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Cognition of parenting:

The effect of biological factors and cognitive processes and their interaction on adult responsiveness to baby signals

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Cognition of parenting: The effect of biological factors and cognitive processes and their interaction on adult responsiveness to baby signals

Chapter 1

Introduction

The mother-child relationship is one of the most important events in the life of an individual. In literature, there is a broad consensus on the fact that a warm and sensitive relationship plays a central role for children's cognitive and socio-emotional development, providing the child with a secure base, from which to achieve a good adaption in their social environment (Ainsworth, Bell, Stayton, 1974; Bornstein, Tamis-Lemonda, Hahn, & Haynes, 2008; Bornstein, 2002). The theory of attachment, taking into account the development of the attachment bond, represents the main theoretical frame in which to interpret the various aspects of the dyadic relationship, as its role on affecting social relationships in childhood and adulthood over the course of life (Bowlby, 1969; Trevarthen & Aitken, 2001).

Aims of this PhD Research Project:

In the last decade, neurobiological studies have focused efforts on investigating the biological substrates (i.e., cerebral structures, neurotransmitters, and hormones) underlying parental attuned behavior to salient infant stimuli (i.e., infant cries), that plays an important role in child affective, social, and cognitive development (Venuti, 2007; Bornstein, 2002). Both human and animal studies have primarily focused on the neurobiology of mothers and have shown that subcortical and cortical cerebral structures such as the prefrontal cortex, thalamocingulate network, hypothalamus, amygdala, and substantia nigra are important in maternal motivation and attuned behaviors (Barrett & Fleming, 2010; Swain, Lorberbaum, Kose, & Strathearn,2007). However, there is a lack of literature concerning gender differences and only a few studies have investigated the sensitivity of response to infant stimuli in non-parent adults (Caria, de Falco, Venuti, Lee, Esposito, Rigo, Birbaumer & Bornstein, 2012; Glocker, Langleben, Ruparel, Loughead, Gur & Sachser, 2009; Parsons, Young, Kumari, Stein & Kringelbach, 2011; Montoya, Landi, Kober, Worhunsky, Rutherford, Mencl, Mayes & Potenza, 2012).

In this research project we focused our investigations on mechanisms in human adults (parents and non-parents) involved in parental care, and in specific: (a) on neural mechanisms underlie BOLD response to infant vocalizations, crying in particular; (b) on brain changes (grey matter volume) occurring during the early postpartum period in new fathers.

Using functional magnetic resonance imaging (fMRI), in the first study (second chapter) we looked at gender differences in resting-state brain activation associated with the cry condition at the default mode network (DMN) level in a sample of healthy adults (parents and nonparents). The design was balanced by parental status and gender. The DMN is preferentially activated when individuals are not involved in externally oriented tasks, namely during the mind wandering and it is deactivated during external goal-oriented activities.

In the second longitudinal study (third chapter) we investigated in new fathers the GM volumes change amongst 2-4 weeks and 3-4 months postpartum in brain areas responsible for parental behaviors over time during the early postpartum period. Anatomical changes and their relationships with parenting behaviors have never been examined in human fathers despite the importance of paternal care for child development.

In the third study (fourth chapter) we investigated, using fMRI and behavioral (Response Time RT) techniques, how the pattern of cerebral activation when listening to infant cry modulates concomitant behavioral tasks, which could require or not require the attention toward the cry stimuli, and thus affecting parental responsiveness.

Parenting: the relevance of findings coming from affective neuroscience researches

Since the last decade, a new research strand is investigating the neurobiology underlying parental care, highlighting biological substrates that underlie the parental responsiveness to infant signals, as vocalization (i.e. crying) and visual cues (i.e. emotive expressions of face) (Bartels & Zeki, 2004; Ranote, Elliot, Abel, Mitchell, Deakin & Appleby, 2004; Seifritz Esposito, Neuhoff, Lüthi, Mustovic, Dammann, von Bardeleben, Radue, Cirillo, Tedeschi & Di Salle, 2003; Swain, Kim, & Ho, 2011; Swain, Lorberbaum, et al., 2007; Swain, 2011). The importance of investigating the neurobiology of parenting, through neuroimaging techniques, functional magnetic resonance imaging (fMRI) in particular, relies on the fact that findings, about specific brain structures and neural networks promoting the development of parental care behavior, could increase the understanding of parenting at risk. The rational lies with the fact that the attachment relationship - a strong, durable and emotionally significant bond, directed towards a specific person - is not directly observable (Bowlby, 1969; Ainsworth, Bell et al., 1974;). What we can do is make inference of it, through the observation of its mediators, namely the child’s and parent's attachment behaviors, activated to reduce the distance between eachother. Physical proximity is critical to the development of attachment, because only with proximity can the child experience the sense of well-being and safety given from such physical contact, which represents the child's secure bases from which to deal with environment exploration. The interruption of proximity makes the attachment visible. In fact the separation anxiety generated by it acts as a trigger for the attachment behavior, aimed at reducing the distance. Attachment behaviors are deactivated as soon as the proximity is restored (Bowlby, 1969; Ainsworth, Bell et al., 1974). Taking in mind this function of attachment behaviors, infant signals act as triggers for parental care. From here, the importance of investigating part of the different mechanisms that come into play during the development of attachment, as the neurobiology of affective and cognitive processes underlying parental responsiveness to baby's signals. Findings in this research field will improve the understanding of what the critical mechanisms that modulate the caregiver response are. Understanding of the biological nature of attachment behaviors, and the factors which interfere with parental care and responsiveness, could help clinical psychology prevent and assess deviant parental behavior in situations at risk.

About the research object of neuroimaging investigations

The focus of first fMRI studies, which investigated maternal neurobiology, was placed on the earliest mother-child interactions, that constitute the starting point from which to develop the bond of attachment (Bowlby 1969). Theories of today assume that during the earliest interactions, within which mother and child build mutual knowledge of eachother, many external environmental and internal factors affecting both infant attachment behaviors and parental responses of care come into play. These factors reflect either the ontogenetic (i.e. environmental factors derived from experience) or the phylogenetic (i.e. innate predispositions) development in each individual (Bowlby, 1969; Lorenz, 1971; Bornstein, 2002). The underlying rational of the fact that most researches have been focused on the infant crying, resides in its importance (of crying) as communicative signal for personal needs, and as a key that drives the development of the relationship with the parents (Cecchini, Lai, & Langher, 2007; Bornstein, 2002; Newman, 2007; Venuti & Esposito, 2008).

