure to them) suggesting that the release of these hormones during labor might promote the motherly care of the offspring (Pedersen et al., 1982).
c) Francis and colleagues (2000) found that individual differences in maternal behavior are directly related to variations in oxytocin receptor levels in the central nucleus of the amygdala. This suggests that this neurohypophysial hormone might stimulate the expression of maternal behavior, in part, by inhibiting fear-related neural activity.

Furthermore, as seen in section *Behavioral changes due to reproductive experience*, the interaction with the infant is not sufficient to enhance performance in some non-maternal abilities linked to motherhood:

a) Macbeth and colleagues (2008) reported that pregnant rats show a better spatial memory and a decrease in anxiety-like behavior compared to non-pregnant rats. These changes correlate to modifications in monoamine levels and activity in specific brain regions, indicating that the dopamine, norepinephrine and serotonin systems may contribute to these differences in behavior.
b) Pawluski and colleagues (2006) aimed to determine if the enhancements in spatial learning and memory performance are due to pregnancy and/or mothering alone, studied five groups of age-matched rats: multiparous (birthed and mothered twice), primiparous (birthed and mothered once), nulliparous, pregnant-only (pups removed within 24 hours of birth) and

sensitized (after 21 days of consisted pup exposure). The two groups that showed a significant improvement in performance were primiparous and pregnant-only, showing the contribution of hormones in the performance of these tasks, and particularly, the significant impact that the first pregnancy and first mothering experience has.

c) Tomizawa and colleagues (2003) showed that oxytocin plays a role in the enhancement of long-term spatial memory in mothers. They report that intracerebroventricular injections of oxytocin in virgin mice improved spatial memory performance, whereas contrary, an injection of oxytocin antagonist in multiparous mice (tested 3 days after birth) obstructed the improved spatial memory.

We can conclude that both the external (sensory stimuli from the infant) and internal (hormonal) environments are implicated in the maternal behavior, being the first one (the interaction with the infant) essential and intrinsic to it, and the second one (the hormonal impression during pregnancy, parturition and lactation) not completely necessary for the appearance of the maternal behavior but a facilitator of it.

Box 3. Breastfeeding and holding

One of the mother-young interactions that has been extensively studied because of its association to the endocrine system is breastfeeding. Several studies in humans have found a correlation between breastfeeding and increased tranquility and composure (Groer et al., 2002; Mezzacappa and Katlin, 2002) which are consistent with studies in lactating rodents were lactation lowers the hormonal stress response via the suppression of the HPA axis (Carter, Altemus, & Chrousos, 2001).

A similar dampening of the HPA axis (both basal, including the circadian rhythm, and stress-induced adrenocorticotrophic hormone and glucocorticoid secretory patterns) occurs in humans during the breastfeeding period and it has been hypothesized that this happens in order to promote wellbeing in the mother (facilitating the immune and metabolic systems; preventing inhibition of lactation caused by stress) and the newborn (protecting him/her against stress-related high cortisol concentrations in the milk and also by avoiding the negative effects of a stressed mother (Brunton and Russell, 2008; Macbeth and Luine, 2010; Neumann, 2003). It has also been shown that the action of just holding one's baby has a similar but less intense anxiolytic effect (Heinrichs et al., 2001; Lonstein, 2007).

Interplay of hormonal and neuronal factors

It is well know that the endocrine and neuronal systems alter each other. The mother's brain is a major force in driving essential endocrine adaptations which may, simultaneously, have an impact in the neuronal chemistry and electrical properties of specific brain regions. But, do they induce structural changes in the adult female brain as well?

In a series of studies, Woolley and McEwen reported that estradiol and progesterone have important effects in the adult female rat brain structure and function (McEwen and Woolley, 1994; Woolley and McEwen, 1993, 1992). They proved that dendrites of neurons in the ventromedial hypothalamus and CA1 region of the hippocampus sprout increased numbers of spines on dendrites and synapses, to lose them afterwards at the end of the estrous cycle with the decline of estradiol and the increase of progesterone. In the hippocampus, these changes occur very rapidly: about 30% of the spines disappeared in just 1 day. In view of that, spine and synapse density on ventromedial hypothalamus and hippocampal CA1 pyramidal cells fluctuate naturally as ovarian steroid levels vary across the cyclicity of sexual behavior.

This has been the first demonstration of such short-term steroid-mediated synaptic plasticity taking place naturally in the adult mammalian brain. Since then, several examples of steroid hormones altering adult neuroanatomy in a short-time period have been discovered, showing the sensitivity of the female's nervous system to the hormones that are predominant during pregnancy (for reviews see Breedlove & Jordan, 2001; Kinsley & Lambert, 2008).

Wooley and McEwen's research was replicated in humans by Hagemann and collaborators (2011). They used magnetic resonance (MR)-volumetry to study short-term brain volume alterations during the menstrual cycle. Seven women participated and the measurements took place during menses, at time of ovulation and in the midluteal phase. They found a total brain volume increase at ovulation accompanied with CSF volume loss. No significant changes were found in the control group composed by 7 men. This volume peak did not correlate with estradiol or progesterone hormone levels, but the results still give evidence of the short-term structural brain changes across the menstrual cycle in women.

Resulting, we can conclude that the brain is the conductor of the hormonal symphony that takes place within our bodies, but is also highly sensitive to the hormones it directs, to the extent of experimenting changes in its own anatomy.

Interplay of neuronal and behavioral factors

This close interaction and mutual influence described above between the neuronal and the hormonal factors can also be observed among the neuronal and the behavioral factors.

The nervous system is continually being modified in accordance to the interactions with others and the environment. This allows the brain to be molded or yield to a certain degree and this quality is called plasticity. Disagreeing with the postulation that changes in brain networks is only possible during the infancy, modern neuroscience assume the idea of a permanently plastic brain (Draganski and May, 2008; Johansson and Center, 2004; Pascual-Leone et al., 2005). Brain plasticity is not something that happens when certain conditions are met, but an intrinsic property or normal on-going state of the nervous system throughout its lifespan (Pascual-Leone et al., 2005). It refers to functional as well as structural changes that occur in the brain in order to adjust to modifications in the external environment or internal milieu, and this plastic neuro-reorganization can result either in beneficial or maladaptive consequences (Doidge, 2007; Pascual-Leone et al., 2005) (see boxes 4 and 5 for "Neuroimaging studies assessing plasticity" and "Knowledge in neuroplasticity is leading to more efficient medical approaches").

Box 4. Neuroimaging studies assessing plasticity

Several neuroimaging studies in humans uses as paradigm novel experience and new skill learning for studying different aspects of brain plasticity (Draganski and May, 2008). For example, longitudinal studies based in MRI morphometry methods have demonstrated that anatomical plasticity is noticeable after only three months of juggling practice (Draganski et al., 2004), after three months of studying for the German preliminary medical exam (Draganski et al., 2006) and after two months of playing the video game Super Mario for at least 30 minutes daily (Kühn et al., 2014).

It has also been proved that transcranial magnetic stimulation causes macroscopic gray matter changes as early as within five days of continuous intervention (May et al., 2007). And most remarkably, Pascual-Leone (2005) perform an experiment were subjects underwent daily physical vs. mental practice of learning a five-finger exercise in piano: the results showed the same pattern of changes in cortical output maps with either form of practice. This evidences the capability of the brain to be molded in concordance to merely mental activity, which have been reconfirmed by other experiments (Hölzel et al., 2008; Lazar et al., 2005; Pagnoni and Cekic, 2007).

Hereafter, plasticity is a consequence of all neural activity, mental practice included, were any changes in the sensory input, mental associations and awareness, motor actions and output targets will lead to changes in the nervous system that might be apparent at an anatomical or functional level (Pascual-Leone et al., 2005). Likewise, changes in the nervous system can be reflected in behavior (Pascual-Leone et al., 2005) and thoughts as well as other manifestations of the mind like emotions, feelings, memories and unconscious processes (Damasio, 2010).

Under this comprehension, neural states and mental states are considered as two faces of the same process, or as the same phenomenon studied by different perspectives (Vinent, 2009). Brain and mind are considered to be immanent, like left and right. "Notions such as psychological processes as distinct from organic-based functions or dysfunctions cease to be informative" (Pascual-Leone et al., 2005, p. 379). Hence, neuronal changes have a repercussion in its inherent mental system and vice versa: the mind, a phenomenon that is thoughtful not to be physical, produces changes in the physical nervous system (Damasio, 2010, pp. 467–471).

Following this approach, the behavioral changes observed during motherhood should have an equivalent measurable physical change in the neural system. The aim of this study is to see if those assumed changes are measurable with MRI.

Box 5. Knowledge in neuroplasticity is leading to more efficient medical approaches

Knowledge in neuroplasticity is leading to more efficient medical approaches and neurorehabilitation' techniques in several diseases that include: brain lesion (stroke, intracranial injury), the lack of sensory input to an intact brain (amputation, peripheral nerve lesions) maladaptive plasticity (like focal hand dystonia), neurodegeneration (Parkinson's, Alzheimer's, Huntington's disease and others) and congenital disorders with brain anomalies and children with learning difficulties. Also, the comprehension of structural and functional brain reorganization is being applied to delay the onset of a neurodegenerative disease and aging by means of several treatments and trainings (Doidge, 2007; Johansson and Center, 2004) (Young and Tolentino, 2011).

In order to treat these diseases effectively, we have to better understand the mechanisms underlying neural plasticity. "The challenge we face is to learn enough about the mechanisms of plasticity to modulate them to achieve the best behavioral outcome for a given subject" (Pascual-Leone et al., 2005, p. 377).

Brain changes related to pregnancy and neuronal mechanisms underlying motherhood

Throughout pregnancy, birth and postpartum, some brain modifications at the structural, functional and molecular levels may be required in order to safeguard and promote the fetus growth and delivery, as well as in order to achieve the maternal behavior. There has been an increasing interest towards these specific neural mechanisms and some of these brain adaptations have been recently identify.

In rodents

As we have seen before (see section: *Interplay of hormonal and neuronal factors*), steroid fluctuations during the estrous cycle mediates synaptic plasticity. Pregnancy comprises a significantly longer duration of considerably elevated estrogens and progesterone compared to the estrous cycle and, in concordance, even greater concentration of dendritic spines have been reported in the hypothalamus (Keyser-Marcus et al., 2001) and the CA1 region of the hippocampus (Kinsley et al., 2006) in late pregnant rats.

For instance, neuronal plasticity related to pregnancy has been observed in the medial preoptic area (mPOA) (Keyser-Marcus et al., 2001), a region of the hypothalamus that regulates some components of maternal behavior (Jacobson et al., 1980; Numan, 1994, 1974; Numan et al., 2005). In this brain area, the cell body size and other measures of dendritic structure were significantly increased in late pregnant rats as well as in virgins hormone-treated mimicking pregnancy (with sequential progesterone and estradiol) compared to diestrous, ovariectomized and lactating rats (Keyser-Marcus et al., 2001).

Also, dendritic spine density is increased in the hippocampal CA1 in late pregnant and lactating rats in comparison with virgin rats in the different stages of the estrous cycle (Bergland et al., 1968; Kinsley et al., 2006). And when comparing ovariectomized no hormone-exposed vs. sequential progesterone and etsradiol-treated, the group with the regimen mimicking pregnancy displayed significantly more dendritic spines per 10 than those females not exposed to hormones. The number of dendritic spines of the

sequential progesterone and estradiol-treated group were similar to those of late pregnancy and lactating groups (Kinsley et al., 2006). A supposition is that these hippocampal changes may support foraging and other aspects of maternal behavior by enhancing spatial reference and working memory (Macbeth et al., 2008; Pawluski et al., 2006).

Besides, both areas (mPOA and hippocampus) showed increases in glial fibrillary acidic protein immunoreactivity and astrocytic complexity (Kinsley and Lambert, 2008) and significant differences in monoamine and metabolite levels (Macbeth et al., 2008) in relation to pregnancy. These neural changes denotes increased cellular activity that might be reflected in modifications in both maternal and non-maternal components of maternal behavior, like nest building, pup manipulation, foraging and spatial memory.

Pregnancy-induced morphological synaptic plasticity has also been reported in other areas of the mammal brain. Postpartum rats showed more spines in the anterodorsal medial nucleus of the amygdala (Rasia-Filho et al., 2004) and significant increases in the number of GABAergic, glutamatergic and noradrenergic synapses impinging on oxytocin neurons (concomitant with a reduction of glial coverage of the neurons) in the supraoptic and paraventricular nucleus of the hypothalamus (Theodosis and Poulain, 2001).

Moreover, it has been proved that pregnancy stimulates neurogenesis: during gestation, prolactin encourages the production of neuronal progenitors in the forebrain subventricular zone (Furuta and Bridges, 2005; Shingo et al., 2003). The destinations and phenotypes of these new cells are not completely understood, but some of them migrate to produce new olfactory interneurons contributing to the establishment of maternal behavior since olfactory discrimination is critical for pups recognition and rearing (Shingo et al., 2003). Kopel and colleagues (2012) analyzed the dynamics and morphological characteristics of adult-born granule cells innervating the olfactory bulb of primiparous lactating mothers and conclude that these adult-born neurons undergo enhanced integration into the bulbar circuitry supporting changes in olfactory coding in the new mothers.

The postpartum period has likewise been associated with increased number of dendritic spines in pyramidal neurons located in the medial prefrontal cortex (mPFC) accompanied by better performance on an attentional set-shifting task (Leuner and Gould, 2010). In other words, mother rats showed increased dendritic spine number in

the mPFC which concurs with improved attention and behavioral flexibility (Leuner and Gould, 2010).

Contrary to the neuronal growth described above, several studies have shown that the postpartum period inhibits adult neurogenesis in the hippocampus (Katharina M. Hillerer et al., 2014; Leuner et al., 2007). In accordance to the decrease of the hippocampal cell proliferation, lactating rats show a reduction in hippocampal volume and, interestingly, also brain weight have been shown to be lower in lactating rats as compared to nulliparous females (Katharina M. Hillerer et al., 2014).

Concerning the cause of this decreases, Leuner and colleagues (2007) detected that it was dependent on elevated basal glucocorticoids levels associated with lactation and offspring interactions; they observed that the weaning or the removal of nursing pups reduced basal corticosterone levels and reestablish the production of new hippocampal granule cells in the dentate gyrus of the primiparous female rats (Leuner et al., 2007). But recently, Hillerer and colleagues (2014) reveal that basal corticosterone is only partly involved in the regulation of hippocampal neurogenesis during lactation and that other hormones such as prolactin might play a major role: paradoxically, they found that the inhibition of hippocampal neurogenesis during lactation can be prevented by stress exposure.

Pregnancy and mothering also decrease neural activity in regions that underlie stress and anxiety (da Costa et al., 1996; Wartella et al., 2003). After being exposed to a stress paradigm, primiparous, multiparous and gravid females showed reduced numbers of c-fos immunoreactivity[1] in CA3 region of the hippocampus and in basolateral amygdala compared with non-pregnant neither pup exposed females (Wartella et al., 2003). Also, late pregnant and primiparous females have significantly decreased c-fos mRNA expression in areas associated with stress activation and regulation, including the hypothalamus, medial amygdala, and lateral septum (da Costa et al., 1996). So, in concordance to the inhibition of the HPA axis, an hypothetical explanation is that motherhood may mitigate the usual neural responses to stress providing an advantage in coping with the stresses of birth and offspring care (Leuner and Shors, 2006; Macbeth and Luine, 2010).

[1] C-fos expression can be used as a transynaptic marker of stress-induced neuronal activation.

A lot of questions are still unanswered. Recently, mayor progress has been made in understanding these changes at a molecular level, but this goes beyond the scope of this dissertation. For a detailed review of the organization and molecular mechanisms of the neuroendocrine networks that govern mammalian parturition, lactation, maternal behavior and maternal stress responsiveness, see Brunton and Russell (2008), and Hillerer, Jacobs, Fischer and Aigner (2014).

In conclusion, several mammal studies reveal that pregnancy is accompanied by an important reorganization of the brain by means of both progressive and regressive events mainly involving regional alterations in cell proliferation and dendritic morphology. The affected regions comprise structures that regulate maternal behavior like the medial preoptic area and the olfactory bulb, and structures not directed associated with these behaviors such as the hippocampus and the mPFC.

In humans

Despite modern non-invasive neuroimaging techniques, human studies assessing changes in brain structure linked to the reproductive experience are still scarce.

Pituitary enlargement during pregnancy

It seems that the first association between pregnancy and human brain differences, specifically pituitary enlargement, dates from the year 1898 and was formulated in a doctoral thesis by the physician Louis Comte presented in the University of Lausanne (Comte, 1898). Since then, a few postmortem studies comparing the size of the pituitary gland of pregnant women with those of non-pregnant woman found substantial volumetric enlargements in the first ones (Bergland et al., 1968; Erdheim and Stumme, 1909; Rasmussen, 1938). Erdheim and Stumme (1909) described that during the course of pregnancy there is a progressive decrease in granulocytes (white blood cells, specifically eosinophils and basophiles) and a progressive increase of cromophobe cells, (responsible for producing the hormones of the anterior pituitary and releasing them into the bloodstream) which also became altered by an increase in the amount of cytoplasm. They then, named this altered cromophobe cells as “pregnancy

cells". Latter, Bergland and colleagues (1968) specified that those cell were prolactine cells and that they were increasing not only in size but also in number.

This autopsies' evidence of pregnancy resulting in physiologic pituitary enlargement has been corroborated in vivo using MRI. Comparing women at different stages of pregnancy and postpartum with control groups, expecting women showed a significant increase in pituitary volume in correlation with the progression of pregnancy (Dinç et al., 1998; Elster et al., 1991; Gonzalez et al., 1988). At the end of pregnancy, expectant women had a pituitary overall increase of 136 percent compared with that of the control group (Gonzalez et al., 1988), reaching the highest values during the 1st week postpartum for latter return rapidly to its normal size within 6 months (Dinç et al., 1998).

Whole brain morphological changes during pregnancy

Whole brain morphological changes related to pregnancy is the specific research area of the present study. Before this study, only one study has address this matter and therefore I will explain it in detail:

Oatridge and colleagues (2002) were the pioneers in searching for the effects on pregnancy on the whole brain. They investigated the changes in brain size during and after pregnancy in healthy women and in women with preeclampsia. They obtained T1-weighted MR images of 9 healthy women during pregnancy and after delivery. In addition, some of these participants were also scanned before pregnancy, during pregnancy and within 52 weeks after delivery. Besides, 5 women with preeclampsia were also examined (Figure 1, A).

The method consisted in segmenting the brain from the surrounding tissue with a knowledge-based semiautomated segmentation program to latter perform a within subject subvoxel image registration in order to align images on a common coordinate system. The reference or baseline image was the last images acquired before delivery (the ones obtain at term in the healthy group and the ones obtained immediately before delivery in the preeclamptic group). A registered differences image was obtained to illustrate the relative location and the type of change (increases or decreases), and to monitor their time course. The registered subtraction images of each subject were visually assessed and qualitatively categorized in a nine-point scale by two experienced

observers. Also, volume measurements of the brain and ventricles (lateral and third ventricles but not the aqueduct or the forth ventricle) were obtained by a semiautomatic contour and thresholding technique (see examples of the contour in Figure 1, B). Threshold values were calculated by means of histogram analysis and a binary image of the brain and cerebrospinal fluid were generated representing the pixel count of each of the two tissues. From the pixel[2] count the total voxel[3] count for each image section was calculated in order to obtain the volume measurements. The statistical analysis consisted in paired-sample *t*-test to assess the significance of changes between the different time points, and also between the healthy and the preeclamptic groups. The Spearman rank correlation coefficient was used to evaluate the relationship between the visual assessment and the changes in volume.

In the healthy group, both techniques (the visual assessment of brain and ventricles as well as the semiautomatic contour and thresholding technique) resulted in a brain volume loss during pregnancy, with a minimal volume at term that reversed by six months after delivery (Figure 2). Compared with the size at term, as early as six weeks after delivery the increase in brain size was highly significant ($p<0.001$). Also at 24 weeks the increase was very significant ($p<0.001$) as well as at the latter post-delivery images ($p<0.001$). With regard to the decreases in brain size, in the two participants who were examined before conception, reductions of 4.1% and 6.6% were evident at term. And in the other two participants who were scanned at gestational weeks 15 and 19, the brain decreased in size a 4.5% and 2% at term.

The ventricular size presented an equivalent increase in size during pregnancy and the corresponding decrease in size after delivery (Figure 3). Compared with the size at term, the reduction was highly significant at 6 weeks ($p<0.001$), 24 weeks ($p<0.001$) and 40 weeks or later ($p<0.013$).

The same pattern, decreases in brain size and increases in ventricular size during pregnancy, was found in the participants with preeclampsia (Figure 2 and 3).

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[2] A value on a regular grid on two-dimensional space.

[3] A value on a regular grid on three-dimensional space.

Change in Brain Size uring and after Pregnancy:
Study in Healthy Women and Women with Preeclampsia

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Basant K. Puri, Luca Fusi and Graeme M. Byddner

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A.