Baby's crying, and its interaction with parental behaviors

The attachment relationship could be driven by instinctive behavior, in both adults and children, aimed at maintaining the proximity between caregiver and offspring. The human brain would show innate predispositions to react not only to threat stimuli but to all biologically salient stimuli independent of their valence (Lorenz 1971; Scherer, 2011). The human infant face and cry represent essential sources of communicative signals through which adults modulate their interactions with infants. For example, there is behavioral and neurobiological evidence that morphological features of a human baby's face (baby schema) seem to represent an highly biologically relevant stimulus that capture attention and reward of adults, and to which humans might be innately prepared to respond (Brosch, Sander, & Scherer, 2007; Caria, de Falco, et al.,, 2012; Glocker, Langleben, et al., 2009;

Kringelbach, Lehtonen, Squire, Harvey, Craske, Holliday, Green, Aziz, Hansen, Cornelisse & Stein, 2008).

Crying, which is the focus of this research project, is one of the first communicative signals that children display during early social interactions, and it can be used by infants to express their needs and communicate with their environment, eliciting attuned adults' responses (Newman, 2007; Venuti & Esposito, 2008). Although characterized by a great morphological variability among species, crying is universally present in infant humans as well as in other infant mammals (e.g. Furlow, 1997; Newman, 2007; Zeifman, 2001). In fact, the occurrence of crying is the result of a sequence of muscle contractions ascribable to a universal motor pattern, present in different cultural and ethnic groups, and also present in individuals, who have not had the opportunity to observe the different muscle contractions in other people (i.e. blind people). By virtue of its characteristics, crying is a universal and instinctive vocalization understood by anyone. Crying is a natural expression of the state of the child, not only in humans but also in other mammal species (Darwin, 1872; Lorenz, 1971).

Referring to Lorenz (1971), the attachment theory defines infant cry like an innate releasing mechanism, a key stimulus that activates another mechanism present in the mother underlying the behavior of care. These two mechanisms constitute the functional unit of the attachment behavior. Instinctive components of attachment relationship are especially visible in very young children (up to about 6-8 months), when the attachment behavior is unorganized and undifferentiated, and put in place every time the child feels a discomfort or a change of physical and psychological nature. At this level, one of the efferent systems that drives behavior in the child are those underlying the crying (Bowlby, 1969). This way, even maternal disposition in care cannot disregard from innate mechanisms, whose purpose is to increase the availability to care for the offspring. Innate predisposition could act at different levels in mothers, either through the modulation of specific hormones occurring before and after birth, which seem to amplify parental response or through cerebral mechanisms activated in response to a baby's signals, enhancing responsiveness and motivation in parental care (Barrett & Fleming, 2011; Montoya et al., 2012; Strathearn, Fonagy, Amico, & Montague, 2009).

Neurobiology of parenting

Studies on psychological, ethological and neurobiological fields evidenced in mammals (in particular rodents) and in humans common care behavior patterns, and a set of brain structures involved in supporting the parental response (Numan, Fleming, & Levy 2006; Numan and Insel, 2003; Swain, 2008; Swain, Lorberbaum et al., 2007).

Neurobiology of maternal care coming from animal models represented the theoretical frame within which to interpret the first fMRI studies in human parenting. With the aim of studying circuits that mediate parental responses during the first few interactions with the infant in the human brain, the fMRI research object is represented by maternal brain response during exposure to emotive signals from their infants, crying in particular. Parents could implement care behavior driven either by internal motivations or in response to a specific sensorial perception of signals emitted by children.

In the second case, the activation of parental response depends on the sensorial elaboration and appraisal of infant cue, which activates different cortico-limbic systems underlying reflexive subcortical mechanisms, cognitive processes (i.e. decision making, mentalization) and affective (emotion, alarm, preoccupation) systems. Parental behavior of care is the result of their mutual interaction (Swain, 2008, 2011). Behavior of care presupposes a complex integrated system that has to take into account different kinds of information processing, including the goal, and external and internal affordable actions to achieve it. In other word the complexity in parental response is the result of decision making processes, continuous over time (Barrett & Fleming, 2011).

Maternal care in rodents: critical subcortical structures that promote the genesis of maternal care and support over time the maternal motivation

The rodent is the mammal species on which many studies have been focused, and on which most of the knowledge on cerebral structures involved in maternal behaviors of care toward offspring has been based. In mice, components of postpartum behaviors that regulate interactions between new-mothers and pups, and through which is possible to qualify the competence and the effectiveness of parental care, are: seeking behavior, cleaning, nurturing and nutrition of pups, and the behavior in building and maintaining the nest. From animal models comes the first evidence within which to interpret the role of neural circuits involved in maternal responsiveness at the early postpartum period (1).

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(1) Methodological issue: One of the techniques used in animal studies involves the administration of temporary/permanent unilateral/bilateral lesions in neural structures, at different time windows during the early postpartum period. The underlying motivation assumes that, if the effect of a lesion, which is administered before the bond formation between mother and infant, turns out to be alternatively an obstacle that prevents or delays the emergence of the behaviors of care, then that specific structure is critical to the development of the maternal care. On the other hand, if the effect of a lesion administered after the consolidation of the parental bond, turns out to inhibit existing behaviors of care, such concerned structure should play a critical role for the motivation on long-term maintenance of care behaviors. Another kind of effect could affect the efficiency of specific behaviors of care, for example behaviors of searching for the offspring could be carried out in more time and/or not lead to the retrieval of the all offspring. In this case the lesion undermines the degree of responsiveness of the mother to the offspring.

Findings evidenced a differential role of subcortical structures on parental care on the dynamics of first approaches of new-mothers with their pups, and on the parental motivation to put in place care behaviors over time (Numan, Fleming, et al., 2006). The aim was to evidence the cerebral systems that caused the special bond and responsiveness to own pup, that are the foundation of pup-directed parental care and the motivation to maintain attuned response to infant signals over time.

From animal models (particularly rodents) a brain structure has been identified, the medial preoptic area (MPOA), which appears to play a critical role in both the genesis (Terkel, Bridges, & Sawyer, 1979) and the maintenance of the behavior of caregiving, previously consolidated. The MPOA with the ventral bed nucleus of the stria terminalis (VBST), a telencephalic structure adjacent to the MPOA, resides in rostral position respect to the hypothalamus. In particular, the dorsolateral afferents and efferents of MPOA seem to be critical, in fact any injury sustained on this level would destroy the care behavior already consolidated. This behavioral disorder tends to be temporary with unilateral lesions, whereas with bilateral ones it becomes permanent (Numan, McSparren & Numan, 1990). The efferent pathways project from MPOA / VBST complex to two groups of structures is involved in two different types of behavior:

(a) anterior hypothalamic nucleus (AHN) e periaqueductale gray (PAG): the AHN / PAG complex is involved in aversion and escape behaviors in front of novel stimuli. The AHN / PAG complex receives indirect inputs from olfactory bulbs (OB), via the medial nucleus of amygdala (MeA), and these structures together represent a neural circuit activated as a result of an olfactory stimuli. Mice facing at new stimuli tend to put in place escape and aversion behaviors, likewise virgin female mice tend to implement such behaviors even in the face of pups of their species. However, mothers during the postpartum period do not reject the new olfactory stimuli coming from their pups. Even if afferent pathways from olfactory bulbs elicit behaviors of aversion in proximity of unknown stimuli, presumably the GABAergic efferent pathways (gamma-aminobutyric acid) coming from MPOA / VBST inhibit the AHN / PAG complex allowing the first approaches between mother and new born. A possible explanation of this phenomenon may depend on the presence in MPOA of neurons with receptors for hormones involved in gestation (estradiol, prolactin), whose action would activate the MPOA, which in turn would inhibit the action of AHN / PAG. This data suggests that also the MPOA plays a critical role in the genesis of the behavior of care, not only in maintenance (Numan, McSparren, et al., 1990; Insel & Young, 2001).

(b) ventral segmental area (VTA) e retrorubar field (RRF area mesolimbica dopaminergica): VTA / RRF complex receives afferents from MPOA / VBST complex and interacts with the dopaminergic circuit (Numan & Nagle, 1983; Factor, Mayer & Rosenblatt, 1993; Hansen & Kohler 1984; Numan, Morrell & Pfaff, 1985; Numan & Nagle, 1983; Numan & Smith 1984), and could be involved in motivation processes in front of salient stimuli. A lesion at this level does not destroy care behavior, but undermines the motivation and consequently the efficiency, especially in active behaviors such as the search of offspring. It has been suggested that a specific motivational circuit for offspring care (MPOA / VBST), triggered by hormones associated with pregnancy, interacts with another specific motivational circuit for salient stimuli (VTA / RRF), and that their joint action could improve responsiveness during maternal care. To summarize, MPOA could have on the one hand an inhibitory role for aversive behaviors to novel stimuli, including unfamiliar puppies, and on the other hand a role for maternal responsiveness to new salient stimuli, just like the puppies.

Furthermore, the VTA / RRF complex sends dopaminergic efferents to mesolimbic regions, in particular toward nucleus accumbens (NA), which are part of the septal gray matter located at the base of the frontal lobe, and projects efferents toward the substantia nigra (SN) (Numan, Fleming, et al., 2006). Lesions at the level of SN alter behaviors of care. The SN is a structure that plays a role in the extrapyramidal motor functions, and may have a role in promoting the beginning of actions towards external stimuli. After lesions in SN and/or in lateral afferents from MPOA to SN, behaviors of care are temporarily destroyed, above all the component of searching for offspring. In fact, within a period of about 9-10 days maternal behavior reappears, but the search of the offspring appears to be less efficient than at the premorbid condition (Numan & Nagle, 1983). This data could suggest that within the range of behaviors of care, the most affected components by SN are those that require voluntary and active actions, such as the active search of the offspring. The mesolimbic dopamine circuit is a non-specific motivational system that modulates the degree of responsiveness of behaviors toward salient stimuli. Given by its involvement in the dopaminergic circuit, the NA is another important structure in maternal behavior, that modulates the degree of responsiveness to salient features of stimuli as the little baby.

Oxytocin is a hypothalamic hormone, which is involved during the delivery and lactation, and also acts as a neurotransmitter. Some nuclei of the hypothalamus are one of the main sources of the oxytocin regulation, which is poured into the blood via the pituitary gland (Kendrick, 2000). At the level of MPOA, VTA and olfactory bulbs many neurons with oxytocin receptors are located. In fact, lesions localized in cerebral regions mediated by oxytocin or administrations of oxytocin antagonists in the same regions, destroy behaviors of care (Numan, Fleming, et al., 2006; Insel & Young, 2001; Kendrick, 2000). Findings suggested that oxytocin could plays a role in promoting the acceptance of the new born, favoring the formation of the mother-pup bond. For example, oxytocin inhibiting olfactory bulbs prevents aversion responses towards the unknown olfactory stimulus, in this specific case the newborn (Numan, Fleming, et al., 2006).

Neurobiology of parental responsiveness to baby's cry in humans

This paragraph will be focused on the human cerebral systems activated/used in response to infant crying. Neural circuits that process adult and infant cries are the same, or does the baby's cry activate different circuits? An adult listener responds the same way to their own baby and unknown cries or do the child's cries receive a dedicated processing? One of the first studies (Lorberbaum, Newman, Dubno, Horwitz, Nahas, Teneback, Bloomer, Bohning, Vincent, Johnson, Emmanuel, Brawman-Mintzer, Book, Lydiard, Ballenger & George, 1999; Lorberbaum, Newman, Horwitz, Dubno, Lydiard, Hamner, Bohning & George, 2002) showed, in breastfeeding mothers during a task of passive listening to unfamiliar baby crying, the involvement of subcortical structures that had been highlighted in animal models in regard to the genesis, the efficiency and the motivation of maternal care behavior (Numan, McSparren et al., 1990; Numan & Nagle, 1983; Numan, Fleming, et al., 2006). Results showed an increased activity in response to the baby's cry and the control sound in anterior and posterior cingulate cortex (ACC, PCC), medial thalamic nuclei, subcortical structures (midbrain, hypothalamus, septal region, dorsal and ventral striatum), medial prefrontal cortex (mPFC), right orbitofrontal (OFC)/insula/temporal polar cortex region, and right lateral temporal cortex (LTC)