	Imaging times						
Subjects	Before conception	15-30 weeks' gestation	Before delivery	6 weeks after delivery	24 weeks after delivery	40 weeks after delivery	52 weeks after delivery
Healthy group (n=9)	2	4	9	9	7	3	3
Preeclamptic group (n=5)	0	0	5	5	3	2	3

B.

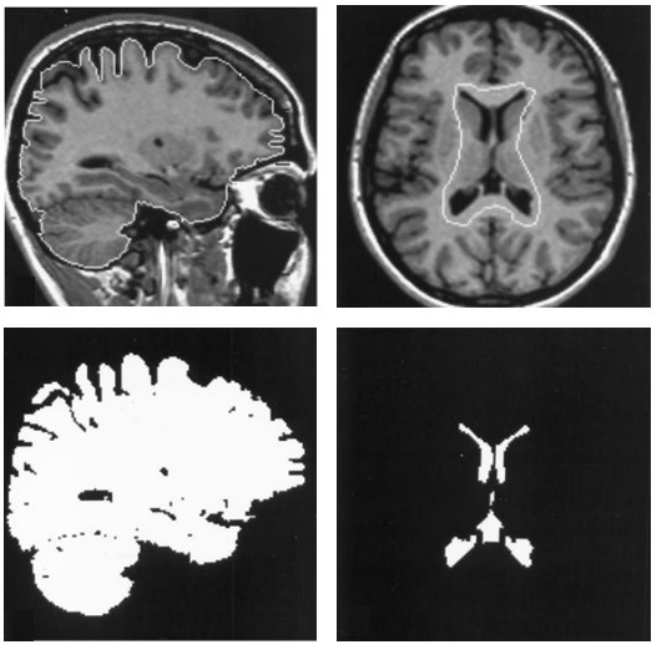

Figure 1. Information extracted from Oatridge and colleagues (2002) concerning the methods. **A)** Relation of subjects in the healthy and preeclamptic groups and the moments in which they were scan. **B)** 3-dimentional T1-weighted MR image with the brain and the ventricular contour, and underneath the binary images corresponding to the brain and the CSF. Adapted from Oatridge et al. (2002) (Figures replicated with AJNR permission).

While comparing healthy versus preeclamptic groups, results show that the brain of the preeclamptic women was significantly smaller before delivery (p=.049), at 6 weeks after delivery (p=0.05), at 24 weeks after delivery (p=0.05) and at 40 weeks after delivery (p=0.028). No significant differences were found in the ventricles' size between these two groups.

TABLE 4: Absolute ventricular volumes (cm^3) before, during, and after pregnancy

Subjects	Before Pregnancy	15 Weeks' Gestation	20 Weeks' Gestation	25 Weeks' Gestation	30 Weeks' Gestation	35 Weeks' Gestation	Before Delivery (Term)	6 Weeks after Delivery	24 Weeks after Delivery	40 Weeks after Delivery	52 Weeks after Delivery
Healthy group											
1							29.9	27.4	27.9	28.1	
2							14.9	12.2	11.1		
3							11.2	7.8	6.9	7.6	6.7
4							17.5	17	15.4	15.1	15.3
5							17.4	15.4	15.1	14.1	15.4
6	6.7	6.7	7.4	7.1	7.1	8.6	9.5	6.8	6.3		
7		14.8	15.6	16.1	16.8		18.1	14.0	11.6		
8	17.6		19.8	20.1	20.0		21.3	18.6	17.3		
9			17.1		17.9		17.8	15.6			
Preeclamptic group											
1							11.5	10.9	8.7	7.9	9.0
2*							20.7	16.7	15.2		15.1
3							12.1	10.4		9.2	
4							35.2	30.4	30.3		29.0
5							13.0	11.5			

* Patient treated with diuretics.

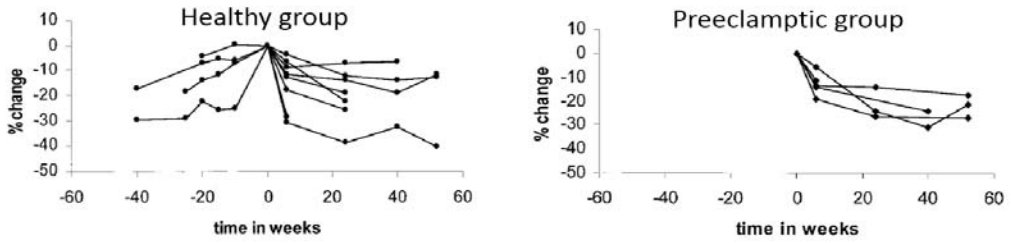

Figure 2. Information extracted from Oatridge and colleagues (2002) concerning the brain volume results. The table shows the absolute brain volume (cm3) before, during and after pregnancy in both groups. The scatter plots diagrams shows the percentage of change in brain size at the different time-points: the brain decreases in size until delivery (represented by 0) and then it recovers (Table and graphics replicated with AJNR permission).

TABLE 4: Absolute ventricular volumes (cm^3) before, during, and after pregnancy

Subjects	Before Pregnancy	15 Weeks' Gestation	20 Weeks' Gestation	25 Weeks' Gestation	30 Weeks' Gestation	35 Weeks' Gestation	Before Delivery (Term)	6 Weeks after Delivery	24 Weeks after Delivery	40 Weeks after Delivery	52 Weeks after Delivery
Healthy group											
1							29.9	27.4	27.9	28.1	
2							14.9	12.2	11.1		
3							11.2	7.8	6.9	7.6	6.7
4							17.5	17	15.4	15.1	15.3
5							17.4	15.4	15.1	14.1	15.4
6	6.7	6.7	7.4	7.1	7.1	8.6	9.5	6.8	6.3		
7		14.8	15.6	16.1	16.8		18.1	14.0	11.6		
8	17.6		19.8	20.1	20.0		21.3	18.6	17.3		
9			17.1		17.9		17.8	15.6			
Preeclamptic group											
1							11.5	10.9	8.7	7.9	9.0
2*							20.7	16.7	15.2		15.1
3							12.1	10.4		9.2	
4							35.2	30.4	30.3		29.0
5							13.0	11.5			

* Patient treated with diuretics.

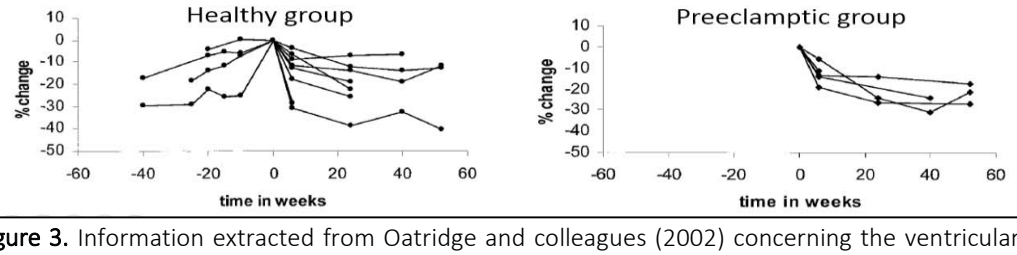

Figure 3. Information extracted from Oatridge and colleagues (2002) concerning the ventricular volume results. The table shows the absolute ventricular volume (cm3) before, during and after pregnancy in both groups. The scatter plots diagrams shows the percentage of change in ventricular size at the different time-points: the ventricles increases in size until delivery (represented by 0) and then they decrease (Table and graphics replicated with AJNR permission).

It is worth mentioning that in all nine healthy participants an increase in the pituitary gland was observed at term, with the subsequent decrease to a normal size as early as six weeks after delivery.

Despite the novelty of the results, this research has received little attention; the reason might be that the study presents several caveats. With regard to the study design:

- Most of the subjects lack a pre-pregnancy scan
- The lack of a control group
- The small size of the sample
- The inclusion of a clinical sample: a third of the sample had preeclampsia and received a short course of steroids treatment

With regard to the MRI acquisitions and analysis, the main handicap of this methodology is:

- the percentage of changes are calculated using as reference the last images acquired before delivery, instead of having as the baseline the pre-pregnancy scan
- it does not allow to identify the regions of the brain in which the reduction is focused

Of course, we do not ignore the fact that there has been an increasing evolution in neuroimaging techniques in this last decade so that recent studies present considerable technical advantages (see section *A Brief description of MRI based neuroanatomical techniques*).

Whole brain morphological changes during postpartum

Kim and colleagues (2010a) also assessed morphological changes of the mother's brain during the postpartum period. To my knowledge, this is the only study addressing this and hence I will also describe it in detail.

Nineteen mothers participated in the study. They were all the biological mothers of full-term heaty infants and were breastfeeding. Eight were multiparous. They presented no signs of depressive symptoms.

Mothers were scanned high-resolution magnetic resonance images at two time points during the postpartum: the pre-scan was between 2-4 weeks postpartum and the post-scan between 3-4 months postpartum. A voxel based morphometry (VBM) assessment was used, which, unlike the method used by Oatridge and collaborators, allows identifying the specific brain regions that suffer longitudinal changes.

Mothers' subjective perception on parenting and baby was also measured with the semi-structured interview Yale Inventory of Parental Thoughts and Actions – Revised.

Results revealed that from time 1 (2-4 weeks postpartum) to time 2 (3-4 months postpartum) mothers showed increases in gray matter (GM) volume in superior, middle and inferior prefrontal cortex, precentral and postcentral gyrus, superior and inferior parietal lobes, insula and thalamus ($p<0.05$, false-discovery-rate corrected, >100 voxels). No decreases in GM volume was observed between the two time-points. In midbrain areas, increased gray matter volume in hypothalamus, substantia nigra and amygdala was positively correlated with maternal subjective positive perception of her baby.

These results suggest that the first months of motherhood in humans are accompanied by structural changes in brain regions implicated in maternal motivations and behaviors.

Unfortunately, this study has the limitations that no control group was included.

Changes in cerebral metabolism during pregnancy

Little is known of the physiological changes in cerebral metabolism during pregnancy in humans.

Rutherford and colleagues (2003) studying if there were brain changes in preeclamptic women, included a sample of healthy pregnant primiparous women and a control sample of non-pregnant nulliparous women, which lead to knowledge about the healthy pregnant brain as well. A part of their research was to investigate whether normal pregnancy conveys any changes in the concentration of the cerebral metabolites *N*-acetyl aspartate (NAA), choline, creatine and lactate using proton MR spectroscopy. They found that the NAA/choline ratio was significantly higher in the pregnancy group compared to the control group ($p<0.05$), especially at the second trimester and at the

late third trimester (34-36 weeks of gestation) ($p<0.01$), which was accompanied by a significantly lower choline in the expecting women ($p<0.05$). There were no other significant differences between the groups. At the late postpartum (14-24 weeks after giving birth), there were no significant difference with regard to the NAA/choline ratio either. In other words, they detected a gradual increase in the NAA/choline ratio through pregnancy and a marked decrease at the postpartum. They also measured cerebral vasospasm or vasoconstriction with magnetic resonance angiography but the subjects did not show any demonstrable narrowing of the cerebral vessels (Rutherford et al., 2003).

Holdcroft and colleagues (2005) used phosphorus-31 MR spectroscopy to assess changes in brain metabolism in a longitudinal study involving pregnant women and a control group. Participants of the experimental group were scanned at term, at 6 weeks after birth and, if possible, at 6 months postpartum. The control group was scanned twice, a month apart. Results showed that pregnant women and control women had no significant differences in the relative levels of any of the metabolite associated with cerebral bioenergetics and cell membrane metabolism (phosphomonoester, inorganic phosphate, phosphodiester, phosphocreatine and three nucleoside triphosphates). Nevertheless, an increase in brain intracellular pH was observed in the mothers at 6 weeks after delivery in comparison to the control group, to the measurement at term and to the measurements at 6 months after delivery, showing that this observed alkalosis returns to normal within half year postpartum.

These elucidations made by Rutherford (2003) and Holdcroft (2005) reflect altered cellular metabolism associated with pregnancy and postpartum in some parameters of energy regulation and cellular activity. Nevertheless, the study of this matter is on its initial phase and further investigation needs to be done, since it will extend our understanding of fundamental neurophysiological mechanisms like the interplay between neurons, blood flow and glial cells.

Functional brain changes underlying motherhood

In contrast to the few studies approaching structural brain changes in human mothers, various are the studies that assess brain activity in front of own-infant stimuli using fMRI. These studies provide avenues to identify regions of the brain involved in motherhood by measuring enhanced blood oxygenation in the mother's brains in

response to their babies' auditory or visual stimuli. Accumulating evidence suggests that mothers present a different pattern of brain response when viewing/hearing their own *vs.* other infants.

The pioneers that studied brain activity in mothers were Lorberbaum and colleagues (1999). Since a good recognition and evaluation of infant vocalizations plays a major role in bonding and in guaranteeing the baby's well-being and survival, they used infant cries as stimuli. This stimuli continues to be utilized to study maternal-paternal brain response in healthy populations (Kim et al., 2010b; Musser et al., 2012; Seifritz et al., 2003; Swain et al., 2008) as in depressed mothers (Laurent and Ablow, 2012).

Another broadly employed stimuli are pictures or videos of the own-child. Bartels and Zeki published in 2004 one of the most influential studies of this kind: "The neural correlates of maternal and romantic love". Since them, several studies have utilized this kind of visual stimuli to assess mother's brain responses in front of pictures or videos of their own child in contrast to another child with an comparable age (Atzil et al., 2011; Leibenluft et al., 2004; Lenzi et al., 2009; Nitschke et al., 2004; Noriuchi et al., 2008; Strathearn et al., 2008; Wan et al., 2014).

The interpretation of the areas involved in front of owns child stimuli is complex, as studies uses a mixture of stimuli (baby cries, laughter, child pictures, child videos and/or videos of mother-infant interaction) that presents different baby affects, examining a varied time windows, and accompanied by executing different tasks during the scan. But even if the results show inconsistencies across studies, taking together, they present an up to date perspective for our understanding of the neural substrates that underlie the expression of parental care. In an attempt to summarize and contrast them, I have elaborated a table that synthetizes the studies that assess mother's brain activity employing visual stimuli (see appendix 1). The results of this examination matches with Swain and collaborators' review (2014) who also integrates fMRI studies that employs auditory stimuli, as well as the responses of healthy fathers and mothers with psychopathology.

The ground-breaking work by the group of Dr. Swain (2014) proposes a model based on these functional brain imaging studies of parenthood as well as on animal studies, (see Figure 4 for a graphic representation of Swain and collaborators' model).

The model exposes that the reception of the infant stimuli (A), activates in parallel a set of cortico-limbic circuits (B) and generates an output which is the basis of parental sensitivity and behavior (C) and has an influence in the child. The cortico-limbic circuits (B) are differentiated in four units that interact with each other:

i) analyzes the sensory input and salience toward motivation and reward (sensory cortex, amygdala, ventral striatum and hippocampus);

ii) reflexive caring impulses such as sensitive touch (licking and grooming in mammals), vocalizations and feeding (mostly subcortical areas: hypothalamus, medial preoptic area, lateral septum, extended amygdala and thalamus);

iii) top-down regulation of intense emotions (mPFC, anterior cingulate cortex (ACC), orbitofrontal cortex and insula);

iv) cognition circuits, including mentalization, empathy, theory of mind and complex planning (mirror neuron systems: frontal, insula and superior-temporal-parietal cortex, cingulate).

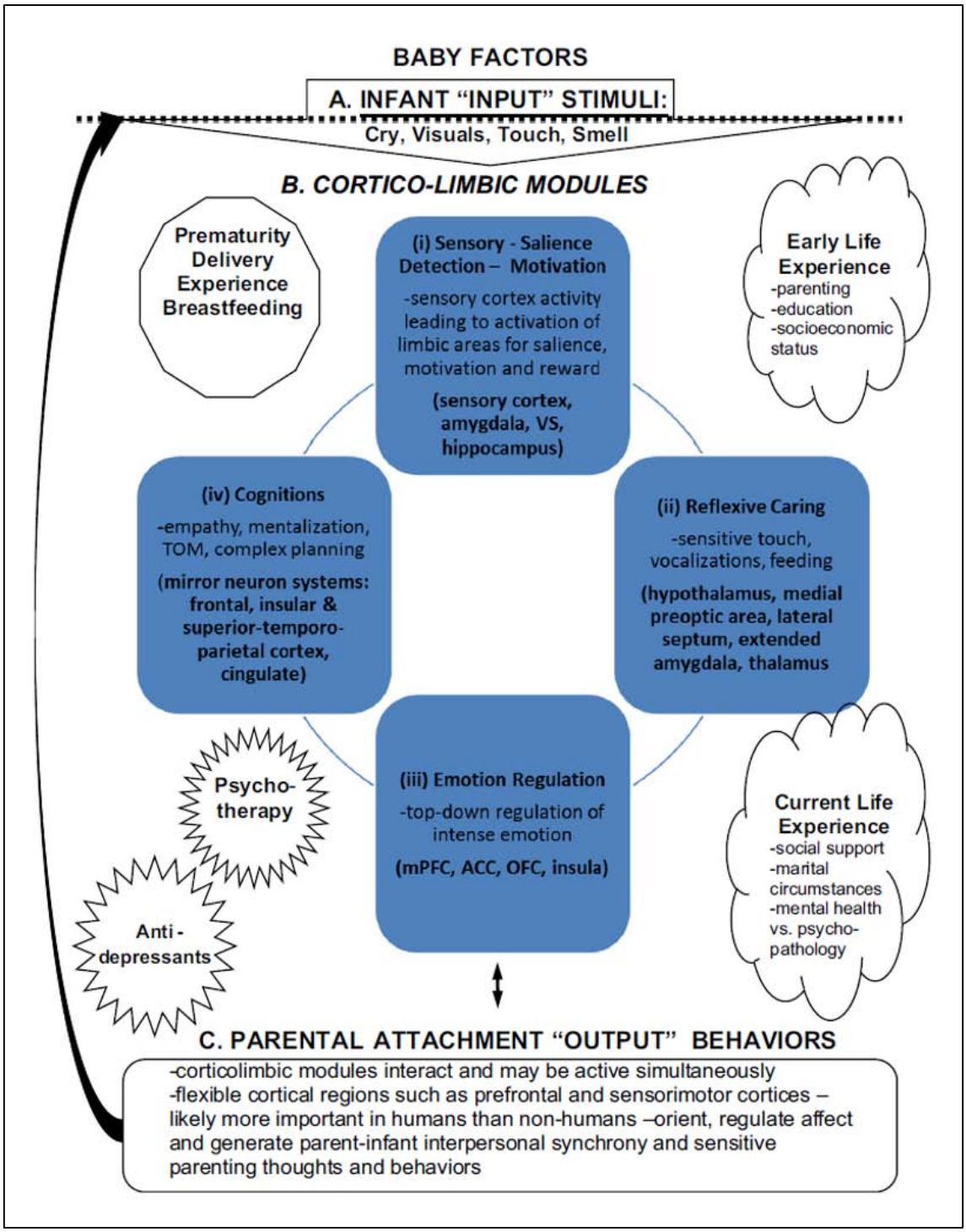

Figure 4: Swain and collaborators' model of the human parental brain circuits based on human and animal studies (figure replicated with the author's permission). "*Human parental circuits. Brain regions expected to be important to human parenting. This is based on human and animal studies. Based on brain imaging of parents at this point, the following model is presented to stimulate discourse on the brain basis of parenting behaviors. First, key parenting sensory signals, including cry, visuals as well as touch and smell from baby (A) activate in parallel a set of cortico-limbic circuits (B) to (i) analyze the sensory input and update saliences toward motivation and reward and coordination and other modules for (ii) reflective caring, (iii) emotion regulation, and (iv) complex cognitions, including mentalization, empathy and theory of mind. The output (C) of these modules forms the basis of parental sensitivity and influences child development. This inclusive and general model may be dissected in future studies involving different stimuli and specific measures of behavior and cognition*." (Swain et al., 2014, p. 90).

In conclusion, several animal and human studies assessing pregnancy and motherhood considered collectively allow us to make up a discrete assemblage of interacting brain areas that sustains maternity, but still many questions remain to be answered and it is worth it to look after them (see box 6 for "Applications of studying the neurobiological substrates of motherhood").

In order to advance our understanding of the human parental brain, which has a potential far reaching impact (see box 7 for "Parent-infant interactions and its repercussion on the infant's health"), future fMRI studies should deeply explore the significance of the neural correlates by relating brain activity to parental behavior and emotions outside the scanner, and should study deeply specific populations, like mothers with depression. But most primarily, the study of **morphological brain changes** that might occur in the human women who undergoes pregnancy can give us important knowledge about motherhood as well as about the human brain in general. As Kinsley says (1999, p. 137, penultimate paragraph): "neural activity brought about by pregnancy and the presence of the pups may literally reshape the brain, fashioning a more complex organ that can accommodate an increasingly demanding environment".

Box 6. Applications of studying the neurobiological substrates of motherhood

The knowledge about the neurobiological substrates of motherhood can be applied to areas specifically related to motherhood— the health of the mother and the infant-mother attachment — as well as to areas related to the general brain mechanisms.