(Lorberbaum, Newman, et al., 2002). Furthermore, findings highlighted the involvement of the thalamo-cingulate network, an important cerebral structure which underlies complex maternal behaviors when approaching the offspring, and sensitive response versus infant signals, such as crying (McLean, 1990). From animal studies lesion occurring in ACC have been evidenced to disrupt retrieval behavior and responsiveness to emotive signals by offspring (Slotnick, 1967; Stamm, 1955). Accordingly with these suggestions, many findings in neuroimaging studies of human parenting highlighted the involvement of anterior medial brain structures in association to the burst of the infant crying (Barrett & Fleming, 2011; Swain, 2011). A recent longitudinal study (Kim, Feldman, Mayes, Eicher, Thompson, Leckman & Swain, 2011) investigated brain activity in breastfeeding mothers and formula-feeding mothers in response to their own infant crying, during the first post-partum month. Results showed higher activity in subcortical regions (right lateral globus pallidus/putamen, right putamen, amygdala), left inferior frontal gyrus (IFG), and right superior prefrontal gyrus and precuneus in breastfeeding mothers. However, in all mothers, cerebral activations during the first month postpartum were found positive correlated with maternal sensitivity at 3–4 months postpartum. Maternal sensitivity was assessed through observations of mother–infant dyadic interactions. Same authors, investigating mothers' brain plasticity responsible for parental behaviors during the early postpartum period (from 2-4 weeks to 3–4 months postpartum), found a grey matter (GM) volume increase in prefrontal cortex, hypothalamus, amygdala, and substantia nigra, which have an important role in maternal motivation and attuned behaviors (Kim, Leckman, Mayes, Feldman, Wang, & Swain, 2010). These regions in association with the thalamo-cingulate circuits were found involved in human maternal BOLD response associated to own infant cry and picture (Barrett & Fleming, 2011; Swain, Lorberbaum, et al., 2007; Swain, 2011).

Furthermore, the increase GM volumes in the striatum was found to be associated with mothers' positive thoughts and feelings about their own babies (a semi structured interview assessed positive thoughts and feelings about own baby and parental role) (Kim, Leckman, et al., 2010). In addition, a recent study (Swain, Tasgin, Mayes, Feldman, Constable & Leckman, 2008) showed that mothers who have had a natural childbirth (vaginal delivery) than mothers with cesarean section delivery, during the listening to own baby cry at the first postpartum month, showed greater brain activation in subcortical areas, such as the hypothalamus and regions of pons, involved in hormone neuroregulation, such as oxytocin. As mentioned in the previous paragraph (pag.11), oxytocin is a hormone, whose production is stimulated during childbirth (by uterine contractions) and lactation. Natural childbirth involves a series of biological interactions that could facilitate childcare, through greater involvement of brain structures underlying motivation, reward and sensory processes. In other words, authors suggested that a natural hormonal balance, during postpartum period, may be part of those internal factors that would facilitate the evolutionary task of parental care.

These studies, that have been focused in the postpartum period more or less close to the childbirth, allow to figure out the brain systems in parents that comes into play in response to infant signals during the earliest interactions between mother and child. In an attempt to investigate how the brain response to infant vocalizations could be modulated by parental status and gender, Seifritz and colleagues (Seifritz, Esposito, et al., 2003) recruited a sample of adults balanced by gender and parental status (parents with children around 3 years). Authors found two interesting pieces of data. First, results showed gender differences in activation of right anterior cingulate cortex and the right mesial prefrontal cortex in response to vocalizations, considering together crying and laughing. In specific, women showed a decrease of activity in this region than men. However, this data was not investigated in further studies. This gender difference will be resumed in the experimental part of this thesis. Two experiments were conducted in order to shed light on possible gender differences in brain structures involved during the listening to crying (2nd and 4th chapters). Second, differences were also found between parents and non-parents at amygdala activation level. In particular, no parents, regardless of gender, showed lesser activation for cries, and higher for laughs. Note that this dissociation was not found in parents, who showed a similar signal intensity in association to crying and laughter.

Overall, findings of the neurobiology underlying the responsiveness to the baby's cry showed variability in highlighted brain regions in response to infant crying. This is in part an effect due to different research protocols such as: duration (from 6 to 30 seconds), meaning/reason of crying (for hunger or discomfort, during diaper changes), characteristics of the adult population (parental status, primiparous or multiparous parents, age, distance from childbirth). Nevertheless, there are some brain regions that tend to emerge systematically in relation to a baby's cry. A framework that takes into account findings from both animal and human studies proposed that infant crying could trigger: (1) brain structures underlying the regulation of arousal motivation and decision making, as amygdala and structures mediated by the neurotransmitter dopamine; (2) structures underlying the regulation of stress, mediated by corticoid hormones, as the hypothalamus; (3) these recruited systems activate in parents a brain response that promotes parental care, modulating the involvement of brain structures mediated by the hormone oxytocin; (4) when the baby's cry subsides and the child becomes calm, adults perceive a feeling of satisfaction, mediated by brain structures related to opiacee endogenous substances, such as the anterior cingulate, the medial frontal and the orbitofrontal cortex. This represents a positive reinforce for put in place behaviors of care, and promotes the interaction with the child (Swain, 2008, 2011; Swain, Kim et al., 2011).

Chapter 2

Gender Differences in Directional Brain Responses to Infant.

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Abstract

Infant cries are a critical survival mechanism that draw the attention of adult caregivers, who can then satisfy the basic needs of otherwise helpless infants. Here, we used functional neuroimaging to investigate the effects of infant hunger cries on brain activity of adults who were in a cognitively non-demanding mental state of awake rest. We found that the brains of males and females, independent of parental status (parent or non parent), reacted differently to infant cries. Specifically, dorsal medial prefrontal and posterior cingulate areas, known to be involved in mind-wandering (the stream of thought typical of awake rest), remained active in men during exposure to infant cries, whereas in women activity in these regions decreased. These results reveal gender-dependent modulation of brain responses to infant requests to be fed, and specifically they indicate that women interrupt mind-wandering when exposed to the sounds of infant hunger cries, whereas men carry on without interruption.

Keywords

Parenting, infant cry, mind-wandering, brain, medial prefrontal cortex, posterior cingulate cortex, default-mode network.

Introduction

Lacking agency, new-born babies and young infants communicate their needs and physiological states mainly through vocalizing and facial expression. Infant cries communicate hunger, distress, or the desire for physical closeness (Zeifman, 2001), and they effectively induce a broad range of caregiver responses, such as proximity (Bowlby, 1969) or endocrine reactions (Swain, Kim, Ho, 2011).

In the present study, we analysed gender differences in brain activations in response to infant hunger cries. Women and men, mothers and fathers have different relationships with their children. By many accounts, several cross-cultural in nature, human mothers provide more direct care to children than do fathers (Whiting & Edwards, 1988; Clutton-Brock, 1989). Maternal responses to infant cries are critical for infant survival and the development of wholesome mother–infant emotional bonding (Feldman, 2007). Women rate infant cries as more likely to evoke sympathy and caregiving than men, and men rate cries as more aversive, as eliciting more irritation and anger, and evaluate infants who cry as more spoiled (Boukydis & Burgess, 1982; Zeifman, 2003).

Several neuroimaging studies have investigated adult brain activity to infant cries, but so far have produced conflicting findings (Swain, 2008). Few neurobiological studies have included males. In one exception, Seifritz et al. (Seifritz, Esposito, Neuhoff, Luthi, Mustovic, Dammann et al., 2003) assessed female and male (parents' and nonparents') responses to crying and laughter of unfamiliar infants; females showed greater prefrontal activation than males to infant vocalizations regardless of parental status.

The main goal of our study was to investigate neural responses associated with listening to infant cries during rest and mind-wandering. We asked participants to lie in the functional Magnetic Resonance Imaging (fMRI) scanner, and to think of nothing in particular, and so let their minds wander freely. They were told that they would hear various sounds intermixed with phases of rest, and that they were required to do nothing with these sounds. In the key condition, participants heard cries of hungry babies.

We chose to study the brain's spontaneous reactions to infant cry, because immersion in "internal" thoughts, without being focused on external stimuli, is acknowledged to be the most common mode of thinking, occupying almost half of our daily awake mental activity (Killingsworth & Gilbert, 2010) This situation has the additional advantage that it emulates ecological validity: when a baby begins to communicate a physiological or psychological need through crying, this signal likely reaches a caregiver who is not already attending to the baby, but who is instead mind-wandering or may be mentally focused elsewhere. The developing neuroimaging literature on mind-wandering has revealed that this mental state usually involves coherent and spontaneous low-frequency fluctuations in a specific brain network that includes medial prefrontal, posterior cingulate, hippocampus, superior temporal, and inferior parietal regions, collectively called the default-mode network (Buckner, Andrews-Hanna & Schacter, 2008). In particular, medial regions of the default-mode network (the medial prefrontal and posterior cingulate cortex) are involved in self-reflection and self-centred thinking (Northoff & Bermpohl, 2004). By contrast, when a person focuses on external stimuli, the default-mode network is deactivated (Weissman, Roberts, Visscher & Woldorff, 2006). Thus, the deactivation of the default-mode network is a reliable marker of the extent and efficiency of the observer’s engagement with the external world (De Pisapia, Turatto, Lin, Jovicich & Caramazza, 2012); for example, it is interpreted to indicate awareness in patients with disorders of consciousness (minimally conscious or vegetative state) during passive sentence listening (Crone, Ladurner, Holler, Golaszewski, Trinka & Kronbichler, 2011). The default-mode network encompasses brain regions that show task-induced deactivation, and while its activity is thought to represent on-going and organized cognitive processing that occurs when the brain is not actively involved in another task, its deactivation reflects an interruption of on-going mind-wandering (McKiernan, D'Angelo, Kaufman & Binder, 2006).

Materials and Methods

Participants

Eighteen healthy adults (9 females: *M* age = 31.50 years, *SD* = 4.27; and 9 males: *M* age = 35.38 years, *SD* = 4.63) were recruited through the University of Trento webpage and local advertisements. Nine were parents of children older than 4 years (4F/5M), and nine were non-parents (5F/4M). All participants were right-handed, and none reported neurological or psychiatric disorders. Participants were ethnically homogeneous of European heritage. All gave written informed consent for participation. The procedures were approved by the ethical committee for experiments involving humans at the University of Trento.

Acoustic Stimuli

In our main condition, we analysed brain responses to infant hunger cries vis-à-vis the adult at rest. We used 14 sec for the rest period between acoustic stimuli. We also compared responses during hunger cries to two types of auditory control stimuli: white noise and atypical cries. All acoustic files were edited using the computer software Praat (www.praat.com) to normalize volume, equate for duration (10 sec), and remove all background noise. A total of 10 acoustic excerpts of natural infant hunger cries from 10 1-year-old infants (5 girls/5boys) were selected from a pool of home videos of typically developing infants who did not present any significant medical or developmental concerns (confirmed by their normal scores on the Child Behavior Checklist; Achenbach & Rescorla, 2001). Atypical cries were extracted from home videos of 10 (5 girls/5boys) approximately 1-year-old infants who later, as children of ~3 years, were diagnosed with Autism Spectrum Disorder (clinical diagnosis was made by a child psychiatrist according to DSM-IV-R criteria and confirmed by ADI-R, ADOS-G). Atypical cries differ from hunger cries in morphological characteristics, especially their fundamental frequency (atypical cries > hunger cries). The fundamental frequency (f0) is generated by vibration of the vocal folds and is heard as the pitch of the cry. f0 influences adult responses and caregiver perceptions: for example, higher-frequency cries are regularly perceived as more aversive and distressed than low-frequency cries (Venuti, Caria, Esposito, De Pisapia, Bornstein & de Falco, 2012). To ensure that hunger cries and atypical cries were representative of the typical expected range of cry sounds for typical and atypical children, respectively, we analysed their f0. A long-term average spectrum (LTAS) was employed to provide spectral information for each cry. For all cry stimuli the First Spectral Peak (FSP) of the LTAS was obtained. FSP is the frequency value (in Hz) of the first amplitude peak across the LTAS. It is an estimate of the average f0 of the cry episodes. The FSPs of hunger cries were M = 526.87 (SD = 60.33) and of atypical cries were M = 637.87 (SD = 66.56), $F(1,16)=18.80$, $p<.001$.