Mothering is complex and involves a vast range of behavioral propensities that are regulated primary by the brain. "To mother appropriately requires the action of multiple systems in the domains of sensation, perception, affect, reward, executive function, motor output and learning" (Barrett and Fleming, 2011, p. 369). Thus, the neuroscientific study of normal pregnancy and mothering provides remarkable opportunities to characterize the neurobiological basis of, for example, stress response, aggressiveness, mood changes and bonding, to latter translate the findings to the prevention and treatment of disorders in non-pregnant individuals as well.

Box 7. Parent-infant interactions and its repercussion on the infant's health

The parent-child relationship, besides ensuring the continuation of the species, provides the foundation for the infant's neurobiological, cognitive and socio-emotional development. As the relationship with the parents is of a close dependence on the early years of life, the bond that parents establish with their baby will leave an imprint, a model of what to expect and not of their environment, an understanding of the consequences of their behavior and a pattern of attachment (Barrett and Fleming, 2011; Bowlby, 1969; Brazelton and Cramer, 1991; Fonagy et al., 1993; Gerhardt, 2004; Music, 2010; Raphael-Leff, 2002; Shonkoff et al., 2012; Spitz, 1945; Swain et al., 2014).

The imprint will be positive, empowering growth and a factor of resilience to the extent that the infant have had a good-enough-experience with sensitive and contingent caregivers that have covered their basic physical and emotional needs. If the infant's experience is mostly adverse (insensitive, neglectful, abusive or depressed caregivers) the physiological alterations that affect brain development may persist for life leading to mental illness (McCrory et al., 2012; Shonkoff et al., 2012; Teicher et al., 2006; Thompson, 2014; Wan and Green, 2009). It has been argued that the association of insensitive parenting with poor developmental outcomes in the child could be driven by genetic or environmental factors shared by parents and offspring, but cross-fostering experiments in animals defend a causal link (Champagne and Meaney, 2001; Danchin et al., 2011; Maestripieri et al., 2007).

Shonkoff and colleagues (2012) based on the advances of multidisciplinary sciences of human development —fields of investigation as diverse as neuroscience, molecular biology, genomic, developmental psychology, epidemiology, sociology and economics— synthesize that:

1. "*Early experiences are built into our bodies;*
2. *significant adversity can produce physiologic disruptions or biochemical memories that undermine the development of the body's stress response systems and affects the developing brain, cardiovascular system, immune system, and metabolic regulatory controls; and*
3. *these physiologic disruptions can persist far into adulthood and lead to lifelong impairments in both physical and mental health*."

This advocates that diverse adult diseases are, in fact, developmental disorders that begin early in life, when the constitution of the bonding with the parents is crucial. "It is widely acknowledge that the nature of the maternal care a child receives can have long-term repercussions" (Meaney and Szyf, 2005, p. 456). Recent research in humans also suggest that an adverse quality of care in the family of origin may negatively affect subsequent parenting (Champagne and Meaney, 2001; Kim et al., 2010b).

Nowadays, advance technologies make possible a growing scientific understanding about the common roots of health, learning and behavior in the early years of life. This presents a potentially transformational opportunity for the future of mental health, were perinatal and early infancy sciences are emerging as a promising focus for creative investment. Therefore, the comprehension of the neurobiology of the maternal brain is fundamental.

"The parent-infant bond is so central to the human condition, contributes to risks for mood and anxiety disorders, and the potential for resiliency and protection against the development of psychopathology throughout life, not to mention the far-reaching aspects of human attachment across individual behaviors and between cultures" (Swain, 2011, p. 1251).

(For more information see Nadine Burke Harris' talk at:
http://www.ted.com/talks/nadine_burke_harris_how_childhood_trauma_affects_health_across_a_lifetime/transcript?language=en#t-852628).

A brief description of MRI based neuroanatomical techniques

In the last years, research on human brain plasticity has been boosted by modern neuroimaging techniques. Among neuroimaging techniques, Magnetic Resonance Imaging (MRI), the technique used in the study presented here, is widely used because is a non-invasive tool, has a good spatial resolution and offers the possibility to combine structural data with other techniques like fMRI. Hence, MRI has revolutionized the way we can study the structure and the function of the human brain *in vivo* throughout the entire life span.

MRI works by placing the human body in a strong static magnetic field (B0; 0.5 to 7.0 T) and applying a brief pulse of electromagnetic energy. This pulse produces an oscillating magnetic field that excites hydrogen atoms since they have magnetic properties. Besides, hydrogen atoms constitutes the most abundant substance in the body, water, and there for the whole body is measurable by MRI. The excitation of hydrogen atoms consist in making the little dipoles formed by the hydrogen nuclei rotate away from their axes and, in turn, measure the time it takes for the nuclei to "relax" back to their original position by detecting a radio frequency signal emitted by these atoms. The contrast between different tissues is defined by the rate in which excited atoms return to the equilibrium state. By minimally changing the static magnetic field at different positions is possible to establish the spatial origin of the signal and ultimately to create a 3-dimentional image of the measurement.

What is measured depends on the combination of several imaging parameters or on what is technically called the acquisition sequence. The present study consist in a T1-wighted in order to quantify GM volume (see box 8 for "Imaging brain structure and function").

In order to convert the structural magnetic resonance imaging information into a characterization of brain's anatomy and quantitative biomarkers, there has been an increasing implementation of specific algorithms and software. These neuroimaging analysis procedures are called under the name *brain morphometry techniques* and allow quantifying anatomical features such as GM volume. This provides a useful framework to assess brain's anatomy characterization over time and across individuals, and it is also a prerequisite for the interpretation of functional data.

Box 8. Imaging brain structure and function

For imaging **brain structure**, the most common acquisition sequences are:

- T1-weighted and T2-weighted images: used for quantifying the volume of GM and white matter (WM) (in a global and a regional manner), and estimating the cortical thickness or other morphological properties of the cerebral cortex, such as its folding.
- Diffusion-tensor images and magnetization transfer images: used to characterize structural properties of WM (global and regional). Diffusion-tensor images allows to measure the location, orientation and anisotropy of the WM tracts since the architecture of the axons and their myelin sheaths in parallel bundles promotes the diffusion of the water molecules preferentially along their main direction (Hagmann et al., 2006). Magnetization transfer images offers a nonspecific indicator of the structural integrity of the tissue by measuring the hydrogen atoms that has a restricted motion (generally conceived as being bound to macromolecules such as proteins and lipids) and those that moves with many degrees of freedom. This technique improves the detection of changes in the structural status of the WM enabling the characterization of tissue and pathologic entities (Grossman et al., 1994).
- T1 and T2 relaxometry: it is based on the physical aspects of nuclei relaxation to the ground state after being excited by the electromagnetic pulse. As the relaxation rate depends strongly on the microscopic environment (kind of tissue, mobility, etc.) this imaging technique can detect variations on relaxometry measurements caused by abnormalities on a specific region (Carneiro et al., 2006).
- Spectroscopy: uses the hydrogen proton signals to quantify a target metabolite concentration in the brain (choline-containing compounds, creatine, inositol, glucose, N-acetyl aspar, alanine and lactate). This allows to obtain biochemical information in a non-invasive way for medical research or clinical diagnosis (Jansen et al., 2006).

For imaging **brain function** or the operational organization of the brain, the most common acquisition sequences is T2-weighted fast spin-echo pulse which allows to measure Blood oxygenation-level dependent (BOLD) signal.

Blood oxygenation-level dependent signal reflects the proportion of oxygen-rich and oxygen-poor blood in a given brain region at a given moment. Because there is a strong correlation between the regional cerebral blood flow and the amount of synaptic activity, the BOLD signal is a good, although indirect, measure of brain activity or brain function. In other words, the BOLD signal maps the neural activity in the brain by measuring the change in blood flow. This measure can be accompanied by a given paradigm consisting in any kind of sensory, motor or cognitive stimuli/task, in order to detect the brain regions that are likely to respond to such stimuli/task. It is also possible to measure the brain function or regional interactions that occur when the person is not performing any explicit task or receiving any specific stimuli, which is called Resting-state-fMRI.

One of the most utilized whole brain morphometry tool is the VBM (Ashburner and Friston, 2000). This analysis technique uses th statistical approach of *statistica parametric mapping* (SPM)[4] and allows to register the brain to a template to later compare the image volume across brains at every voxel.

[4] (http://www.fil.ion.ucl.ac.uk/spm/)

The recent VBM variation for longitudinal data, called *longitudinal diffeomorphic modeling tool* (Ashburner and Ridgway, 2013), is the method utilized in the present study. It assess gray matter volume and is specifically designed for longitudinal two time-points data, which requires proper image processing, modeling algorithms and statistical models due to the dependence of repeated measurements within-subjects (see in Methods, section *MRI data analysis* for a broader description of this technique).

Contributions of this study

As described before, Oatridge and collaborators (2002) were the pioneers addressing whole brain morphological brain changes related to pregnancy (see section *Whole brain morphological changes during pregnancy*), but the technique they employed does not allow to identify the specific brain areas involved in the changes. In addition, they lack a control group and included a subsample of women with preeclampsia. Therefore, the study presented here aims to surpass the handicaps of Oatridge and collaborators (2002).

Table 1 presents a strength comparison of both studies, were the improvements of the studies presented here are noticeable. The only aspects in which Oatridge et al. (2002) presents an advantage is that it presents several measurements during pregnancy and during the postpartum period. We decided not to scan during the pregnancy because it might have lowered the number of participants (since, even if a MRI scan is meant to be save, a pregnant women usually does not want to expose herself to any extra strange situations) and because scanning more than two times per subjects would have significantly increase the expenses of the study.

In other words, the contributions of this study are to elucidate if pregnancy causes gray matter volume changes, in which brain areas and to what extent in a very well controlled manner.

Table 1. Strength comparison chart

	Oatridge et al. 2002	Present study
Strengths of this study		
Sample size	14	25
Inclusion of a clinical sample	Five of the subjects had preeclampsia and received a short course of steroids treatment	17 participants achieved pregnancy with a fertility treatment but no subject presented any clinical condition
Pre-pregnancy scan	Only 2 subjects	All 25 subjects
Comparable control group	No	Yes
Men (fathers) control group	No	Yes
MR scanner system	1.0 Tesla	3.0 Tesla
MRI analysis	Does not allow to identify the regions of the brain in which the reduction is focused	It allows to precisely identify the affected brain regions and it is specifically designed for longitudinal data.
Strengths of Oatridge's study		
Scans during pregnancy and postpartum	Several	One scan pre-pregnancy and one scan post-partum; no scans during pregnancy

Table comparing the strengths between Oatridge et al. 2002 and the present study.

OUTLINE, OBJECTIVE AND HYPOTHESIS

That reproductive experience modifies the female mammal's brain is now undeniable. And in relation to humans, it has been broadly hypothesized that the adult brain may undergo morphological changes in relation to pregnancy and birth. One study have assessed this before (Oatridge et al., 2002) but the small and heterogeneous sample with lack of good controls, as well as the image processing method used that only allows to know about differences in global brain volume, aims to take up again the question. We consider this a highly intriguing area of research: the neural plasticity inherent in reproduction itself.

Therefore, we conducted a longitudinal study to examine GM changes using a pairwise longitudinal registration voxel based morphometry on high-resolution magnetic resonance images of first time mothers. The fathers — who experiences the psychologic and environmental changes of having a baby but not the physiologic changes of pregnancy — also participated in the study, as well as a comparable control group consisted of nulliparous women and their male partners: stable couples who were also willing to become parents but not during the next year. The measurements were at two time points: before conception and in the postpartum period. Dispositional empathy and cognitive measurements were also obtained to make correlations.

The hypothesis is that **the reproductive experience causes gray matter volume changes in the human brain** and that this changes might correlate with the dispositional empathy and cognitive measurements. Is not possible to have a clear indication of the localization of the brain changes based on the actual studies. With regard to the direction of the changes, the only previous study that asses morphological brain changes related to pregnancy in humans found a brain volume loss during pregnancy (Oatridge et al., 2002), therefore, our a priori hypothesis is that **pregnancy will cause GM volumetric reduction**.

METHODS

Study design

This is a longitudinal experimental study where first-time mothers were scanned using magnetic resonance imaging at two time points: before the pregnancy (pre session) and during the postpartum period (post session). The fathers also participated in the study as well as a comparable control group formed by nulliparous women and their couples. Neuroimaging results were correlated with cognitive and empathy measurements.

The hypothesis is that in humans, pregnancy (independent variable) causes gray matter volume changes (dependent variable).

Participants

Sixty-six women and most of their respective couples (58 men) participated voluntarily in the study. Forty-three of them wanted to become pregnant for the first time and were assigned to the experimental group. The remaining 23 women were not willing to become mothers during the next year and so they were assigned to the control group.

They were recruited from the fertility center *Instituto Valenciano de Infertilidad* and by means of another non-medical source, mainly word of mouth.

The exclusion criteria included:

- women who had previous pregnancies that lasted more than the first trimester;
- participants with ages under 24 or over 50;
- any psychiatric or neurological condition;
- any personality disorder or history of drug consumption;

These standards were assessed by an interview in each session directed by clinical psychologists and the application of the MINI International Neuropsychiatric Interview (Sheehan et al., 1998).

At the post session, the Edinburgh Postnatal Depression Scale (Cox et al., 1987) adapted to Spanish (Castañón and Pinto, 2008) was also administered to the experimental group in order to detect postpartum depression symptoms. One out of 25 mothers showed postpartum depression symptoms and was already being helped by a specialist.

The study protocol was approved by the local ethics committee (*Comitè Ètic d'Investigació Clinica de l'Institut Municipal d'Assistència Sanitària*) and all subjects gave written informed consent.

Thirty seven percent of the experimental group did not become pregnant after six months of the first scan, so these 33 participants were excluded from the study. Also, 3 participants were not included due to a neuro-pathological condition encountered during the MR, another participant could not tolerate being inside of the scan, and 3 scans could not be used due to poor image quality. This left a final experimental group sample of 25 women (mean age 33.4 years, standard deviation (SD) 3.9) and 19 men (mean age 35.2 years, SD 4.3) and a control group sample of 20 women (mean age 31.1 years, SD 5.6) and 17 men (mean age 31.6 years, SD 6.4).

Seventeen of the 25 women of the experimental group achieved pregnancy with a fertility treatment. Five of the couples had twins. The mean age of the baby at the time of the post pregnancy session is 73.5 days (SD 47.8), which is equivalent to 2.4 months (SD 1.5).

Data acquisition procedure

All acquisitions were conducted over a period of 2 years and 7 months.

The study was performed at the Barcelona Biomedical Research Park and *Parc de Salut Mar*, Barcelona, where the couples came individually for an hour and a half when requested. They already had information of the experiment by means of the study's web page (http://www.elcervellsocial.org/plasticidad/) but there was also extra time allocated to explain the procedure involved and to answer any questions or reservations they had. Each signed informed consent.

The structural scan was followed by two fMRI paradigms, which are not part of the project described here, but the total time that the subject was in the scan was 30 minutes. Also, as part of the fMRI study, blood extractions were acquired in order to measure several hormone levels. The order in which the fMRI scans, the blood extractions and the tests were done was randomized between women and men.

As described before, each participant had a personal interview that included the medical and psychiatric history as well as the structural Mini International Neuropsychiatric Interview (Sheehan et al., 1998) in Spanish (Ferrando et al., 2000). They were also was asked to complete the following test and questionnaires:

- Interpersonal Reactivity Index[5] (IRI) (Davis, 1980) adapted to Spanish (Pérez-Albéniz et al., 2003), to measure dispositional empathy,
- *Test de Aprendizaje Verbal España Complutense* [6] (TAVEC) (Benedet and Alejandre, 1998), to assess verbal memory,
- Subscale "digits" from the Wechsler Adult Intelligence Scale III (WAIS-III) (Wechsler, 1997), to assess working memory,
- 2N-back cognitive task[7] to assess working memory,
- Simple reaction time task[8] to assess attention and reaction time.

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[5] The Interpersonal Reactivity Index is a measure of dispositional empathy that takes as its starting point the notion that empathy consists of a set of separate but related constructs. The instrument contains four seven-item subscales, each tapping a separate facet of empathy. The perspective taking (PT) scale measures the reported tendency to spontaneously adopt the psychological point of view of others in everyday life. The fantasy (FS) scale measures the tendency to imaginatively transpose oneself into fictional situations. The empathic concern (EC) scale assesses the tendency to experience feelings of sympathy and compassion for unfortunate others. The personal distress (PD) scale taps the tendency to experience distress and discomfort in response to extreme distress in others.

[6] Based in the California Verbal Learning Test.

[7] The subject is presented with a sequence of letters and the task consists of indicating when the current letter matches the one from 2 steps earlier in the sequence.

[8] A test that measures simple reaction time through delivery of a known stimulus to a known location to elicit a known response. The only uncertainty is with regard to when the stimulus will occur, by having a variable interval between the trial response and the onset of the stimulus for the next trial. As soon as the participant sees the square on the screen, they must press the button on the press pad.

The last two tests were performed while the subjects were inside the scanner during the anatomical reference acquisition, after being previously instructed outside the scan. The stimuli were presented using Presentation software (http://www.neurobs.com/menu_presentation) on a computer with a translucent projection screen with a resolution of 1024 X 768 pixels. The responses were captured using hand buttons, one per hand.

The POST session followed in the same way. At the end we gave the couples a present for the babies.

MRI acquisitions parameters

Magnetic resonance acquisitions were obtained in a Phillips 3T scanner of the corporation "CRC Corporació Sanitària" in *Parc de Salut Mar*, Barcelona. For anatomical reference, a T1 weighted (SENSE) pulse sequence was employed using the following parameters: repetition time (TR) 500ms.; echo time (TE) 50ms.; number of signals averaged (NSA) 1; 256x256 matrix size; field of view (FOV) 240mm.; 180 slices; 1.5 x 1.5 x 1.5 mm. voxel size; no gap; acquisition time (TA) 5'07"; flip angle (FA) 8°. The total duration of the acquisition was 7 minutes.

Due to a technical unexpected problem, the 8-channel head coil was replaced for some months with a 16-channel head coil. Fifty-three acquisitions were made with the first one and 28 with the second one: all PRE acquisitions were made with the 8-channel head coil and for the POST scan the distribution of the coil types across the groups was relatively consistent. A chi-squared test shows no significant differences between the samples regarding the head coil utilized (χ^2=0.421, p=0.240). In all mass-univariate analysis the head coil is introduced as a nuisance covariate in order to control for the effects of this variable.

MRI data analysis

The MRI structural data was processed using the SPM12b Longitudinal Diffeomorphic Modeling Tool (Ashburner and Ridgway, 2013). This recently

incorporated registration approach is specifically designed for longitudinal data, which requires proper image processing, modeling algorithms and statistical models due to the dependence of repeated measurements within-subjects (see in Introduction the section *A brief description of MRI based neuroanatomical techniques*). The main improvements of this group-wise intra-subject modeling framework are that it combines rigid-body registration as well as non-linear diffeomorphic registration, and incorporates a correction for the intensity inhomogeneity, an artifact usually seen in MRI data. Another important upgrading of this approach is its symmetry and transitivity: in earlier approaches either image was chosen as a fixed reference and the other one as the moving source, but this has been proved to cause substantial bias (Thomas et al., 2009; Yushkevich et al., 2010). In order to assess this problem, the Longitudinal Diffeomorphic Modeling Tool registers both time-points to a within-subject average image. Also, an additional advantage is that all steps are performed in an interleaved fashion versus a pipeline, which is an optimal solution where the conditional dependencies among model parameters are taken into account.

The procedure is described right after and is done for each subject individually (Figure 5):

The first step is to define the within-subject template space, or in other words, to compute the right dimensions and position of the pre and post images so that they match each other. In order to do so, the dimensions are determined in order to cover the field of view of the images and the voxel-to-world maps encoded in the image headers are used to get the start positions of all three spatial coordinate axes in world coordinates. The purpose is to have the template in an average position such that bias introduced by interpolation is minimized.

After that, both images of each subject are processed together using pairwise longitudinal registration (Figure 5, point 1). The aim is to estimate a smooth, continuous mapping between several points of both images. For achieving that, three group-wise steps are performed in an interleaved fashion: a) the rigid body registration, b) the inhomogeneity correction and c) the diffeomorphic registration. This pairwise registration leads to a mid-point average image of each subject and a map of the Jacobian determinants, which is the map of the differences between the two time-points.

Subsequently, using a segmentation algorithm (Ashburner and Friston, 2005) the subject mid-point average image is segmented into tissue classes: scalp, skull, cerebrospinal fluid, white matter (WM) and GM (Figure 5, point 2).

Then, the Jacobian determinant image from the pairwise registration is multiplied by the GM segment, creating maps of volumetric changes in GM tissue (jd*GM) (Figure 5, point 3).

A DARTEL normalization is then applied to bring these images into the space defined by the Montreal Neurological Institute (MNI) template (Ashburner, 2007) (Figure 5, point 4). DARTEL is a high dimensional warping process that increases the registration between individuals, which improves localization and increased sensitivity in analyses. This procedure begins by creating a mean of all the participants' "mean average images" doing a simultaneous registration of GM with GM, WM with WM and 1-(GM+WM). This is used as an initial template made specifically for the study's sample. Thus, a second normalization step is performed to bring the DARTEL processed images into MNI space, a brain template that is representative of the general population. The normalization parameters are then applied to the maps of volumetric changes in GM tissue (jd*GM).

To finish, a smoothing kernel of 12mm. full width at half maximum (FWHM) is applied on the space domain (Figure 5, point 5).

The product images (the volumetric pre-post differences in GM tissue smoothed and normalized into MNI space) of each subject are then entered into the design matrix of the general linear model for statistical inference.

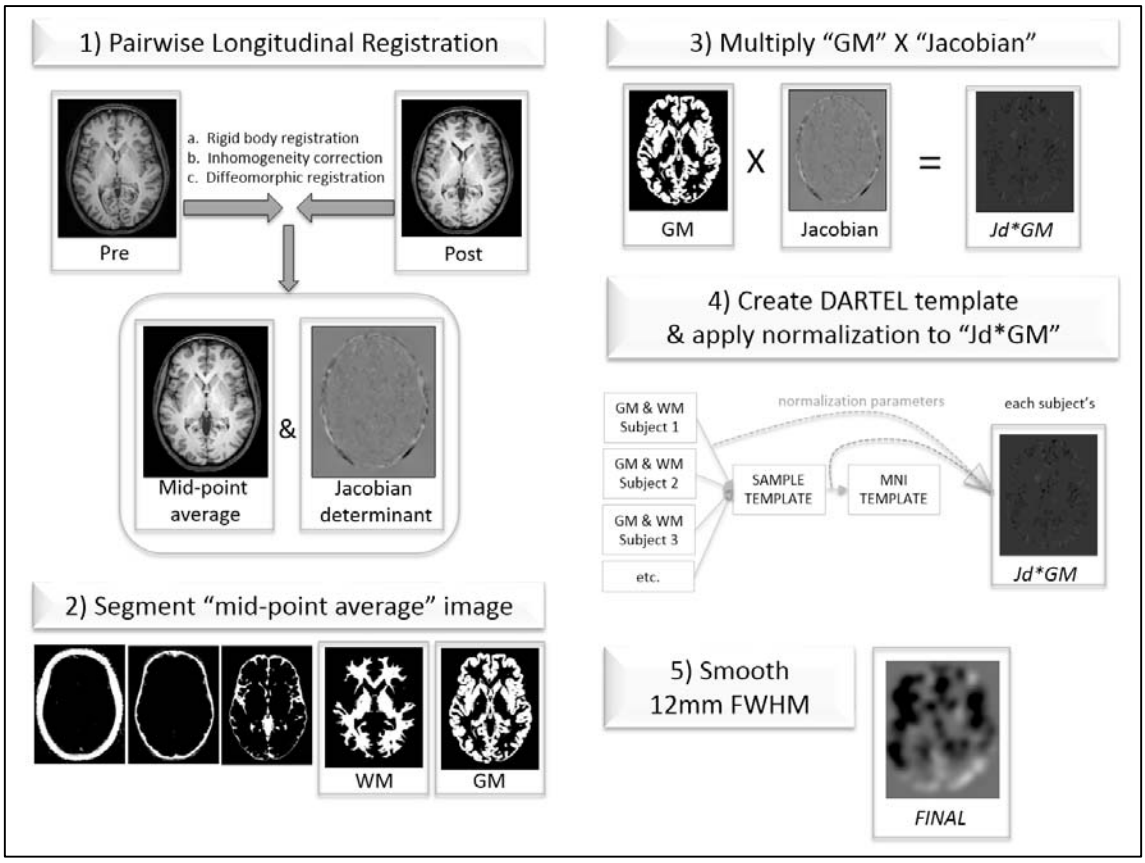

Figure 5. Symmetric diffeomorphic modeling of longitudinal structural MRI procedure. 1) Both images of each subject are processed together using pairwise longitudinal registration. 2) The mid-point average image generated in the previous step is segmented into tissue classes. 3) Jacobian determinants from the pairwise registration is multiplied by the GM segment creating a map of volumetric changes in GM tissue (jd*GM). 4) A DARTEL normalization is applied to bring jd*GM into MNI space. 5) Smoothing kernel of 12 FWHM is applied on the space domain.

Statistical test

The statistical test applied are divided in two different kinds of analysis:

- A set of mass-univariate analysis which are the analysis of a massive number of simultaneously measured dependent variables (voxels) via the performance of univariate hypothesis test.
    - A whole-brain threshold of $p<0.05$ family-wise error (FWE) corrected was applied to all mass-univariate analyses and only clusters over 10 voxels were reported.
- A multivariate pattern analysis that involves the observation and analysis of more than one statistical variable at the time.
    - Permutation tests with 1000 permutations were used for applying a threshold of $p<0.001$.

Mass-Univariate Analysis

1. Main model (ANCOVA): Four groups plus head coil as nuisance covariate

This is the main model. Here the images of volumetric changes in GM tissue resulting from the longitudinal diffeomorphic modeling tool described above are compared between the four groups (female experimental, female control, male experimental, male control). A covariate for the type of radiofrequency head coil that was used for the acquisitions was entered into each of the models.

a. Group comparisons

In order to examine if there were any GM volume differences between the several groups, a set of contrasts was applied where the order of the groups was as follows: female experimental (F_EXP); female control (F_CTR); male experimental (M_EXP); male control (M_CTR). Each contrast defines and test for a particular pattern of differences among the means (Table 2).

Table 2. Contrast applied to the ANCOVA to test the group comparisons

Contrast				Explores
F_EXP	F_CTR	M_EXP	M_CTR	
1	-1	0	0	F_EXP changes > F_CTR changes
-1	1	0	0	F_CTR changes > F_EXP changes
0	0	1	-1	M_EXP changes > M_CTR changes
0	0	-1	1	M_CTR changes > M_EXP changes
-1	1	1	-1[9]	F(CTR ch. > EXP ch.) > M(CTR ch. > EXP ch.)
1	-1	-1	1[10]	M(CTR ch. > EXP ch.) > F(CTR ch. > EXP ch.)

Contrast applied to the ANCOVA and the pattern of differences they explore. F_EXP= female experimental; F_CTR= female control; M_EXP= male experimental; M_CTR= male control.

b. Effect for each of the groups

From the set of contrasts described above we know if there are significant differences between the groups, but we cannot know if those differences are due to increases or decreases in the groups involved. In order to know the effects for each of the groups individually and obtain information about the divergences from cero and the direction of the differences (increases or decreases of GM volume changes in a particular cluster of a particular group) another set of contrasts was applied (Table 3).

[9] -1 1 1 -1 = -1 1 – (-1 1)

[10] 1 -1 -1 1 = 1 -1 – (1 -1)

Table 3. Contrast applied to the ANCOVA to know the effects of each group

Contrast				Explores
F_EXP	F_CTR	M_EXP	M_CTR	
1	0	0	0	F_EXP GM volume increases
-1	0	0	0	F_EXP GM volume decreases
0	1	0	0	F_CTR GM volume increases
0	-1	0	0	F_CTR GM volume decreases

Contrast applied to the ANCOVA and the effects they test for each individual group. F_EXP= female experimental; F_CTR= female control; M_EXP= male experimental; M_CTR= male control.

2. Comparison of two independent samples: "experimental females not-assisted" vs. "experimental females assisted"

Furthermore, to investigate whether the way the woman became pregnant affected the results, we directly compared the women who became pregnant naturally (F_EXPnat, n=8) and those who underwent a fertility treatment (F_EXPtrt, n=17) to each other and to the control women (F_CTR, n=20). An ANCOVA was performed using the head coil as nuisance covariate. As in the previous case, a whole-brain threshold of $p<0.05$ FWE corrected was applied and only clusters over 10 voxels were reported.

Multivariate pattern analysis

In addition to the above-described mass-univariate statistical approach, we also performed a pattern recognition analysis. This is a method that stems from machine learning, and uses a multivariate approach to investigate spatially distributed information in MRI data —which is intrinsically multivariate— and hereby allows modelling signal patterns in the images. In our study, we used the analysis pipeline for pattern recognition analyses provided by PRoNTo v1.1 (http://www.mlnl.cs.ucl.ac.uk/pronto). This pipeline can be used to automatically search for regularities in the data and train a classifier function that models the relation between spatial signal patterns and experimental factors based on a training dataset (Schrouff et al., 2013). This classifier can then be used to predict the group a new image belongs to, using the spatial distribution of the signal within the image, and compute the accuracy with which groups can be discriminated from one another based on whole-brain spatial signal patterns.

To perform this pattern recognition analysis, we trained and tested a linear support vector machine (SVM) pattern classifier for the volumetric difference maps of the women who had undergone pregnancy between the two scans from those of the women who had not, to assess the accuracy with which they could be discriminated from one another based on the distribution of GM changes. A sample-specific GM mask was created using the SPM Masking Toolbox[11], and this was used as the mask image in PRoNTo (Ridgway et al., 2009). We selected the binary SVM and a leave-one-out cross-validation strategy. This cross-validation strategy computes the accuracy of classifiers by leaving one subject out at a time and predicting the group label of this subject based on a training dataset including all remaining subjects, which is repeated for each subject. The results of all these runs are then used to compute the accuracy of the discriminant function. A threshold of $p<0.001$ was used at the permutation testing. Since the current version of PRoNTo does not yet allow the inclusion of covariates, the multivariate analysis was repeated on the residuals to account for the effect of the radiofrequency head coil.

[11] (http://www0.cs.ucl.ac.uk/staff/g.ridgway/masking/)

RESULTS

Demographic data

There were no significant differences between the four groups in age as assessed by ANOVA (F=2.576; p=0.06; degrees of freedom (df) intergroup=3; df intragroup=77). Accordingly, two sample t-tests do not show significant differences between the mean ages of the F_EXP and F_CTR (p=.123). Likewise, we did not observe significant differences in age for either the men (M_EXP vs. M_CTR) (p=.063) or the experimental couples (F_EXP vs. M_EXP) (p=1.47) (Table 4).

The educational level of the participants were: F_EXP=2 reached secondary school; 4 college; 19 university or above. F_CTR=2 secondary school; 3 college; 15 university. M_EXP=1 primary school; 1 secondary school; 4 college; 13 university. M_CTR=1 secondary school, 3 college, 13 university. Pearson's chi-squared test gave a significance level of p=.99 (df=6) indicating there are no significant differences between the groups.

As for the time spent between the pre and the post session, experimental and control group were found to be comparable groups as well (ANOVA: F=1.233; p=0.304; df intergroup=3; df intragroup=77) (Table 4).

Thus, analysis of the demographic data of the four groups (F_EXP, F_CTR, M_EXP and M_CTR) showed no significant differences between these variables.

Table 4. Demographic data

	Gender	EXP mean (sd)	CTR mean (sd)	P EXP *vs.* CTR	P F_EXP *vs.* M_EXP
Age (years)	F	33.36 (3.97)	31.1 (5.63)	0.123	0.147
	M	35.21(4.3)	31.64 (6.41)	0.063	
Time PRE to POST	F	463.52 (108.33)	413.05 (106.86)	0.126	0.895
(days)	M	459 (117.46)	419.17 (93.17)	0.272	

The age is presented in years. The time between the PRE and the POST session is presented in days. EXP= experimental group. CTR=control group. sd=standard deviation. F=females. M=males. P EXP *vs.* CTR= significance value of the difference comparing EXP *vs*. CTR. P F_EXP *vs*. M_EXP= significance value of the difference comparing females and males of the experimental group.

Dispositional empathy and cognitive measurements

With regard to dispositional empathy and the cognitive measurements, there are no significant differences among experimental vs. control groups (F_EXP vs. F_CTR; M_EXP vs. M_CTR), neither between the females and males of the experimental group (F_EXP vs. M_EXP) (Table 5. Dispositional empathy and cognitive data).

Table 5. Dispositional empathy and cognitive data

	Gender	EXP mean (sd)	CTR mean (sd)	P EXP *vs.* CTR	P F_EXP *vs.* M_EXP
IRI PT (post-pre)	F	0.32 (3.77)	-0.1(2.65)	0.676	0.169
	M	-1.15 (3.02)	-1.00 (6.20)	0.922	
FS (post-pre)	F	-2.12 (5.95)	-1.65 (3.68)	0.759	0.958
	M	-2.05 (2.06)	-1.41 (6.54)	0.703	
EC (post-pre)	F	0.20 (3.00)	-0.05 (2.50)	0.767	0.625
	M	-0.31 (3.95)	-0.58 (4.43)	0.847	
PD (post-pre)	F	0.24 (3.84)	-1.50 (3.53)	0.125	0.984
	M	0.26 (3.82)	0.17 (3.02)	0.941	
TAVEC Correct (post-pre)	F	0.40 (6.48)	2.90 (5.40)	0.174	0.415
	M	-1.21 (6.36)	2.64 (9.96)	0.171	
Intrusion (post-pre)	F	-0.88 (1.69)	-0.60 (1.98)	0.612	0.756
	M	-1.10 (3.03)	-0.35 (1.27)	0.349	
Perseverance (post-pre)	F	-0.48 (3.66)	-1.45 (3.39)	0.367	0.996
	M	-0.47 (4.12)	-0.88 (3.91)	0.763	
Digits (post-pre)	F	0.40 (2.10)	-0.25 (1.98)	0.330	0.418
	M	0.89 (1.82)	-0.09 (1.70)	0.155	
2NB (post-pre)	F	1.57 (6.29)	0.34 (3.01)	0.425	0.235
	M	-0.57 (5.23)	2.10 (3.49)	0.084	
SRT (post-pre)	F	12.49 (21.69)	9.87 (23.77)	0.702	0.939
	M	12.95 (17.46)	2.37 (18.88)	0.090	

The punctuation analyzed is the difference between the pre punctuation and the post punctuation. IRI=Interpersonal Reactivity Index, with its subscales: PT= perspective taking, FS= fantasy, EC= empathic concern, PD= personal distress. Digits= the subscale "digits" from the WAIS. 2NB= 2N-Back test. SRT= simple reaction time task. F= females. M= males. EXP= experimental group. CTR= control group. sd= standard deviation. P EXP vs. CTR= significance value of the difference comparing EXP vs. CTR. P F_EXP vs. M_EXP= significance value of the difference comparing females and males of the experimental group.

MRI results

As a reminder, the final images resulting from the symmetric diffeomorphic registration approach, represent a map of the volumetric differences in GM tissue between the two time points of each subject individually. In this final map, a positive voxel represents a GM volume increase (more GM volume in the post session compared to the pre session), while a negative voxel represents a GM volume decrease (less GM volume in the post session compared to the pre session) in that particular brain area where the voxel is located.

These final images are the ones entered into the statistical test and all the results are derived from these images of volumetric changes in GM tissue between the two time points.

Mass-Univariate Analysis

1. Main model (ANCOVA): Four groups plus head coil as nuisance covariate

a. Group comparisons

The analyses reveal a symmetrical pattern of regions where the image codifying change (POST-PRE) shows a greater GM volume in F_CTR than in F_EXP (F_CTR changes > F_EXP changes; whole-brain $p<0.05$ FWE corrected). No regions were found significant when testing for the opposite contrast, which is for greater GM volume changes in the F_EXP group as compared to the F_CTR group.

Furthermore, the contrasts between the male samples does not yield significant differences at the selected threshold in any of the directions (Table 6, Figure 6).

Table 6. Full results of the whole-brain GM volume change comparisons

Contrasts	Regions	L/R	MNI coordinates			T	P FWE corrected	Cluster size (# voxels)
			x	y	z			
F EXP changes> F CTR changes	-							
F CTR changes> F EXP changes	Superior temporal sulcus, Middle/Superior temporal gyrus	R	57	-18	-11	8.84	<0.001	4001
			33	-24	-18	6.19	<0.001	
			33	-37	-14	6.92	<0.001	
		L	-54	-18	-11	6.40	0.001	866
			-56	-33	-6	6.08	0.004	
	Precuneus, Posterior cingulate cortex	L/R	0	-48	30	7.56	<0.001	2674
			-6	-57	21	7.43	<0.001	
			8	-55	22	6.96	<0.001	
	Superior medial frontal cortex, Anterior cingulate cortex, Medial orbitofrontal cortex	L/R	0	53	12	7.15	<0.001	1828
			-14	53	4	6.18	0.003	
			0	48	-6	5.98	0.006	
	Inferior Frontal Gyrus	R	41	14	25	7.51	<0.001	933
		L	-50	12	16	5.85	0.010	161
			-45	9	28	5.57	0.028	
	Inferior orbitofrontal gyrus, Insula	L	-39	24	-2	6.54	0.001	283
	Middle/Superior frontal gyrus	L	-24	25	45	6.30	0.002	509
	Fusiform, Inferior temporal gyrus	R	45	-54	-18	5.78	0.014	123
		L	-44	-54	-14	6.45	0.001	722
			-35	-42	-17	5.49	0.037	
	Hippocampus, Parahippocampal g.	L	-32	-21	-18	6.07	0.005	148
M EXP changes> M CTR changes	-							
M CTR changes> M EXP changes	-							

ANCOVA analysis results. Regions of significant GM volume change differences were found only in the comparison "F_CTR changes > F_EXP changes" in the indicated brain areas. H= hemisphere. MNI= Montreal Neurological Institute neuroimaging coordinates. T= T standardized score of the peak intensity. P value at peak voxel. P<0.05 whole-brain FWE-corrected. F= female. M= male. EXP changes= GM volume changes across pregnancy. CTR changes= GM volume changes across the two sessions.

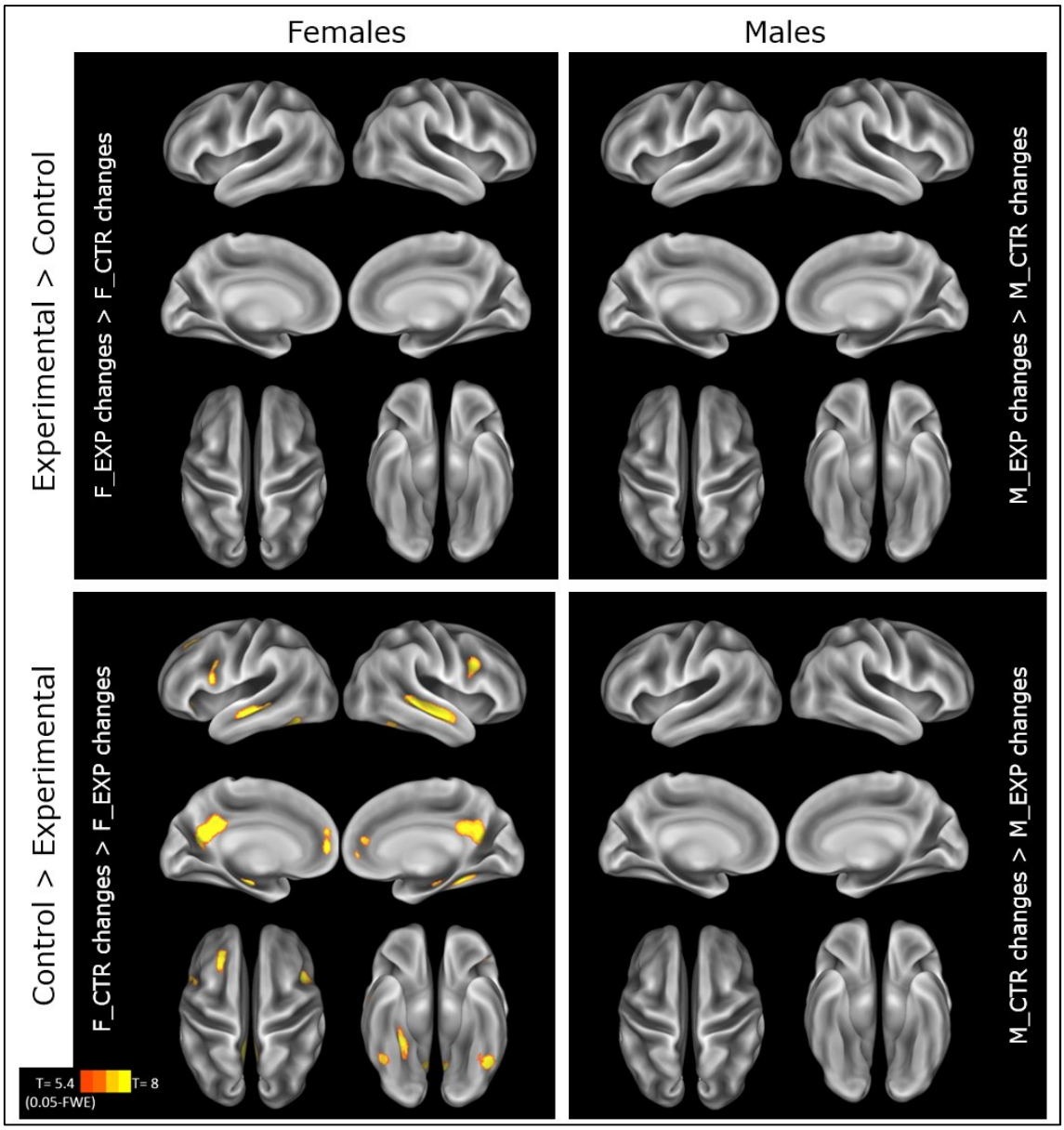

Figure 6. ANCOVA analysis results. Regions of significant GM volume change differences were found only in the comparison "F_CTR changes > F_EXP changes". Maps are projected onto the cerebral 7 hemispheres of the PALS surface (PALS-B12) provided with Caret software using the "interpolated voxel algorithm". The minimum t value threshold of 5.4 used for display of between-group effects is equivalent to a p value <0.05, FWE corrected.

b. Effect for each of the groups

For the significant effects we check the results in the involved groups separately to examine the direction of the effect. These analyses indicate that each of the clusters in the "F_CTR changes > F_EXP changes" contrast, corresponds to volumetric GM reductions across pregnancy in the experimental group (Table 7).