fMRI Protocol

During functional scanning, participants were asked to listen passively to the acoustic stimuli presented binaurally at ~75 dB SPL using Serene Sound (Resonance Technologies, Northridge, CA) headphones, with stereo quality sound (40 Hz to 40 KHz frequency response) and passive scanner noise attenuation (30 dB). Participants underwent a single fMRI run in which stimuli were presented in a blocked design. Acoustic stimuli of each category (hunger cries, atypical cries, white noise) lasted 10 sec, with an inter-stimulus interval of 14 sec during which no stimuli was presented (rest). These stimulus categories were presented in a fixed order a total of 10 times. The 10 cry stimuli in each category were different, and they were pseudo-randomized between participants. Each cry was presented once to minimize habituation effects.

fMRI Data Acquisition

Participants underwent MRI scanning at 4 Tesla in a MedSpec Biospin MR scanner (Bruker Ettlingen, Germany) using an 8-channel birdcage head coil. Mild external head restraint was used to minimize head movement. Before collecting functional images, a high-resolution T1 weighted image of the whole brain (MPRAGE: 176 slices, GRAPPA acquisition with an acceleration factor of 2, FOV=256×256 mm^2, voxel size = 1×1×1 mm, TI = 1020 ms TE = 4.18 ms, TR = 2700 ms) was acquired for the purpose of spatial coregistration. Whole-brain functional data were acquired using echoplanar imaging, sensitive to Blood Oxygenation Level Dependent (BOLD) contrast (34 slices, tilted 18° from intracommisural plane, FOV=192×192 mm^2, voxel size = 3×3×3 mm^3, slice gap = 15%, flip angle (FA), 73°, TE = 33 ms, TR = 2 s per volume). We performed an additional scan to measure the point-spread function (PSF) of the acquired sequence, which served for distortion correction as is expected with high-field imaging. The experimental session consisted of 489 whole brain images per participant, including four dummy scans at the start of each time series to allow for T1 equilibration. The experiment lasted 16 min and 10 sec.

fMRI Data Analysis

Imaging data analyses were performed with BrainVoyager QX 2.1 (BrainInnovation). For preprocessing, we corrected for distortions in geometry and intensity in the EPI images, and we applied distortion correction on the basis of the PSF data acquired before the EPI scans. Then, we performed 3D motion correction with trilinear interpolation and slice timing correction with ascending interleaved order, using the first slice as reference. Functional data were temporally high-pass filtered at 3 cycles/run length. A Gaussian kernel of 8 mm was applied to spatially smooth the images. Next, we aligned the first volume of each functional run to the high-resolution anatomy. Both functional and anatomical data were transformed into Talairach space (Talairach & Tournoux, 1988) using trilinear interpolation. Predictor time courses were convolved with a canonical hemodynamic impulse response function starting at the beginning of each trial and included 3D-motion correction parameters.

Using general linear models, we explored the sensitivity of brain regions to cries of hungry healthy infants. We identified brain regions that were more or less active during white noise compared to rest for all participants. This contrast allowed us to localize brain regions that – independent of gender or parent status – were responsive to sudden neutral sounds while individuals were resting and free to let their minds wander. Subsequently, we conducted orthogonal region of interest (ROI) analyses within the individual regions identified in the previous contrast. For all reported contrasts, we used random effects and False Discovery Rate (FDR) to correct for multiple comparisons.

Results

Consistent with extant literature (Greicius & Menon, 2004), the first analysis showed that, during white noise auditory stimulation, left and right superior temporal lobe regions were more active (in particular, centred on the Heschl's gyri, otherwise known as transverse temporal gyri; Brodmann area 41), whereas the dorsal medial prefrontal and posterior cingulate cortex (BA 23) regions – two key medial components of the default-mode network - were less active (see Table 1). A follow-up comparison of group differences (male versus female; parent versus non parent) in activity during white noise compared to rest revealed no differences (minimum $p = 0.12$), indicating that neither gender nor parenthood status affects these regions differently when listening to white noise compared to rest (see Fig.1, panel B for the male versus female comparison).

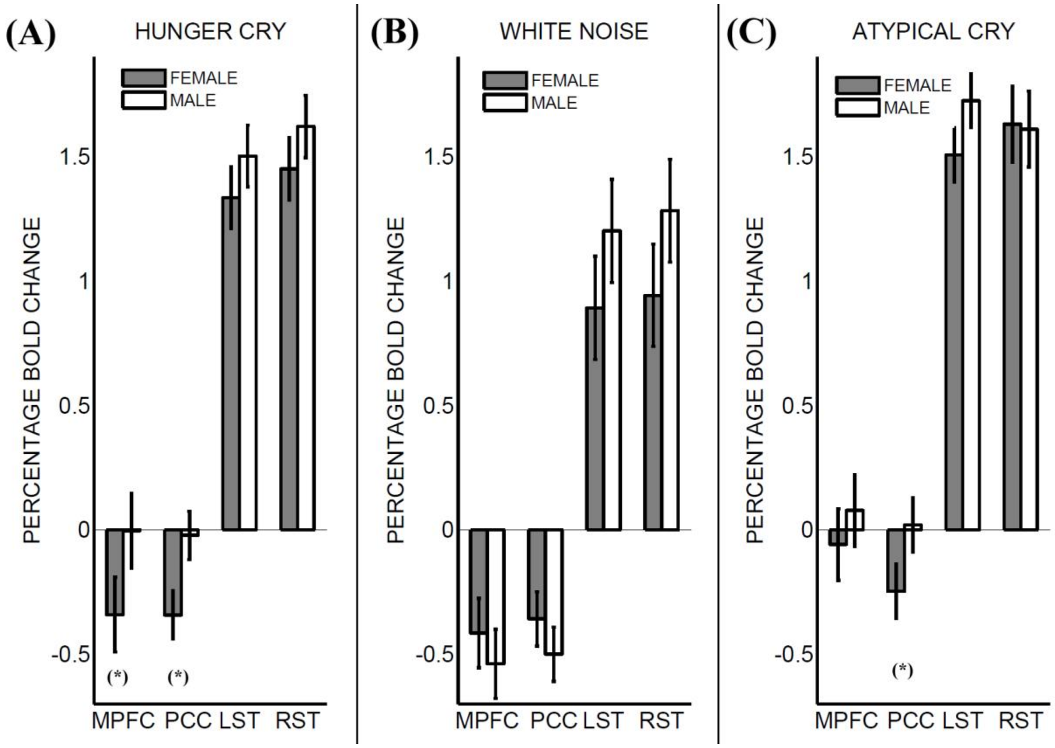

Figure 1. Percentage BOLD (Blood Oxygenation Level Dependent) signal change versus rest in males and females in three conditions: (panel A) Hunger Cry, (panel B) White Noise, and (panel C) Atypical Cry. Asterisks denote significant differences between males and females' percentage bold change (p<0.05). MPFC stands for dorsal medial prefrontal cortex, PCC for posterior cingulate cortex, LST for left superior temporal gyrus (Heschl's gyrus), and RST for right superior temporal gyrus (Heschl's gyrus). For precise coordinates of regions, see Table 1. Error bars are standard errors. Deactivation in dorsal medial prefrontal cortex and posterior cingulate cortex during hunger cry – distinctive of the mind-wandering interruption – took place only for the female group, but not for the male group. During atypical cry, this gender difference was significant only in posterior cingulate cortex, but not in dorsal medial prefrontal cortex.