The primary changes comprise GM volume reductions in the bilateral lateral temporal cortex extending to medial sections such as the fusiform gyrus, the bilateral lateral prefrontal cortex, medial frontal cortex (mPFC and ACC), the posterior cingulate cortex (PCC) and precuneus (PC) (Table 7, Figure 7)

Table 7. Increases and decreases of GM volume in experimental and control women

Contrast	Regions	H	MNI coordinates			T	P	Cluster size
			x	y	z		FWE corrected	#voxels
F_EXP 1	—							
F_EXP -1	Posterior cingulate, Precuneus, Superior temporal sulcus	L/R	2	-48	31	12.30	<0.001	53809
			9	-54	24	11.14	<0.001	
	Middle/Superior/Inferior temporal cortex, Fusiform gyrus, Hippocampus, Parahippocampal gyrus		57	-18	-11	11.03	<0.001	
	Inferior/Middle frontal cortex, Insula	R	41	12	28	12.24	<0.001	6837
			36	32	6	8.71	<0.001	
			41	-3	13	5.52	0.034	
	Middle/Inferior/Superior frontal cortex, Anterior cingulate, Insula	L/R	0	50	12	11.08	<0.001	34000
			-44	6	27	10.19	<0.001	
			-39	24	-0	10.16	<0.001	
	Middle/Superior frontal cortex	R	27	27	48	7.45	<0.001	674
	Inferior frontal cortex, Superior temporal cortex	R	39	21	-21	6.63	0.001	152
	Cerebelum posterior lobe	L	-12	-55	-47	6.04	0.005	156
		R	18	-72	-27	5.95	0.007	81
F_CTR 1	—							
F_CTR -1	—							

ANCOVA analysis results. The female experimental group shows GM volume reductions. H= hemisphere. MNI= Montreal Neurological Institute neuroimaging coordinates. T= T standardized score of the peak intensity. P value at peak voxel. P<0.05 whole-brain FWE-corrected. F_EXP 1= GM volume increases across pregnancy. F_EXP -1= GM volume decreases across pregnancy. F_CTR 1= GM volume increases across the two sessions. F_CTR -1= GM volume decreases across the two sessions.

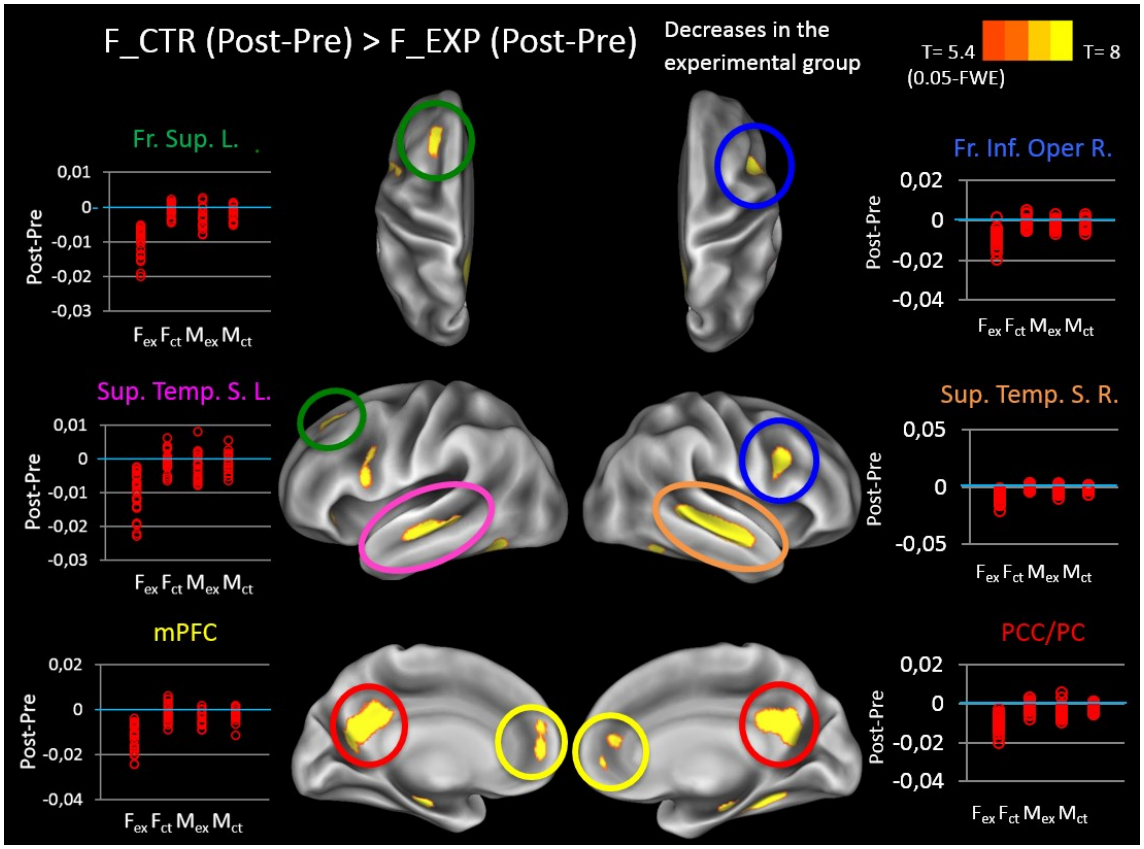

Figure 7. Results of the main model ANCOVA. Whole-brain group comparisons of GM volume changes (POST minus PRE as obtained from the longitudinal diffeomorphic modeling tool). Supra-threshold clusters represent the results of the interaction between session ("pre" and "post") and group (25 women scanned before and after pregnancy, and 20 control women scanned at the same time interval to correct for contingent age- and repetition-related changes). The clusters with the higher t-value correspond to the brain regions: frontal superior left (Fr. Sup. L) in green; frontal inferior operculum right (Fr. Inf. Oper. R) in blue; superior temporal sulcus left (Sup. Temp. S. L) in pink; superior temporal sulcus right (Sup. Temp. S. R) in orange; medial prefrontal cortex (mPFC) in yellow; and posterior cingulate/precuneus (PCC/PC) in red. The scatter plot diagrams (were a plot per subject represent the maximal t-value threshold of that cluster) shows that the differences represent GM volume reduction in the experimental women and that the changes are consistent between subjects. Maps are projected onto the cerebral 7 hemispheres of the PALS surface (PALS-B12) provided with Caret software using the "interpolated voxel algorithm". The minimum t value threshold of 5.4 used for display of between-group effects is equivalent to a whole-brain p value <0.05 FWE-corrected.

c. ROI data

For visualization purposes, each of the areas that presented a significant GM volume change between groups was selected as a region of interest (ROI) in order to separately extract the volumetric difference for each of the subjects. This, in addition to allow us to better illustrate the findings, permits us to see whether the results were consistent between subjects or if they were driven by outliers. Analyses reveal that the results are not driven by outliers (see the scatter plot diagrams in Figure 7).

d. Post hoc analysis

d.1. Comparison with the male experimental group

In order to compare the mothers with the fathers, an analysis of the interaction of all four groups was run. Since it is more appropriate to examine changes in the mothers and fathers relative to a control group of their own gender rather than directly comparing changes in male and female brains, we used an interaction contrast in which the experimental groups were first contrasted to their own control group (contrast -1 1 1 -1 and 1 -1 -1 1) (see Table 2 in the Methods section for a map of the contrasts applied).

Results of the interaction:

"(F_CTR changes > F_EXP changes) > (M_CTR changes > M_EXP changes)"

are indicated in Table 8. For this interaction contrast with the 4 groups, not all of the clusters of the main contrast surfaced at a whole-brain threshold of $p<0.05$ FWE-corrected. However, at a more lenient threshold of $p<0.0001$ a very similar set of regions was observed to those appearing in the contrast "F_CTR changes > F_EXP changes".

Table 8. Full results of the whole-brain GM volume change comparisons of the interaction contrast

Contrasts	Regions	H	MNI coordinates			T	P	Cluster size
			x	y	z		<0.0001	# voxels
FEMALE (CTRch. > EXPch.) > MALE (CTRch. > EXPch.)	Front. Inf. Operculum	R	41	14	25	5.69	*<0.001	1294
	Superior temporal sulcus, Middle/Superior temporal gyrus	R	56	-16	-11	5.48	*<0.001	16310
			48	-33	-3	4.95	<0.001	
	Precuneus, Posterior cingulate cortex	L/R	-5	-55	22	5.42	*<0.001	1287
	Superior medial frontal cortex, Anterior cingulate cortex, Medial orbitofrontal cortex	L/R	0	50	13	4.88	<0.001	808
			-14	53	4	4.52	<0.001	
			29	27	49	4.32	<0.001	134
			-23	23	46	4.28	<0.001	67
			-2	44	-9	4,18	<0.001	64
	Frontal Inf. Orbitral, Insula	L	-35	26	-5	4.27	<0.001	87
	Parahippocampal gyrus, Hippocampus,	L	-27	3	-29	4.24	<0.001	52
			-32	-18	-21	4.19	<0.001	161
			-38	-10	-21	4.16	<0.001	
	Fusiform,	L	-27	-54	-8	4.23	<0.001	161
	Inferior temporal gyrus	R	-45	-51	-12	3.97	<0.001	15
			48	-51	-15	4.19	<0.001	116
			33	-39	-14	4.09	<0.001	38

ANCOVA analysis results of the interaction contrast. Regions of significant GM volume change differences were found only in the comparison "FEMALE (CTR ch. > EXP ch.) > MALE (CTR ch. > EXP ch.)" in the indicated brain areas. H= hemisphere. MNI= Montreal Neurological Institute neuroimaging coordinates. T= T standardized score of the peak intensity. P value at peak voxel. P<0.0001. * Also significant at a whole-brain threshold of P<0.05 FWE-corrected.

d.2. Additional nuisance covariates

Additional analyses involving further nuisance covariates were also performed in order to examine whether the observed effects were not driven by those factors (whole-brain $p<0.05$ FWE corrected). The nuisance covariates introduced in the model were:

- subject's age
- time difference between the pre and post scans
- time since birth (age of the baby at the post scan)

As expected, the main findings were maintained when including these covariates as a nuisance covariate to the statistical models, thus suggesting that our results are not driven by them.

d.3. Correlations with the age of the baby

Another post hoc analysis consisted of the correlation with the age of the baby at the post scan, , i.e. the duration of the postpartum period since this second acquisition, allowing us to further examine the potential impact of postpartum factors in the observed findings. It was performed in SPM12 after applying a mask of the brain regions involved in the results. A threshold of $p<0.05$ FWE corrected was applied. No results were found at $p<0.05$ FWE corrected and even when lowering the threshold to $p<0.001$ uncorrected, no sign of any positive correlation with the time since birth could be seen within these clusters.

d.4. Comparison between singleton and twin pregnancies

In order to explore if the mothers who had twins (N=4) show any differences in brain volume changes compared to singleton pregnancies (N=21), a comparison was done between these two subsamples. No significant differences were found but a bigger sample in the twin-pregnancy's group is required in order to study this properly.

d.5. Pituitary enlargement

As previous post-mortem (Bergland et al., 1968; Comte, 1898; Erdheim and Stumme, 1909; Rasmussen, 1938) and in-vivo studies have shown an increase in the pituitary gland studies (Dinç et al., 1998; Elster et al., 1991; Gonzalez et al., 1988), we examined this specific area performing a ROI of the pituitary gland by placing a 5 mm radius sphere at the coordinates 0 6 -31. The ROI was then applied using Small Volume Correction in SPM and a smoothing kernel of 8mm FWHM.

The contrast assessing differences between the two sessions in the experimental group ("F_EXP 1") indicates a significant increase of the pituitary gland in the women having undergone pregnancy (coordinates x=2; y=2; z=-30, T=3.00, p=0.016). Furthermore, when comparing to their control group, the results of the contrast "F_EXP changes > F_CTR changes" showed a significant difference, being the pituitary of the mothers significantly bigger in size than the pituitary of the control women (coordinates: x= 2; y= 2; z=-30, T=2.57, p=0.043).

2. Comparison of two independent samples: "experimental females not-assisted" vs. "experimental females assisted"

No significant differences were found between the two experimental subgroups: women who got pregnant without medical support (F_EXPnat, n=8) and women who got pregnant with an assisted reproduction treatment (F_EXPtrt, n=17). In addition, both groups show a similar pattern of GM volume differences with regard to the control women (F_CTR, n=20) (Table 9 and 10, Figure 8).

Table 9. Whole-brain GM volume changes comparisons between the experimental-not-assisted, experimental-assisted and control women

Contrasts	Regions	H	MNI coordinates			T	P	Cluster size
			x	y	z		FWE corrected	#voxels
F_EXPnat changes > F_EXPtrt changes	—							
F_EXPtrt changes > F_EXPnat changes	—							
F_EXPnat changes > F_CTR changes	—							
F_CTR changes > F_EXPnat changes	Parahippocampal gyrus,	R	35	30	-15	6.93	0.003	319
	Hippocampus		44	-33	-6	6.32	0.014	
	Posterior cingulate cortex, Precuneus	L/R	-3	-52	25	6.35	0.013	188
	Superior temporal sulcus	R	59	-15	-14	6.22	0.019	90
F_EXPtrt changes > F_CTR changes	—							
F_CTR changes > F_EXPtrt changes	Middle/Superior/Inferior temporal cortex	R	59	-16	-12	7.82	0.000	806
	Posterior cingulate cortex, Precuneus	L/R	-6	-55	22	7.26	0.001	798
	Parahippocampal gyrus, Hippocampus	L	-32	-21	-18	6.12	0.025	15
	Superior temporal sulcus	L	-53	-18	-11	6.02	0.033	18

ANCOVA analysis between the females groups: F_EXPnat, F_EXPtrt and F_CTR, including the type of head coil as covariate. No significant differences were found between the two experimental subgroups. H= hemisphere. MNI= Montreal Neurological Institute neuroimaging coordinates. T= T standardized score of the peak intensity. P value at peak voxel. P<0.05 whole-brain FWE-corrected. F_EXPnat changes= GM volume changes across pregnancy achieved without fertility treatment. F_EXPtrt changes= GM volume changes across pregnancy assisted with a fertility treatment. F_CTR changes= GM volume changes across the two sessions.

Table 10. Increases and decreases of GM volume in experimental-not-assisted, experimental-assisted and control women

Contrast	Regions	H	MNI coordinates			T	P	Cluster size
			x	y	z		FWE corrected	#voxels
F_EXPnat 1	—							
F_EXPnat -1	Middle/Inferior frontal cortex, Insula	R	42	12	31	8.80	<0.001	2237
			29	-23	49	6.34	0.013	
		L	-38	32	3	7.98	<0.001	3133
			-42	5	30	7.88	<0.001	
			-50	12	18	7.03	0.002	
		L	-23	23	7	6.54	0.008	68
		R	39	33	7	6.86	0.003	161
	Posterior cingulate cortex, Precuneus	L/R	0	-51	28	8.62	<0.001	3344
			11	-54	25	8.11	<0.001	
	Middle/Superior/Inferior	R	45	-33	-6	7.60	<0.001	2237
	temporal gyrus,		35	-33	-14	7.22	0.001	
	Parahippocampal gyrus,		29	-42	-8	6.78	0.004	
	Hippocampus,	L	-35	-19	-15	6.98	0.002	198
	Fusiform gyrus		-27	-16	-9	6.19	0.020	
		R	47	-63	24	6.03	0.032	48
		L	-45	-55	-15	6.73	0.004	546
			-26	23	40	6.25	0.017	140
	Superior temporal sulcus,	L	-41	-55	24	7.45	0.001	4406
	Supramarginal gyrus		-50	-22	-8	7.31	0.001	
			-48	-63	25	7.22	0.001	
		R	53	-43	18	6.41	0.270	134
	Middle/Superior frontal cortex,	L/R	-18	48	6	7.12	0.001	1499
	Anterior cingulate		-3	47	18	6.97	0.002	
			0	35	25	6.70	0.005	(continues...)

	Inferior orbitofrontal cortex, Superior temporal cortex	R	42	23	-21	6.85	0.003	141
	Superior orbitofrontal cortex	L	-27	56	-3	6.19	0.020	26
F_EXPtrt 1	—							
F_EXPtrt -1	Posterior cingulate cortex, Precuneus	L/R	2	-49	30	10.11	<0.001	4879
	Middle/Inferior frontal cortex,	R	41	12	28	9.20	<0.001	1107
	Insula	L	-44	6	30	7.53	<0.001	1287
			-50	12	18	7.33	0.001	
		L	-41	27	-0	7.06	0.002	612
			-36	35	6	6.29	0.015	
		R	36	29	4	7.06	0.002	361
	Middle/Superior/Inferior	R	57	-22	-8	9.06	<0.001	3231
	temporal gyrus,		54	-40	-3	7.26	0.001	
	Fusiform gyrus,	L	-53	-16	-11	7.95	<0.001	3412
	Parahippocampal gyrus,		-57	-36	-8	7.40	0.001	
	Hippocampus		-47	-57	-14	6.81	0.004	
		L	-33	-21	-17	8.50	<0.001	393
		R	29	-42	-9	7.63	<0.001	466
	Middle/Superior frontal cortex,	L/R	-2	48	13	7.33	0.001	3001
	Anterior cingulate, Medial		0	38	21	7.32	0.001	
	orbitofrontal cortex		0	44	-8	7.24	0.001	
		L	-23	29	43	6.93	0.003	436
		L	-27	57	-2	6.27	0.016	38
	Angular gyrus	L	-45	-63	30	6.46	0.010	308
F_CTR 1	—							
F_CTR -1	—							

ANCOVA analysis of the F_EXPnat, F_EXPtrt and F_CTR. H= hemisphere. MNI= Montreal Neurological Institute neuroimaging coordinates. The experimental subgroups show a similar pattern of GM volume changes. T= T standardized score of the peak intensity. P value at peak voxel. P<0.05 whole-brain FWE-corrected. F_EXPnat 1: GM volume increases across pregnancy achieved without fertility treatment. F_EXPnat -1: GM volume decreases across pregnancy achieved without fertility treatment. F_EXPtrt 1: GM volume increases across pregnancy assisted with a fertility treatment. F_EXPtrt -1: GM volume decreases across pregnancy assisted with a fertility treatment. F_CTR 1: GM volume increases across the two sessions. F_CTR -1: GM volume decreases across the two sessions.

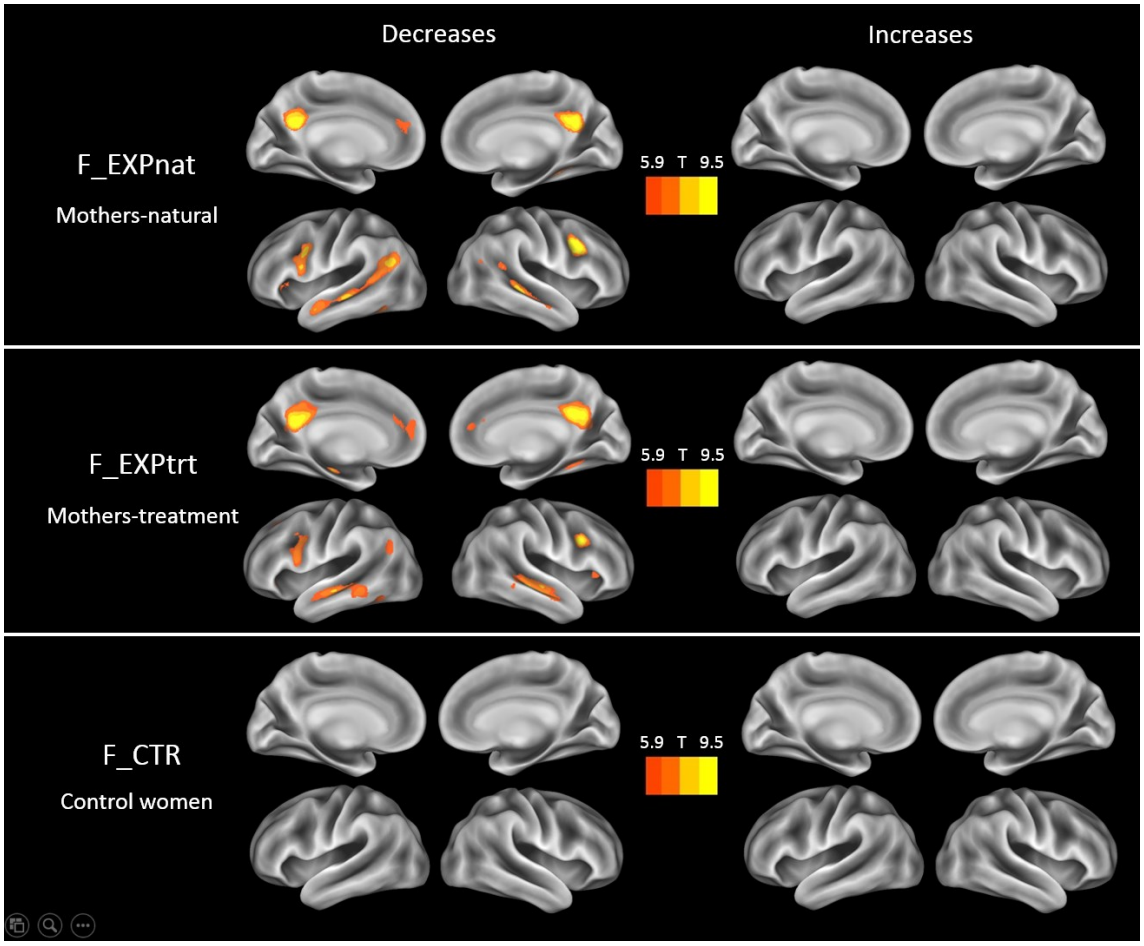

Figure 8. ANCOVA analysis of F_EXPnat, F_EXPtrt and F_CTR. Contrast 1 (**increases** POST minus PRE) and -1 (**decreases** POST minus PRE) for the F_EXPnat, F_EXPtrt and F_CTR groups. The two independent groups that undergo pregnancy, F_EXPnat and F_EXPtrt, show a similar pattern of GM volume reduction. Maps are projected onto the cerebral 7 hemispheres of the PALS surface (PALS-B12) provided with Caret software using the "interpolated voxel algorithm. The minimum t value threshold of 5.9 is equivalent to whole-brain $p<0.05$ FWE-corrected.

Multivariate pattern analysis

The results of the pattern recognition analysis show that 100% of the sample could be automatically classified as having undergone pregnancy or not based on the distribution of GM changes across the brain ($p<0.001$). Balanced accuracy values, which represent the fraction of the subjects for whom a correct class label was predicted using the trained classifier, are provided for this comparison (Figure 9). Since PRoNTo does not yet allow the inclusion of covariates, we ran the model again on the residuals, which rendered identical results (balanced accuracy = 100%, $p<0.001$).

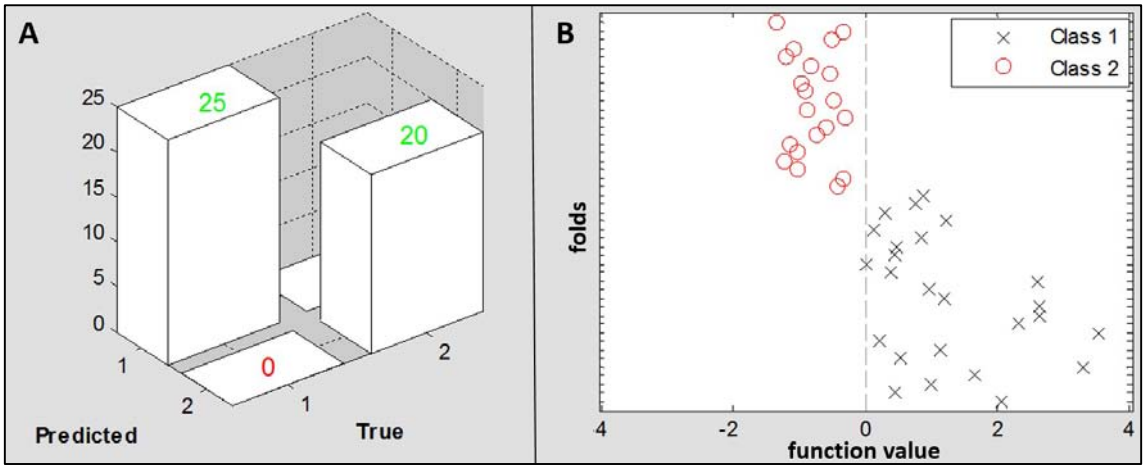

Figure 9. Multivariate pattern recognition analysis for the classification between experimental and control women based on the altered GM distribution across the "pre" and "post" sessions. Depicted are the confusion matrix (A) and predictions plot (B).

DISCUSSION

Pregnancy is a fascinating process that has been extensively studied, but the knowledge about its effects in the maternal brain is still scarce, especially in humans. The study presented here explores brain structure in first-time mothers with the aim to investigate if pregnancy causes GM volume changes in the female human brain and in which areas. With this in mind, a longitudinal study was performed with MRI measurements of the brain in two time points: before conception and at the postpartum. The experimental group was configured by 25 first-time-mothers and 19 of their men couples. The fathers underwent similar environmental/psychological factors of having a baby but not the physiological/endocrine factors of pregnancy. In addition, a comparable control group of couples that didn't become parents participated (20 women and 17 men). Empathic and cognitive abilities were also measured.

Prior to our study, Oatridge and colleagues (2002) detected with MRI that the female brain decreases in size during pregnancy and increases in size after delivery, but their methodology did not allow to detect the regions involved in such changes and the samples exhibit important caveats: lack of a control group, lack of a pre-pregnancy scan in most subjects and the inclusion of a clinical subsample with preeclampsia (see in Introduction section *Whole brain morphological changes during pregnancy*).

The current findings are, to our knowledge, the first to demonstrate that pregnancy causes specific morphological changes in the female human brain.

Overview of the results

The results reveal a significant GM volume reduction in women having undergone pregnancy. Specifically, we found GM volume decreases in the posterior midline (PCC and PC), the medial frontal cortex (mPFC and ACC), bilateral lateral prefrontal cortex (clusters in the ventrolateral and dorsolateral prefrontal cortex) and bilateral temporal cortex (bilateral superior temporal sulcus extending to surrounding lateral temporal sections as well as medial temporal structures such as the fusiform gyrus).

Neither the control women nor the control males showed any significant GM volume changes between the two time points. Also, the fathers did not show any significant changes relative to their male controls.

The interaction comparison of the four groups corrected for the environmental/psychological variables also experienced by the fathers, attributing the GM reduction observed in the mothers to the biological changes of pregnancy.

The following points adds ample statistical validity to the results:

- All four groups did not show a significant difference in age, education and time between sessions.
- The statistical threshold of whole-brain $p<0.05$ FWE-corrected applied in all the mass-univariate analysis is very restrictive[12].
- Graphs extracted from the ROIs analysis revealed that the results were not driven by outliers.
- The results of the pattern recognition analysis ($p<0.001$) showed that 100% of the sample could be automatically classified as having undergone pregnancy or not based on the distribution of GM changes across the brain.
- Both, women who got pregnant without medical support (F_EXPnat) and women who needed a fertility treatment (F_EXPtrt)), show a similar pattern of GM volume reductions.

In addition, a pituitary enlargement —which is the only previously well-established structural brain change related to pregnancy— has also been observed in the present experimental sample. The pituitary gland of the female experimental group is significantly bigger in size in the postpartum compared to their own pre-pregnancy scan ($p=0.016$) and also bigger compared to the control group ($p=0.043$).

[12] It offers a high specificity with a low false-positive rate in exchange for not taking into account some false negative, lowering the sensitivity.

In conclusion, the neuroimaging results uncover a symmetrical pattern of significant GM volume reductions in women having undergone pregnancy (whole-brain $p<0.05$ FWE-corrected) at the bilateral lateral temporal cortex extending to medial sections such as the fusiform gyrus, then, the bilateral dorsolateral prefrontal cortex, the medial frontal cortex and the posterior midline. The changes are remarkably consistent across subjects since 100% of the sample can be automatically classified as having undergone pregnancy or not, based on the distribution of GM changes across the brain. The mothers did not show any significant changes in the cognitive and empathic scales. The neuroimaging results provide primary understandings into the way a woman's brain is modified by pregnancy.

Interpretation of the results

The purpose of this section is to interpret the current findings in the light of a variety of studies concerning:

- the potential neurobiological mechanisms underlying these GM volume reductions, and
- the brain areas implicated

Latter, the section called *Possible evolutionary purpose and implications for the mother* is dedicated to integrate this points with our findings, pointing to the possible implications in the behavior and mental health of the mothers, and the likely evolutionary purpose.

Potential neurobiological processes underlying the GM volume reductions

Brain changes captured by T1-weighted images are not specific enough to be translated in terms of a precise neurobiological process. Nevertheless, here some potential mechanisms are suggested such as a "stereotyped neural pruning" and a "neural apoptosis". For an organizational purpose they are described separately, but in reality they can be simultaneously implicated. Here is also exposed the likelihood that

these mechanisms are triggered by the vast endocrine changes such as those occurring during pregnancy and delivery.

Pregnancy is probably the most extreme endocrine event of human life that occurs naturally (O'Leary et al., 1991; Pepe and Albrecht, 2009) and hormones have proven to render vast plastic changes in the central nervous system. As it has been exposed in the Introduction (see section *Interplay of hormonal and neuronal factors*), there is now compelling evidence that steroid hormones represent a powerful neurotrophic agent that regulate most major developmental events including neurogenesis, neuronal migration, neural pruning, cell death and neurotransmitter plasticity (reviewed by Simerly, 2002). Estrogen mediates synaptic plasticity in less extreme endocrine changes, like the estrous cycle in the female rat (McEwen and Woolley, 1994; Woolley and McEwen, 1993, 1992), the menstrual cycle in women (Hagemann et al., 2011), the menopause (Comasco et al., 2014; Goto et al., 2011; Peng et al., 2014) and exogenous steroids hormones treatments (Erickson et al., 2010; Matsumoto and Yasumasa, 1997). Moreover, animal studies comparing pregnant rats with virgin hormone-treated mimicking pregnancy and have found similar neural alterations in both groups (Keyser-Marcus et al., 2001; Kinsley et al., 2006). In other words: neural alterations produced by pregnancy in the mPOA (Keyser-Marcus et al., 2001) and in the hippocampal CA1 (Kinsley et al., 2006) can be replicated in virgin females with a hormone-treatment mimicking pregnancy consisted in sequential progesterone and estradiol administrations (see in Introduction, section *Brain changes related to pregnancy in rodents*).

Therefore, several authors have associated a reproduction's neuroplasticity with the surges of pregnancy-related hormones such as prolactin, progesterone, estradiol and corticosterone (Brunton and Russell, 2008; Galea et al., 2008; Kinsley et al., 2012; Pawluski et al., 2009; Shingo et al., 2003). It is worth mentioning that these neuroplastic changes of pregnancy seems to be profound and persistent (Kinsley and Amory-Meyer, 2011).

Conclusively, hormones affect the neural system in its function and structure, and pregnancy might not be an exception. There is a high probability that the brain changes discovered in this study are caused, at least partially, by the extreme hormones surges of pregnancy.

Another comparable non-pathologic life-event that consists in vast endocrine changes is adolescence. Several data proves that adolescence not only results in a number

of body and behavioral changes but also in consistent brain modifications (reviewed by Blakemore, 2012; Durston et al., 2001; Lenroot and Giedd, 2006; Paus, 2005). Gray matter volumes follow an inverted U-shaped developmental trajectory, increasing during childhood, reaching its maximal volume around puberty and progressively decreasing afterwards (Giedd et al., 1999). In other words, there is a pre-adolescent GM increase followed by a post-adolescent GM decrease. Although the precise time of the switch in the developmental curve varies between the different brain areas (Giedd et al., 1999; Gogtay et al., 2004), the puberty onset —with the vast endocrine changes that convey— is considered to play a central role since the age at which several regions peaks correspond to the gonadarche onset (Blakemore et al., 2010). Therefore, it is suggested that this structural reorganization of the brain is triggered by the increased steroids hormone production with the aim to establish and activate neural circuits interceding the reproductive behavior (Sisk and Foster, 2004).

One of the brain areas that peaks at the puberty onset (about age 11 in girls and 12 in boys) is the frontal lobe (Giedd et al., 1999). A postmortem study made by Petanjek and colleagues (2011), assessed microscopically the brain development at this precise lobe, specifically the prefrontal cortex. They showed that during childhood the maturation of the brain displays an increase of dendritic spine density in the prefrontal cortex that reaches values that exceeds adult values by two to threefold until the commencement of puberty, when gradually starts an elimination of this "overproduced" synapsis (Petanjek et al., 2011). This study temporally correlates the GM volume reductions observed with MRI with a decrease in dendritic spines in the prefrontal cortex.

> *Taken together the previous data and the present findings strongly indicate that anatomical and functional changes in the prefrontal cortex observed in vivo during late adolescence and young adulthood reflect the dynamic reorganization of synaptic circuitry rather than solely activity-dependent molecular tuning of the stable synaptic connections* (Petanjek et al., 2011, p. 13284).

In other words, the GM volume decrease of the PFC during adolescence is thought to correspond to synaptic pruning, the elimination of unwanted synapses in

order to optimize brain function (see box 9 for "Progressive and regressive events in neural development").

In relation to the present findings, **a supposition is that pregnancy elicits a stereotyped neural pruning** that involves a selective elimination of axon terminals, dendrites and/or synaptic connections without death of the parent neurons. *Stereotyped*, as described by Schuldiner and Yaron (2015), means that "pruning occurs with a temporal, cell specific, and spatial stereotypy in each and every individual" (*idem*, p.102) and therefore is predictable at a certain developmental stage, in this case, at pregnancy.

Under this comprehension, pregnancy can be considered as a neural developmental stage similar to adolescence. In both cases, the brain undergoes a reorganization visualized in MRI as GM volume decreases of specific regions, accompanied by behavioral modifications (see in Introduction, section *Behavioral changes due to reproductive experience*) and by huge endocrine alterations. Surprisingly, as described before, adolescence's GM reductions in PFC have been correlated with synaptic pruning (Petanjek et al., 2011).

We wanted to better appreciate the impact of the endocrine changes of pregnancy, since there is evidence of the involvement of endocrine factors in neural pruning and since vast hormonal changes also take place during adolescence. In order to do that, we have estimated — based on studies assessing estrogens levels during pregnancy (O'Leary, Boyne, Flett, Beilby, & James, 1991; Pepe & Albrecht, 2009) — that a women might produce more estrogens during one single pregnancy than during her entire non-pregnant reproductive life[13].

[13] This estimation has been made without taking into account the estrogens values during the puberty.

Box 9. Progressive and regressive events in neural development

Ramon y Cajal (1899) was the first in observing that pyramidal neuron spine density is higher during early postnatal development compared to adulthood, but it took a century in clearly corroborate a developmental synaptic loss in humans (Huttenlocher et al., 1982) and mammals (Bourgeois and Rakic, 1993; Innocenti, 1995; Rakic et al., 1994).

Nowadays is acknowledged that synaptic pruning is an important regulatory process; that the development of the nervous system involves progressive as well as regressive events.

Multiple evidence supports a dynamic and concurrent model of neural development were formation and elimination processes coincide: *progressive events* such as neural proliferation, neurite outgrowth and synapse formation establish a wide-ranging arrangement of neural connectivity, while *regressive events* like neural pruning and cell death refine the neural connectivity to a more precise and mature circuitry (Goda and Davis, 2003; Hua and Smith, 2004; Low and Cheng, 2006; Schuldiner and Yaron, 2015).

Therefore, regressive events are a regulatory process crucial for proper brain development and function: they enable the selective removal of exuberant neural connections generated during the early stages, developing a precise neural connectivity between proper sets of neurons (Innocenti and Price, 2005). Besides this role in development, in the adult brain the regressive events permits neuroplasticity processes on behalf of the maintenance of efficient circuits for learning and memory (Chechik et al., 1998; Luo and O'Leary, 2005), and promotes the stabilization and repair in case of injury or disease (Luo and O'Leary, 2005). In addition, reduced synaptic pruning during development —as studied in knockout mice— is associated with persistent deficits in synaptic multiplicity, reduced functional connectivity between brain regions, impaired social interaction and increased grooming behavior (Zhan et al., 2014), emphasizing its critical role in brain function.

In parallel to its implication in development and health, regressive events —particularly cell death— are also related to the intrinsic deterioration of aging and play a central role in the case of neurodegenerative diseases (Coleman, 2005; Schafer and Stevens, 2010; Stephan et al., 2012).

Since the knowledge regarding the modulation of neuronal life and death has an immense therapeutic potential, researchers are putting a considerable effort in understanding how these events are regulated. Nevertheless there is still a vast amount of missing pieces. In rough outlines, brain activity is thought to play an important role in small-scale non-stereotyped pruning following the "use it or lose it" principle (Trachtenberg et al., 2002). Whereas for apoptosis and the large scale stereotyped pruning, some studies suggest the involvement of endocrine and neurotrophic factors (Goda and Davis, 2003; Innocenti and Price, 2005; Schuldiner and Yaron, 2015; Vanderhaeghen and Cheng, 2010). In both cases, the cellular and molecular mechanisms of this neuronal sculpting consist of a complicated variety of strategies, where immune system (Bilimoria and Stevens, 2014; Marin and Kipnis, 2013; Schafer and Stevens, 2010) and phagocytic glia (Freeman, 2006; Schafer and Stevens, 2013; Stephan et al., 2012) play an important role.

Although the understanding of molecular mechanisms that govern neural pruning are scarce, studies with rats (Liu et al., 2012; Lubischer et al., 1992) and Drosophila fly (Kirilly et al., 2011; Kuo et al., 2005; T. Lee et al., 2000; Thummel, 1996; Williams and Truman, 2005) indicates the involvement of steroid hormones. Moreover, there is a vast amount of studies that attributes the actions of steroids hormones to the variation between the female's and the male's brain. Substantial sexual dimorphisms have been acknowledged all over the central nervous system and there is a strong evidence supporting that the biological basis of these functional dimorphisms are

hormonally driven (reviewed by Forger, 2006; Jazin and Cahill, 2010; Morris et al., 2004; Simerly, 2002). Estrogen and testosterone are the hormones that regulate most of these sex differences, being cell death the main way to alter neuron number (Forger, 2009). Besides, evidence shows that some sexual differentiation events can be induced even in adulthood, proposing that there might not be a fixed critical period for steroids to affect the CNS (Johansen et al., 2004).

Taking into account that cell death is the main way to alter neuron number related to estrogen and that pregnancy implies such an extraordinary estrogen production, **the cellular event underneath the present GM volume reductions can be a neural apoptosis**. This, as previously said, can happen alternatively or simultaneously to a neural pruning.

Apoptosis is a coordinated and energy-dependent cell death of specific neuronal populations. Although neurons are not preserved, it is different from a necrosis, in which results from infection or injury and involves inflammation and toxicity.

Just as neural pruning, this naturally occurring cell death is so abundant during neural development that suggests it serves an extremely important function. What that function is and its role as an evolutionary solution is still not understood (Forger, 2009; Schuldiner and Yaron, 2015).

Other feasible hypotheses concerning the causes of these GM volume reductions could be an atrophic process: that it simply results of an erosion, an aggression or a wearing of the brain due to the large effort and physiologic alterations that pregnancy and delivery conveys.

A speculative mechanism for explaining such an atrophic process could be a loss of trophic support. During pregnancy the requirements of essential long-chain polyunsaturated fatty acids (LCPUFA) increases in order to sustain the progressive growth of maternal, placental and fetal tissue. Especially during the third trimester, the fetus requires a higher amount of docosahexaenoic acid (DHA; 22:6n—3), an important structural LCPUFA in neural tissue, in order to synthetize the brain tissue. This supplies depends primarily on placental transfer and thus on the DHA status and supply of the mother (Innis, 1991). It has been hypothesized that this extra DHA demands may be covered by the tissue stores from the mother, comprising some membrane constituents

(Holdcroft et al., 2005). As Al and collaborators explain in their review (2000), data suggest that pregnancy is associated with maternal difficulty in coping with the high claim of DHA. On the contrary, other studies does not find that DHA status is disturbed during pregnancy (Makrides and Gibson, 2000). Further studies are necessary to elucidate this.

Nevertheless, it then calls the attention that the volume reductions are not homogeneous through all the brain but that they appear to be in specific brain regions with a hemispheric symmetry. Could this pattern be accounted for by some alternative explanation that is not linked to neural architecture? One option is that they reflect some poorly understood mechanism of vascular regulation. To my knowledge, there are no studies assessing this topic. Only Oatridge and collaborators mention that no significant correlation was found between the presence of elevated blood pressure and the degree of the brain changes (2002, p. 21), pointing out that at least this hematologic factor is not involved. There is still the possibility that the wearing corresponds to certain neurochemistry pathway or to a hormone-dependent atrophy. For instance, it is estimated that during pregnancy the cortisol level rises (Dörr et al., 1989) to a degree comparable to the Cushing Disease (an endocrine condition characterized by excessive levels of either endogenous or exogenous cortisol) (Kammerer et al., 2006; Trainer et al., 1993) and corticosteroids can lead to apoptotic death in some cells while others are unaffected or even stimulated (Elmore, 2007).