Our main analysis looked for group differences during passive listening to hunger cries versus rest (male versus female, and parent versus non parent) within each of the localized regions identified as more sensitive to sounds. The parenthood group contrast showed no difference (minimum *p*=0.16). However, the gender group contrast revealed significant differences in the two medial regions, namely the dorsal medial prefrontal

Auditory Brain Regions (White Noise<>Rest)	**BA**	**Peak X**	**Peak Y**	**Peak Z**	**Number of Voxels at q(FDR)<0.01**
Decreased Activation (White Noise<Rest)					
Dorsal Medial Prefrontal Cortex	9/10	3	47	28	3926
Posterior Cingulate Cortex	23	0	-46	25	1827
Increased Activation (White Noise>Rest)					
Left Heschl's (Transverse Temporal) Gyrus	41	-45	-19	7	6368
Right Heschl's (Transverse Temporal) Gyrus	41	48	-13	4	7379

Table 1. Passive-listening brain regions. Brain regions resulting from the contrast white noise against rest in the whole group of participants. These regions serve as a mask for auditory sensitive regions (both increase and decrease of activation) during passive exposure to sudden sounds.

cortex (*df*=16; *M* female group BOLD= -0.341; *M* male group BOLD= -0.004; standard error= 0.15; *t*=2.22; *p*=0.041) and the posterior cingulate cortex (*df*=16; *M* female group BOLD= -0.342; *M* male group BOLD= -0.022; standard error= 0.097; *t*=3.76; *p*=0.001). No gender group difference emerged in the left superior (*p*=0.10) or right superior temporal regions (*p*=0.57). Thus, the gender difference consisted in males not deactivating in dorsal medial prefrontal cortex and posterior cingulate cortex during hunger cries relative to rest (Fig. 1, panel A). Gender differences again emerged as significant when we directly compared hunger cries to white noise, in both dorsal medial prefrontal cortex (*df*=16; *M* female group BOLD =-0.268; *M* male group BOLD = 0.531; standard error=0.354; *t*=2.26; *p*=0.03) and posterior cingulate cortex (*df*=16; *M* female group BOLD = -0.327; *M* male group BOLD = 0.544; standard error=0.193; *t*=4.50; *p*=0.0003), but not significant in either the left (*p*=0.75) or right (*p*=0.69) superior temporal regions.

When looking at gender group differences within the same regions for atypical cries (another emotionally charged stimulus produced by infants, but with a difference in frequency; see methods) versus rest (Fig. 1, panel C), we observed a significant difference only in posterior cingulate cortex (*df*=16; *M* female group BOLD =-0.247; *M* male group BOLD = 0.019; standard error=0.109; *t*=2.44; *p*=0.02). There was no difference in the dorsal medial prefrontal cortex (*p*=0.35), in right superior temporal lobe (*p*=0.89), or left superior temporal lobe (*p*=0.09). Thus, the gender difference in the dorsal medial prefrontal cortex (i.e., only the female group deactivated) was specific of hunger cries; it was not found to closely matched atypical cries.

Discussion

In this experiment, adult participants passively listened to hunger cries of infants, cries of atypically developing infants, and white noise. Participants were simply resting in the scanner and not required to perform any task or even to pay attention to the auditory stimuli. During exposure to hunger cries compared to rest and white noise, brain activity of women and men differed considerably in two key medial nodes of the default-mode network, namely the dorsal medial prefrontal cortex and the posterior cingulate cortex (BA 23). Specifically, activity in these regions decreased in women, but not in men. During exposure to atypical cries (sounds closely matching hunger cries, but with higher fundamental frequency), the gender difference emerged only in posterior cingulate cortex, but not in dorsal medial prefrontal cortex.

Deactivation in default-mode network is a common response to sounds that recruit attention during passive sensory tasks (Greicius & Menon, 2004). Researchers studying brain function generally assume that presentation of a stimulus or task will increase neural activity in the brain relative to a resting state. However, many tasks result in decreases in blood flow or blood-oxygenation indexes of neural activity relative to a "resting" baseline, a phenomenon referred to as task-induced deactivation. This change may occur when resources shift from on-going, internally generated processing typical of "resting" states to processing required by an exogenous task. Research demonstrates that task-induced deactivation occurs consistently in default-mode network regions, and researchers speculate that "rest" is actually a state of organized cognitive activity involving many processes, including monitoring the external environment, monitoring body image and state, and processing emotions (De Pisapia, Turatto, et al., 2012; McKiernan, D'Angelo, et al., 2006; , Gusnard & Raichle, 2001; Mazoyer, Zago, Mellet, Bricogne, Etard, Houde, et al., 2001). Included among these possible resting activities is on-going internal "thought" processes that humans experience during resting consciousness, sometimes referred to as "stream of consciousness". Because these "thought" processes are generally self-initiated and self-referential, and not related to specific exogenous task demands, they have been reported as "task-unrelated thoughts" (Giambra, 1989). As task-induced deactivation magnitude increases across task conditions, the frequency of task-unrelated thoughts declines (McKiernan, D'Angelo, et al., 2006). Internally generated cognitive activities (such as task-unrelated thoughts) are suspended due to reduced availability of resources when attention shifts from on-going, internal processes to performance of an exogenous task. As an auditory target detection task increases in difficulty (i.e., increased processing demands), multiple brain regions show correlated decreases in the BOLD signal (i.e., more negative task-induced deactivations values) relative to the resting state (McKiernan, D'Angelo, et al., 2006).