In conclusion, as tempting as it might be to interpret this structural MRI descriptive findings using specific neurobiological processes, there is not enough evidence to support such interpretations. Here are exposed the options that a stereotyped neural pruning and/or a neural apoptosis could be involved, but further investigations are needed. The combination of "in vivo" and "ex vivo" methods allow to connect descriptive and mechanistic levels of analysis in order to answer these questions concerning the neurobiological mechanisms underlying the GM volume reductions related to pregnancy (see section *Contributions, limitations and future directions*).

Brain areas implicated

In order to explore the implicated brain regions, which are primarily in high-order association areas, we propose a network approach instead of a region-centric approach. In a region-centric approach, local brain areas are studied exclusively in its specialization to certain specific functions. A network framework emphasizes that functions arise as emergent properties of reciprocated connected brain areas, which are distributed among the different cortical lobes and subcortical structures, forming the functional unit called network (Mesulam, 1990).

Also, we will center in human studies. In view of the substantial differences in methodological approach and scale, the present MRI results cannot easily be compared to those obtained using in-vitro/ex-vivo animal studies. Nevertheless, it is important to mention that several mammal studies reveal that pregnancy is accompanied by a reorganization of the brain, by means of progressive and regressive events, in areas such as mPFC and hippocampus (see in Introduction Brain changes related to pregnancy in rodents). Both mPFC and left hippocampal formation are implicated in our results. Furthermore, brain weight is lower in lactating rats as compared to nulliparous females (Katharina M. Hillerer et al., 2014) which corresponds with the present GM volume reductions related to pregnancy.

With regard to the network approach, the human cortex can be divided in sensorimotor networks and association networks (Yeo et al., 2011). The sensorimotor networks display a topographical and hierarchical organization where adjacent areas tend to show strong functional coupling with one another and they minimally correlate to distributed cortical regions outside the area in question. By contrast, association networks, involve functionally coupled regions distributed throughout the cortex organized predominantly in a parallel and not so much in a hierarchical manner. They comprise the majority of the cerebral mantle including regions within prefrontal, parietal, temporal, and midline cortices, having nodes of convergence primarily in prefrontal and parietal cortices (Yeo et al., 2011).

As mentioned, **the areas involved in the present study correspond to higher-order association cortices, in particular they overlap significantly with the so called default-mode network (DMN)** which has central nodes in the mPFC and the

posterior midline (Andrews-Hanna et al., 2014) as well as a high involvement of medial temporal lobes (MTLs) extending to the hippocampal formation bilaterally (Andrews-Hanna et al., 2010; Buckner et al., 2008; Yeo et al., 2011) (see Figure 10).

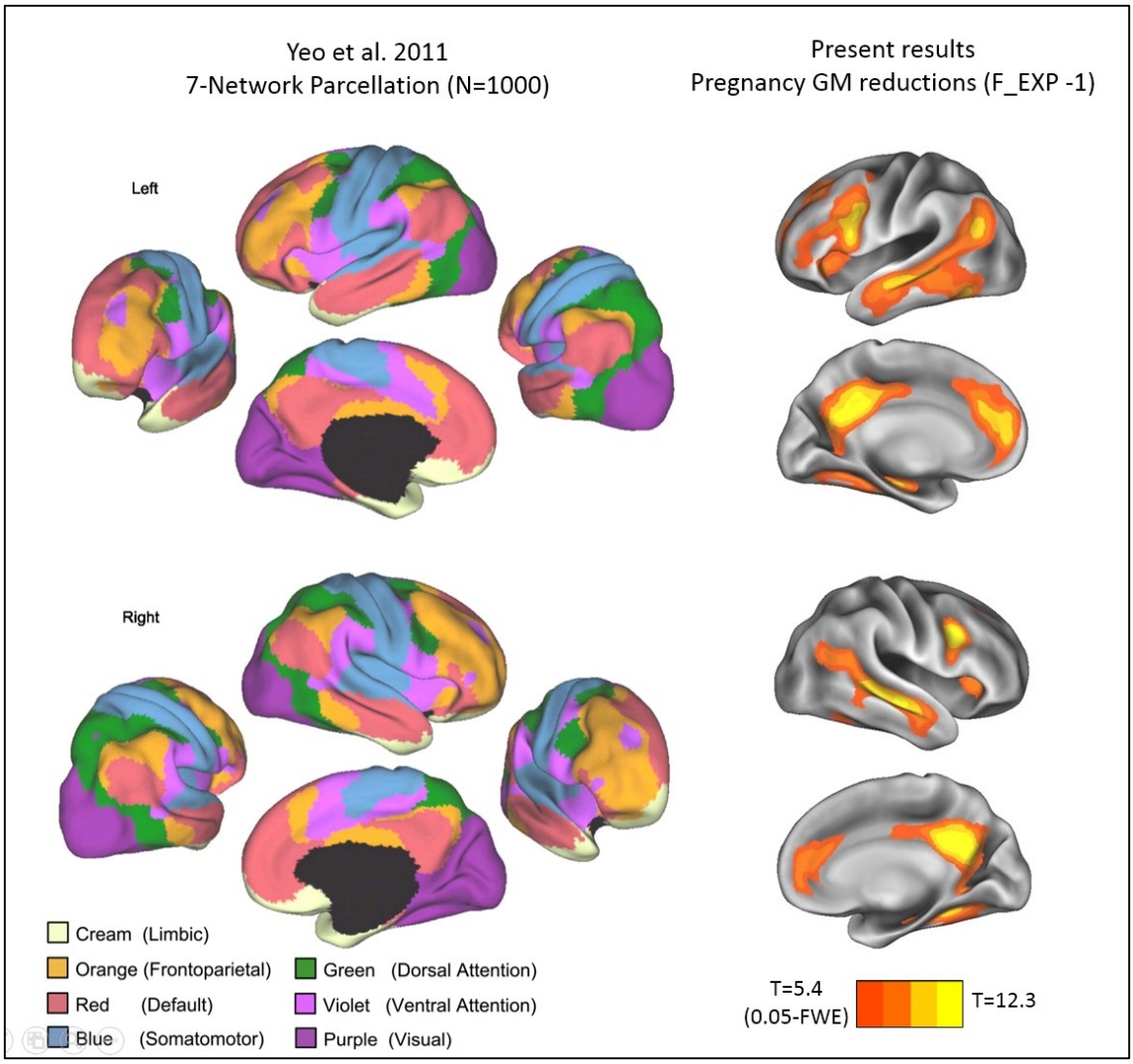

Figure 10. On the left, the 7-Network Parcellation of the human cortex obtained by Yeo et al. (2011) based on the functional connectivity of 1000 subjects, where the default-mode network is represented in red (figure replicated with the author's permission). On the right, structural brain changes associated with pregnancy (F_EXP -1; for visualization purposes is not compared to F_CTR). Note the overlaps in the mPFC, PCC/PC and MTLs.

The DMN, also known as "default network", is a specific brain system that was originally observed in meta-analyses of passive-task data measured with PET (Mazoyer et al., 2001; Shulman et al., 1997) since it is a system that is most active during passive settings (Buckner et al., 2008). It has been anatomically defined via several analysis of connectional anatomy in the monkey (Rilling et al., 2007; Vincent et al., 2007) as well as combining functional connectivity MRI and diffusion tensor imaging in humans, which

demonstrates that the functional connectivity of the default network reflects a structural one (Greicius et al., 2009).

It is organized around a set of interacting association areas distributed along the brain where the main cores are the mPFC and the posterior midline (Andrews-Hanna et al., 2010). By posterior midline is meant the PCC, the retrosplenial cortex and the PC. Another area that is highly implicated in the DMN are the MTLs including the hippocampal formation bilaterally denoting a joint to memory systems (Buckner et al., 2008; Greicius et al., 2009).

Box 10. The finding of the DMN

The brain's DMN was originally observed in meta-analyses of passive task data like lying quietly with eyes closed or a simple visual fixation task (Mazoyer et al., 2001; Shulman et al., 1997). This happened since this network is most active when the person is left to think to himself undisturbed and not focused on the external environment. In other words, what first called the attention was that the DMN is activated when the external attention is diminished and it is deactivated during an externally-cued task (Buckner et al., 2008; Fox et al., 2005; Spreng et al., 2009).

In 2001, two revolutionary reviews from Raichle's laboratory (Gusnard and Raichle, 2001; Raichle et al., 2001) exposed that the DMN is a fundamental neurobiological system with differentiated physiological and cognitive properties and they termed it the "default mode network":

"The regional decreases, observed commonly during task performance, represented the presence of functionality that was ongoing (i.e., sustained as contrasted to transiently activated) in the resting state and attenuated only when resources were temporarily reallocated during goal-directed behaviors; hence our original designation of them as default functions" (Raichle and Snyder, 2007, p. 1086).

This has been one of the most stimulating neuroscientific findings of the past decade: the discovery of brain activity on specific regions when the external task demands are decreased. Afterwards, the DMN emerged as its own research area and received increasingly attention as it has been found to be altered in neurological and psychiatric disorders like Alzheimer disease, dementia, epilepsy, schizophrenia, autism, anxiety and depression (reviewed by Broyd et al., 2009; Buckner et al., 2008; Mevel et al., 2011; Stam, 2014).

To continue, we will first briefly review the functions of the DMN in order to latter translate this overlap into the potential implications of this brain sculpt for the mothers (see next section: *Possible evolutionary purpose and implications for the mothers*).

The nature of the DMN's contribution to adaptive function has been widely discussed (Morcom and Fletcher, 2007) and the mental correlates of this system have proven difficult to interrogate. In spite of the complexity of this network, a matter that

is outside the boundaries of this dissertation, the latest's reviews tend to conclude the following:

First, the notion of the DMN as an exclusively "task-negative" network that supports only passive mental states is nowadays erroneous and can lead to a profound misconception (Andrews-Hanna et al., 2014; Spreng, 2012) (see box 10 "The finding of the DMN"). The DMN is also activated during goal-directed cognition, for instance: autobiographical memory, thinking about one's future, imagine novel scenes, mentally explore and anticipate future situations, infer the mental states of other people (theory of mind), social cognition, reason about moral dilemmas or other scenarios, comprehend narratives, forming associations, semantic memory, self-reflect, self-referential and affective decision making, reference information to one's self, appraise or reappraise of emotional information (reviewed by Andrews-Hanna, 2012; Buckner et al., 2008; Ochsner et al., 2004; Spreng et al., 2009).

Second, what these goal-directed cognitive tasks have in common is that the participants need to actively generate *internally focused thought*, were the goal of the task is of an internal nature or the loci of information processing is endogenous, independent of external stimulus (Gusnard and Raichle, 2001; Raichle et al., 2001).

Then, it is reasonable to think that the DMN is active during resting state, since stimulus-independent mental processes are extremely common during rest. While resting, in the absence of external demands for thought, the mind naturally tends to wander (Mason et al., 2007).

Reports of spontaneous mental processes, also called "stimulus-independent thoughts", show a strong correlation with activity in the DMN (Binder et al., 1999; Christoff et al., 2009; Mason et al., 2007; McGuire et al., 1996; McKiernan et al., 2006, 2003).

It is important to note that the content of this "stream of thought" or "inner-speech" primarily comprises first-person content and is strongly related to one-self:

> *The term mind-wandering should in no way suggest that spontaneous forms of thought are random or meaningless, however. In fact, first-person content reports indicate that, however inexplicable its origin may seem, spontaneous thought is strongly related to one's goals, concerns, and experiences in everyday life (Andrews-Hanna et al., 2014b; Christoff et al.,2011; Fox and*

> *Christoff, 2014; Fox et al., 2013; Klinger, 2008; McMillan et al., 2013; Smallwood and Andrews-Hanna, 2013). Spontaneous thought, then, refers to the type of thought that we recognize as our own creation without yet understanding its ontogeny or purpose — if any (for more detailed discussions, see Christoff et al., 2011; Fox and Christoff, 2014)* (Domhoff and Fox, 2015, p. 612).

Interestingly, the DMN is most active when one takes a first-person perspective centered upon one's own body as opposed to a third-person perspective, and first-person perspective has been considered to be one constituent of human self-consciousness (Vogeley et al., 2004). Furthermore, the cortical midline structures (CMS) of the DMN show activations during tasks that require self-referential processing (D'Argembeau et al., 2010; Northoff et al., 2006; Wicker et al., 2003) and self-projection (Buckner and Carroll, 2007). Therefore, it has been suggested that *the DMN is useful to explore the neurobiology of the self* (Damasio, 2012; Gusnard et al., 2001; Qin and Northoff, 2011; Various authors, 2014) and conscious experience (Mantini and Vanduffel, 2013). This is well represented in Northoff and colleagues' conclusion (2006, p. 454): "current brain imaging data are remarkably consistent with the fact that the CMS is a major locus of control for the cerebral representations of self-referential processing"… "We assume self-referential processing to be at the core of what is called the self" (Northoff et al., 2006, p. 454).

Summing-up, what the tasks eliciting the DMN seems to have in common is that they imply internally focused, self-referential processing.

The DMN has also been observed in a recent groundbreaking meta-analysis accomplished by Yeo and collaborators (2014) in which they explored the organization of the human association cortex by applying a mathematical model to one of the largest data set of neuroimaging experiments available (2194 studies; 10449 experimental contrasts; 83 defined task categories). This study was elaborated under the premise that a certain tasks recruit multiple overlapping cognitive components, which are as well supported by overlapping brain regions (Mesulam, 1990; Poldrack, 2006). From the

meta-analysis a classification of 12 cognitive components emerged[14] and with regard to Component C10, the authors describe:

> *Component C10 had high probability of activating the posterior cingulate cortex, precuneus, posterior hippocampal formation, medial PFC, inferior parietal cortex, temporal cortex, and the temporoparietal junction. The activations associated with C10 overlapped significantly with the default network (Buckner et al. 2008). The top tasks recruiting component C10 were "Theory of Mind," "Rest," and "Fixation* (Yeo et al., 2011, p. 8).

So, this meta-analysis found —using a different and exhaustive methodological approach— a cognitive component that significantly coincidences with the DMN in terms of brain regions and tasks, adding further consistency to this brain network.

Interestingly, **the DMN (or the component C10) is also triggered during tasks labeled under "Theory of Mind"** (ToM) (Iacoboni et al., 2004; Schurz et al., 2014; Yeo et al., 2014) **suggesting that both, self-referring and other-oriented thoughts, share neural bases** (Northoff et al., 2006; Uddin et al., 2007) (see box 11 for "Theory of mind").

To assign and attribute mental states to other person is an ability needed for social cognition (Frith and Frith, 1999) and from an evolutionary point of view is conceived as an effective surviving strategy (Baron-Cohen, 1997). Furthermore, in relation to the present study, **ToM system is consider to be a core component of the human parental brain circuits** (J. E. Swain et al., 2014, p. 90) (Figure 4).

[14] For an interactive version of this 12-component ontology please go to: https://surfer.nmr.mgh.harvard.edu/fswiki/BrainmapOntology_Yeo2015

Box 11. Theory of mind

ToM, often also called as "mentalizing", "mind reading", "mind perception" or "social intelligence" (Schaafsma et al., 2015), is based to the assumption that we possess a theory of mind that allow us to have a reflective function concerning our mental states and to attribute mental states to others, accepting that others can have perspectives, beliefs, desires and intentions different from one's own (Premack and Woodruff, 1978). It involves the understanding that the behaviors of others is motivated by unobservable internal mental states such as thoughts, emotions and believes (Premack and Woodruff, 1978).

People with impairments are not competent to make sense of the observed behavior of others, to determine their intentions or they have a hard time seeing things from any other perspective than their own. Severely impairments are found in autistic spectrum disorders (Baron-Cohen et al., 1985; Blair, 2005), schizophrenia (Mehta et al., 2014; Sprong et al., 2007) and other psychopathologies (reviewed by Brüne and Brüne-Cohrs, 2006).

In order to assess the neural correlates of the ToM, fMRI studies usually utilize tasks that require thinking about the mental states of others, for instance: false belief attribution, trait judgements, strategic games, reading the mind in the eyes, social animations and rational actions (reviewed by Schaafsma et al., 2015; Schurz et al., 2014).

A recent meta-analysis examined activation foci from 73 neuroimaging studies that spanned the six main task groups that elicits ToM (see box 11 for a classification of the tasks). The results show that the core regions of the ToM are the mPFC and bilateral temporo-parietal junction (Schurz et al., 2014). In addition, other regions surrounding this core network are highly involved depending on the task, primarily: PC, temporal lobes and inferior frontal gyrus (Schurz et al., 2014).

Figure 11 compares the present results with the results of this pooled meta-analysis including all 73 studies from every task group under the umbrella of ToM (Schurz et al., 2014). Overlaps in the mPFC, PCC/PC and MTLs are evident.

As mentioned, also overlaps between the ToM's core regions and the DMN are remarkably and have recently linked via meta-analysis of neuroimaging studies (Northoff et al., 2006; Spreng et al., 2009; Yeo et al., 2014).

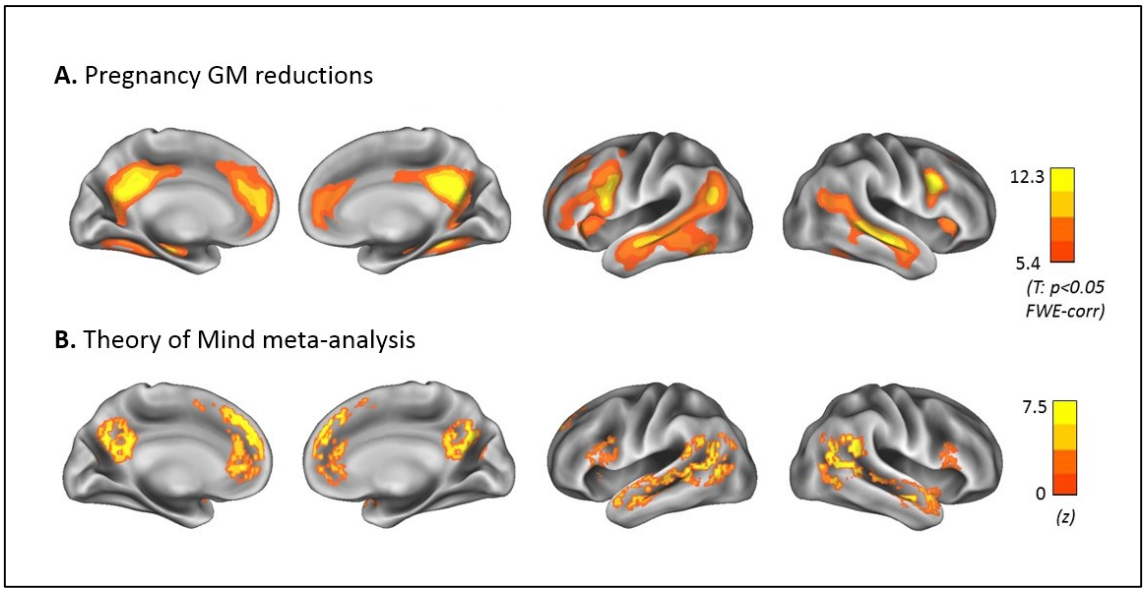

Figure 11. **A**. Structural brain changes associated with pregnancy (F_EXP -1; for visualization purposes is not compared to F_CTR). **B**. pooled meta-analysis performed by Schurz and collaborators (2011) (figure elaborated with the author's permission) The meta-analysis includes 73 fMRI studies that tested 1241 participants assessing different ToM-tasks. Clusters indicate brain activations of the overall summary. Note the overlaps in mPFC, PCC/PC and MTLs.

Furthermore, the analogous involvement of midline structures (mPFC, ACC and PCC, PC) in both self- and other- referential processing have been observed in various fMRI studies (Lamm et al., 2011; Ochsner et al., 2004; Schmitz et al., 2004; Seger et al., 2004). And in relation to this corresponding involvement of brain areas in self- and other- related processing, Uddin and collaborators (2007) say:

> *It seems that these midline structures might be involved more generally in representing both self and others in terms of their mental states or non-physical aspects. It is likely that one function of the so-called 'default network' is to act as a constant monitor of the self and its social relationships; thus, we see increases in activity in this network across a variety of paradigms where the social self is invoked, as well as when processing information about the mental states of others* (Mitchell et al., 2005) (Uddin et al., 2007, p. 155).

How can the involvement of the same core regions in both self- and other-referential processing be interpreted? According to the simulation theory, **we use our own mental state as a model for inferring the mental states of others** (Goldman,

1992) and not by merely simulate being in the other's situation but by simulating "being the other" with his or hers psychological traits (Gordon, 1995).

> *The observer tries to covertly mimic one's mental state of the other person leading to shared mental states between observer and observed persons. Since in mind reading the others' mental states seems to resonate in the own mental state, it might be assumed that mind reading requires self-referential processing* (Northoff et al., 2006, p. 448).

To conclude:

The brain regions that are sculpted in relation to pregnancy overlap significantly with both —the DMN and the core regions of the ToM— in: mPFC, PCC/PC and MTLs extending to the hippocampal formation.

The recruitment of the DMN reflects internally focused thought (Gusnard & Raichle, 2001; M. E. Raichle et al., 2001) supporting different aspects of self-referential processing (Andrews-Hanna et al., 2014; D'Argembeau et al., 2010; Mantini and Vanduffel, 2013; Northoff et al., 2006; Wicker et al., 2003), whereas the core regions involved in ToM are elicitated by other-oriented processes (Schaafsma et al., 2015; Schurz et al., 2014).

Accordingly, self- and other-oriented processes are also met, as our ability to infer other mental states relies on self-referential processes (Goldman, 1992; Heberlein and Atkinson, 2009).

We therefore hypothesized that **the present brain changes are related to the DMN-ToM function of inferring other mental states, particularly the mental stated of the baby** (see next section: *Possible evolutionary purpose and implications for the mothers*).

Possible evolutionary purpose and implications for the mother

In a relative way, the post-reproduction brain is the same as the pre-reproduction brain, although the maternal behavioural repertoire that it now regulates is more efficient and shaped for survival. Why do such effects take place? Simply, to guarantee that the next generation is itself ready to reproduce and perpetuate life.

Craig H. Kinsley & E. Amory-Meyer, 2011, p. 980

It has been said that "it is fortunate for their survival that babies are so designed by Nature that they beguile and enslave mothers" (Bowlby, 1958, p. 19). It is true, babies are captivating. But appears that "Nature", in addition to its charming baby design, also designed the mother's brain for such an evolutionary aim. In humans, the survival of the young is dependent on the exertions of the mother and her brain seems to have evolved in ways that promote an effective offspring protection, care and nurturing.

The working memory test and the scale evaluating empathic concern that were applied to this sample, did not render any significant difference and therefore is not possible to talk about a "mental correlate" of these brain changes (see in Results, section *Dispositional empathy and cognitive measurements*). Nevertheless, this section aims to better understand this neural sculpting by relating it to the mental changes of pregnancy and the early postpartum period. This will be explored by means of integrating the last two segments as well as by an interdisciplinary conceptual exploration attempting to integrate knowledge and conceptualizations from other disciplines addressing the inner-life vicissitudes that accompany the transition into motherhood.

Why GM volume reductions?

It might seem paradoxical that a period like peripartum during which the acquisition of new knowledge is very high coincides with a decrease rather than an increase of GM volume. However, as previously described, the same happens during adolescence: a period characterized by the emergence of executive function mediated by the PFC (Luciana et al., 2005) surprisingly shows regressive events in this particular brain region (reviewed by Blakemore, 2012; Durston et al., 2001; Lenroot and Giedd, 2006; Paus, 2005) which has been correlated to synaptic pruning (Petanjek et al., 2011).

Petanjek and collaborators (2011, p. 13284) interpreted this neural pruning as a circuitry specialization following the selective-stabilization hypothesis, were alteration of synaptic number during development are caused by selective survival of certain synapses and not by regulating their initial formation. (Rakic, Bourgeois, Eckenhoff, Zecevic, & Goldman-Rakic, 1986).

The present results might also correspond to a circuitry specialization concerning the mother's metacognitive capacity to infer the mental state of the infant and her readiness to contemplate these in a coherent manner.

As previously explained (see section *Brain areas implicated*), the GM regions that changes in relation to pregnancy overlap with a brain system that correlates with the ability to infer the mental state of other person (Schurz et al., 2014). Here it is postulated that this inferring capacity is specialized in the mother in order to better envisage the infant as a human being with relatively sophisticated feelings, beliefs, and desires.

In particular, this specialization might serve at least these purposes in the mother:

To understand and explain: to find a meaning in the expressions, actions and behaviors of the baby. Without it, the mother would be confused and overwhelmed by the complexity of the new central situation. Understanding the baby's responses might help the mother to create an order by giving purpose and meaning to them. Parents usually spend a large amount of time just observing their baby. They look continually for baby' signals that gives them the tranquility that their efforts are in the correct direction. They repeatedly need the baby's responses as a confirmation of their care and efforts. The behavior of the baby is their best guide.

To predict: to mentally explore and anticipate future situations (Buckner et al., 2008). Such constructive processes might be adaptive, especially in front of a new vital task like taking full time care of the newborn. A specialization of this capacity around the baby's needs might let the mother to pre-experience situations by means of flexible mental explorations or simulations. This will provide the mother with resources to prepare herself for upcoming events before they happen, being more efficient in her maternal functions. This is observable in the way new mothers adjust to the new situation, sometimes showing an extraordinary creativity concerning the care of the infant.

The consequences of this specialization for the infant might be:

Simply but most importantly, to offer the infant the best care possible, were his/her basic needs are fulfilled and therefore his/her survival warrantied.

To provide the child a good mental development: the mother's capacity to infer the child's mind facilitates the child's secure attachment, as well as a general understanding of minds which, in turn, helps the development of theory of mind (Fonagy, 1996). Thus, this mentalizing capacity in the mother, as well as in the father, is very important as "the theory of mind or, more broadly, reflective-self function, evolves in the context of intense interpersonal relationships" (Fonagy, 1996, p. 84).

The implicated brain system that overlaps with our results (see section Brain areas implicated) is also related to different kinds of self-referential processing, like: self-reflect, self-referential and affective decision making, reference information to one's self, appraise or reappraise of emotional information. Furthermore, some authors suggested that the DMN is useful to explore the neurobiology of the self (Damasio, 2012; Gusnard et al., 2001; Mantini and Vanduffel, 2013; Qin and Northoff, 2011; Various authors, 2014). In order to briefly reflect about this, we choose an interdisciplinary approach to consult disciplines that addresses the inner-life vicissitudes that accompany the transition into motherhood.

It is usually said that becoming a mother is a life-altering event. As described in the Introduction (see *Behavioral changes due to reproductive experience*) in mammals the mother displays evident changes in behavior as soon as the offspring is born. In humans, besides changes in behavior, the mothers manifest that they attach to her new born with

a new and particular emotional experience (Bowlby, 1958; Brazelton and Cramer, 1991; Winnicott, 1975).

Exists remarkable work delving the inner-life variations that go with the transition into motherhood developed by clinical research that aims the understanding of phenomena like: the reorganization of identifications that motherhood conveys, the identifications onto the baby, the mourning processes that take place, the earliest symbiotic relationship between mother and child, the reciprocal developments, and so on (Brazelton and Cramer, 1991; Deutsch, 1925; Langer and Hollander, 1992; Likierman, 1988; Lomas, 1956; Manzano et al., 1999; Mariotti, 2012). To go deep into this perspective is outside the boundaries of this dissertation, but in the big picture, becoming a mother implies a subtle but profound personal transformation. As the saying goes: "it changes your life". It involves modifications in the physiology of the body likely affecting the self-perception (Damasio, 2003); also conveys changes in the priorities, scale of values and preoccupations; the dynamics with the couple also varies; and to affectively attach to the new baby, with the strong bond that conveys, implies a reorganization of other emotional bonds.

For instance, just to give an example, the new mother has to learn to tolerate and enjoy the huge demands due to the total dependency of the baby, which can be specially illustrated by the recurrent baby's hunger which has to be satisfied with her own body (Brazelton and Cramer, 1991).

The change is so profound that some authors consider that the woman experiences a pseudo-transient pathologic state (Brazelton and Cramer, 1991), that the process is comparable to a developmental stage (Benedek, 1959) or that mothers reach a special psychological condition characterized by a state of "heightened sensitivity" or "normal devotion" (Winnicott, 1975, 1960). In the perinatal period, the mother becomes preoccupied with her newborn to the exclusion of other interests –in a way that is normal and temporary– allowing her to adjust delicately and sensitively to the infant's needs at the very beginning.

These studies reflect, indeed, a significant restructuration of the personality. The expected culmination of this transition is a new maternal identity, a focalization of the affective bonds and the capacity to recognize, accept and love a new unavoidable reality.

Does this specialization claim a bill to other functions?

The present study has not found any significant difference in the verbal memory test (TAVEC), neither in none of the two working memory tests applied (Subscale "digits" from the WAIS-III and 2N-back cognitive task) and working-memory capacity is strongly related to measures of the intelligence quotient in general (Conway et al., 2003).

Even more, a longitudinal study that characterized brain development from childhood to adulthood in a large group of 307 normally developing subjects, shows that levels of intelligence are related to the pattern of cortical changes were subjects with superior intelligence show a pronounced cortical thickening during childhood followed by an equally prominent thinning during adolescence. On the contrary, the pattern of cortical changes in subjects with an average intelligence is significantly more subtle being the tinning during adolescence not so marked (Shaw et al., 2006). Hence, surprisingly, intelligence is not represented by more or less GM, rather, it is related to dynamic properties of cortical changes.

Nevertheless, studies examining cognitive functions related to reproduction show a trend towards subtle memory impairments in peripartum (for review see Buckwalter et al., 2001; Henry and Rendell, 2007; Macbeth and Luine, 2010) and the subjective perception of the mothers is that pregnancy does interfere mildly with their cognitive performance (Crawley et al., 2003). For that reason, it is not possible to conclude if pregnancy brain changes are related to a cognitive impairment or not; more investigations are needed in order to elucidate this.

What does seems more feasible is that these structural brain changes imply a certain degree of mental vulnerability that might predispose the new mother to a postpartum mood disorder. The prevalence rates of these mental disorders are high, for instance, it is estimated that 11-20% of new mothers suffer from DSM-defined minor depression and approximately 7% from major depression (Almond, 2009; Earls, 2010; Gavin et al., 2005; Moses-Kolko and Roth, 2004; O'Hara and Wisner, 2014) (see box 1 for "Concurrence of psychopathology in the perinatal period"). If left unrecognized or untreated, the disorder can have far-reaching consequences not only for the mother, at risk for recurrent major depression and a high prevalence of self-harm and suicide (Oates, 2003a, 2003b; Wisner KL et al., 2013), but also for the infant (see box 7. "Parent-infant interactions and its repercussion on the infant's health").

To conclude this section, it is postulated that pregnancy implies an adaptive restructuration of the mother's brain to ensure that adequate maternal care is provided after birth. The GM volume reductions may correspond to a circuitry specialization concerning the mother's capacity to infer the mental state of her infant, promoting an effective offspring protection, care and nurturing. This morphological sculpt is not necessarily innocuous: it seems to predispose the mother to perinatal mood disorders.

Contributions, limitations and future directions

Several reviews points out that adaptations in various brain systems ensure pregnancy, delivery and postnatal care, suggesting in humans a brain plasticity inherent to reproduction itself (Brunton and Russell, 2008; Kinsley and Amory-Meyer, 2011; Swain et al., 2014). Although this question has been previously addressed assessing whole brain changes in size (Oatridge et al., 2002), the current findings are the first in demonstrating that pregnancy causes specific morphological brain changes in women; they explicit the precise volumetric GM reductions that are associated with successful reproduction in human mothers.

The present study also gives important clues concerning the neural basis of motherhood, helping to better understand the transition to motherhood pointing out a period of profound change.

It gives light in a new way to focus future research regarding perinatal mental health, were early identification of vulnerability and prevention measures can make a difference facing these debilitating disorders. This can have far reaching implications, since the type of maternal care a child receives can either provide mental resilience throughout life or contribute to the development of psychopathologies (see box 7 for "Parent-infant interactions and its repercussion on the infant's health").

Concerning brain plasticity in general, the capacity for large-scale changes in brain structure is regarded primarily as a feature of the immature brain, with puberty as the last brain-reshaping stage (Blakemore, 2012; Durston et al., 2001). This study broads this conception by proving that pregnancy conveys morphological brain changes, underlining the capacity of the mature brain to reshape at a large-scale under non-pathological conditions.

In general, the study accomplish optimally the requirements to prove the proposed hypothesis: pregnancy causes GM volume changes in the human brain.

A limitation is that, as mentioned, brain changes captured by T1-weighted images are not specific enough to be translated in terms of a precise neurobiological process. A single voxel of GM captured by MRI contains a complex architecture of several tissues, vascular and glial included, and therefore we cannot make a direct assumption of properly neuronal loss. Another fact to be aware of is that changes in

sulcal and gyral folding patterns could be perceived via MRI as a change in the volume while it is really just a change in the folding.

A different limitation is that the study design does not allow to certainly tell apart the effects of pregnancy, parturition and the postpartum period. Although a measurement right before parturition and right after the birth is technically possible, we did not account with the infrastructure in order to do so and we also considered is quite intrusive for the mother to be scanned in such an intimate and important moment: very likely, many subjects would have reject to participate. However, it should be noted that the GM changes were not observed in the fathers, who also experienced the environmental and psychological changes of having a baby but not the endocrine and physiological changes of pregnancy and parturition (at least not to the same degree). Additionally, we performed correlation analyses with the duration of the postpartum period and observed no significant correlations within the brain structures that changed.

Another inadequacy was the utilization of two different head coils during the acquisitions. Due to a technical unexpected problem, the 8-channel head coil was replaced with a 16-channel head coil for a couple of months. All the PRE acquisitions were made with the 8-channel head coil and for the POST scans the distribution of the coil types across the groups was relatively consistent; chi-squared test shows no significant differences between the samples regarding the head coil utilized. In order to solve it, in all analysis the head coil was used as/was accounted for as a nuisance covariate that allow us to control for the effects of this variable.

With regard to the future directions, an ongoing project using the present data set (see Table 11 for a list of follow-up studies proposed) is to assess the morphology of GM utilizing another brain morphometric technique, surfaced-based Cortical Thickness, since combining these complementary techniques adds additional information concerning the spatial descriptive characteristic of the GM changes.

In order to associate the morphological brain changes related to pregnancy with changes in neural activity, another project is to correlate the present results with the two fMRI paradigms in which the same subjects participated. One paradigm assess brain activity in front of "own-baby" images, and the other one measures brain activity in front of a video of the couple.

An important question that emerges is if the structural brain changes founded are transient or permanent. In order to explore this we will do a follow up scan of the same participants after a couple of postnatal years. Nevertheless, some analyses with the actual data give us a hint about this topic, since there is no evidence of GM volume recovery in such a short time pointing out the probability that the GM volume changes are permanent:

- the inclusion of the covariate "time since birth" did not module the results
- the correlation with the age of the baby and the post scan showed no results at 0.05 FWE corrected and even when lowering the threshold to 0.001 uncorrected, there is no sign of any correlation

The profile of behavioral, endocrine and neural changes observed in pregnancy has some similarities to those observed in adolescence, also characterized by reductions in GM volume across the brain, drastic hormonal changes and changes in mood and behavior. A detailed voxel-wise volumetric comparison with an adolescent sample would lead to significant clues regarding the implicated areas, the endocrine and the neuropsychological processes that accompanied the volumetric changes related to pregnancy.

A better examination of WM tissue can be obtained, in another sample, with a diffusion-weighted sequence*. Considering that the regions of volumetric GM changes are overlapped with a large-scale network of connected association areas, it will be important to explore whether the structural connectivity between these nodes is also reduced, or, in fact, shows a compensatory enhancement. The application of a DWI would allow us to assess the structural integrity of the WM tracts connecting these regions of GM volume change.

In addition, the degree of functional temporal coherence between these regions can be quantified with a resting state functional connectivity MRI (rs-fcMRI)*.

^{1}H-nuclear MR spectroscopy can explore changes in metabolite concentrations within some of the structures showing the strongest GM alterations (for instance, mPFC and PCC/PC)*. This would allow to obtain more information regarding the nature of the biochemical alterations and investigate whether these represent primarily variations in neuronal or glial cell markers.

Assuming that there is a relationship between neural synchrony and brain structural development (Uhlhaas et al., 2009), the brain changes related to pregnancy

can be assessed by measuring neural synchrony with electroencephalography and magnetoencephalography recordings at different times during pregnancy and postpartum.

Postmortem studies of peripartum female mammals and women can discern the degree to which the GM volume changes observed are related to dendritic pruning, cell death or the encroachment of WM on the inner cortical border.

In order to do correlations with the structural neural data, hormonal measurements can be extracted at different times during pregnancy and postpartum*. Also, additional neurofunctional, psychological and behavioral indices of maternal functioning/attachment can give important clues regarding the mental correlates of the brain modifications*. As well, several cognitive test can be applied *.

To finish, with a view to better understand the processes underlying the development of postpartum mood disorders, a close, complete and continuous psychological/psychiatric evaluation would allow to track and study predictors or symptoms*.[15]

* A follow-up study with a new sample has already been set in order to assess this under the direction of Elseline Hoekzema.

Table 11. Follow-up studies proposed

	Study	Objective
actual data set	Cortical thickness	measure GM changes in cortical thickness and surface area
	fMRI own baby	correlate MBCh-pregnancy with changes in brain activity own-baby stimuli
	fMRI couple	correlate MBCh-pregnancy with changes in brain activity couple stimuli
	Follow-up MRI	explore if MBCh-pregnancy are transient or permanent
	Comparison adolescence	compare MBCh-pregnancy with those observed in adolescence
	Comparison hypercorticolism	compare MBCh-pregnancy with those observed in hypercorticolism
	VBM WM	preliminary assessment of WM volume changes
new studies	Diffusion-weigthed sequence	examine integrity WM tracts connecting regions GM volume change
	rs-fcMRI	examine degree of functional temporal coherence between the regions
	MR spectoscopy	measure biochemical alterations in mPFC and PCC/PC
	Electro/Magnetoencephalography	measure neural synchrony during pregnancy and postpartum
	Postmortem	examine neurobiological process microscopically
correlations	hormones	correlate with endocrine changes
	maternal attachment	correlate with maternal functioning/attachment measurements
	cognitive functioning	correlate with cognitive measurements
	psychiatric assessment	correlate with symptoms of postpartum mood disorders

List of potential follow-up studies and their objectives. MBCh-pregnancy = morphological brain changes related to pregnancy. First group can be done or complemented with the “actual data set”. Second group enumerate complete “new studies”. Last group consist in other assessments to do “correlations”.

CONCLUSION

The current findings are the first in demonstrating that pregnancy causes specific morphological brain changes in human mothers, providing primary insights into the way a woman's brain is modified during pregnancy. The primary brain changes comprise GM volume reductions at the posterior midline (posterior cingulate and precuneus), the medial frontal cortex (medial prefrontal cortex and anterior cingulate), bilateral lateral prefrontal cortex (clusters in ventrolateral and dorsolateral prefrontal cortex) and bilateral temporal cortex (bilateral superior temporal sulcus extending to surrounding lateral temporal sections as well as medial temporal structures such as the fusiform gyrus). All p values are below 0.05 familywise-error corrected.

The changes are remarkably consistent across subjects since 100% of the sample can be automatically classified as having undergone pregnancy or not, based on the distribution of GM changes across the brain.

Although the neurobiological mechanisms and physiological meaning of these findings are speculative at the present time, it is hypothesized that pregnancy implies an adaptive restructuration of the mother's brain to ensure that adequate maternal care is provided after birth. Specifically, the GM volume reductions may correspond to a circuitry specialization concerning the mother's metacognitive capacity to infer the mental state of her infant, promoting an effective offspring protection, care and nurturing. This morphological sculpt is not necessarily innocuous, but may aim for a bigger purpose: to guarantee that the next generation is itself prepared to reproduce and perpetuate life.

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Appendix 1. Review of the studies that assess mother's brain activity employing visual stimuli

		Prefrontal		Temporal		Parietal		Occipital		Anterior Cingulate		Posterior Cingulate		Insula		Parahippo-campal		Amygdala		Thalamus & hypothalamus		Basal ganglia & midbrain		Cerebellum	
		L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R
OWN CHILD > OTHER CHILD	Bartels & Zeki 2004	x	x					x	x	x	x			x	x					x	x	x	x		
	Nitschke et al. 2004	x	x					x	x															x	x
	Leibenluft et al., 2004	x	x	x	x	x	x	x	x	x	x		x	x					x	x	x	x	x	x	x
	Strathearn et al., 2008	x	x	x	x	x	x			x	x	x		x	x		x	x		x	x	x	x	x	x
	Noriuchi 2008	x	x		x							x			x					x	x	x	x		
	Lenzi 2008		x		x	x	x								x										
	Atzil 2011	x	x		x	x	x	x			x			x				x	x	x		x	x		
	Wan 2014	x	x		x	x	x	x										x						x	x
OTHER CHILD > OWN CHILD	Bartels & Zeki 2004	x	x	x	x	x	x					x	x					x	x						
	Nitschke et al. 2004			x	x																				
	Noriuchi 2008		x	x	x	x	x									x						x	x		
	Wan 2014	x	x		x																				x

The X indicates a significant change in brain activity in front of the designate comparison: "Own child > Other child" means the indicated brain areas were significantly more active while viewing their own child than while viewing another child; "Other child > Own child" means the indicated brain areas were significantly more active while viewing other child than while viewing their own child. Brain areas are specified in left (L) and right (R) hemispheres.