In this experiment we observed a medial default-mode network deactivation in both gender groups during passive exposure to white noise; by contrast, dorsal medial prefrontal and posterior cingulate cortical activity did not deactivate in men during exposure to hunger cries, but instead remained at the same level as during rest. These medial cortical regions are key nodes of the default-mode network associated with self-reflection activities (Northoff & Bermpohl, 2004), and thus these results suggest that women interrupt their mind-wandering when they are exposed to infant hunger cries, whereas men carry on without interruption.

We found no difference in response to hunger cries depending on parental status. The size of sample did not allow us to make further gender comparisons within each parental group (parents and parents), Nonetheless, our results are indicative of an “alloparental care” predisposition among females, a result common in several mammalian species where adult females act as cooperative breeders and share responsibility for infant care (Briga, Pen & Wright, 2012).

Conclusion

We found a gender difference in brain responses to hunger cries in medial default-mode network regions: specifically, women decrease activity in these regions when they suddenly and passively hear infant hunger cries, but men do not. In functional terms, this finding suggests that, whereas the female brain during hunger cries interrupts on-going mind-wandering, the male brain continues in self-reflection typical of awake resting states.

Statement of Conflicts of Interest and source of funding

We declare no conflict of interest relatively to this study. This research was supported by the Intramural Research Program of the NIH, NICHD.

Chapter 3

Parenting and Neural Plasticity in Human Fathers' Brains

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Abstract

Previous studies have demonstrated brain regions that are important for parenting behaviors in human mothers. However, the neural basis of parenting in human fathers has still been largely unexplored. In the current longitudinal study, we investigated structural changes in in fathers' brain over time during the first four months postpartum. Biological fathers (n=16) with full-term, healthy infants were scanned at 2-4 weeks postpartum (Time 1) and at 12-16 weeks postpartum (Time 2). Longitudinal voxel-based morphometry (VBM) analysis revealed that fathers had significant increases in grey matter volume in left striatum, and right lateral PFC (BA 45,46,47). Grey matter volume increase in left striatum was negatively associated with fathers' depressed mood at Time 2. On the other hand, fathers showed significant decrease in grey matter volume in right orbitofrontal cortex

(OFC) from Time 1 to Time 2. Greater reduction in the OFC was associated with fathers' more intrusive parenting behaviors at Time 2. The findings suggest that parenting experience during the early postpartum period is associated with structural changes in neural regions for parental motivation and behaviors in human fathers. The findings may also identify brain regions of potential importance for early father-infant attachment.

Key words: paternal brain, father, parenting, postpartum, neuroimaging

Introduction

Over the past 20 to 30 years, fathers' involvement in caregiving has become increasingly significant as more mothers join the workforce (Parke, 2002). Infancy is also a period when fathers are often active in parental care (Yeung, Sandberg, Davis-Kean, & Hofferth, 2001) and the quality of paternal care play an important role for the infants' socioemotional and cognitive development (Bornstein, 2002; Feldman, Bamberger, & Kanat-Maymon, 2013; Ramchandani et al., 2011). In human mothers, a growing literature of neuroimaging studies has demonstrated the neural basis of parenting behaviors (Barrett & Fleming, 2011; Kim et al., 2010; Rutherford, Williams, Moy, Mayes, & Johns, 2011; Swain, 2010; Swain, Kim, & Ho, 2011; Swain, Lorberbaum, Kose, & Strathearn, 2007). However, to date, biobehavioral studies on developing parent-infant relationships have mostly targeted mothers and very little has been understood about fathers. Thus, the current longitudinal study examined changes in the neural anatomy over the course of the first four months postpartum in human fathers.

In mothers, non-human studies have identified several brain areas as important for the development of parental behaviors. For example, lesion studies have shown that the medial preoptic areas (MPOA), located in the rostral hypothalamus, and its connections with the amygdala and striatum regions play a critical role in maternal motivation (Flannelly, Kemble, Blanchard, & Blanchard, 1986; Fleming et al., 2002; Hansen, Harthon, Wallin, Lofberg, & Svensson, 1991a, 1991b; Leckman & Herman, 2002; Novakova, Sterc, Kuchar, & Mozes, 1993; Numan & Insel, 2003). The prefrontal cortex (PFC) is also involved in processing social information and regulating parental moods and behaviors (Afonso, Sison, Lovic, & Fleming, 2007). Recent functional magnetic resonance imaging (fMRI) brain studies in human mothers found greater activities in these brain regions in response to infant-related stimuli such as infant pictures, cry sounds and video clips (Barrett et al., 2011; Landi et al., 2011; Leibenluft, Gobbini, Harrison, & Haxby, 2004; Lenzi et al., 2009; Noll, Mayes, & Rutherford, 2012; Noriuchi, Kikuchi, & Senoo, 2008; Ranote et al., 2004; Schechter et al., 2012; Strathearn, Fonagy, Amico, & Montague, 2009; Strathearn, Li, Fonagy, & Montague, 2008). The activations in the midbrain and PFC regions were also positively associated with sensitive parenting behaviors observed during mother-infant interactions (Atzil, Hendler, & Feldman, 2011; Kim et al., 2011) whereas the activations were negatively associated with negative postpartum moods, such as depression, which disrupts the normal development of parent-infant bonding (Laurent & Ablow, 2011, 2013; Moses-Kolko et al., 2010).

There are only two existing functional imaging study in human fathers, both using video clip stimuli of own vs. unfamiliar infant. The first study found increased activity in similar brain regions including prefrontal regions, the orbitofrontal cortex (OFC) and striatal regions including the caudate at 2-4 months postpartum (Kuo, Carp, Light, & Grewen, 2012). The second study found responses in fathers overlapping with mothers in cortical and subcortical regions including the anterior cingulate cortex (ACC), inferior frontal gyrus, medial and lateral PFC, and insula at 4-6 months postpartum (Atzil, Hendler, Zagoory-Sharon, Winetraub, & Feldman, 2012).

Activations of these brain regions during the early postpartum period may also be accompanied by structural changes in the brain. For rat mothers, the amount of experience interacting with their pups correlates with the neuronal development of the hypothalamus, basolateral amygdala, parietal cortex and prefrontal cortex (Featherstone, Fleming, & Ivy, 2000; Kinsley et al., 1999; Lonstein, Simmons, Swann, & Stern, 1998; Xerri, Stern, & Merzenich, 1994).We reported grey matter volume increases in a number of brain regions of human monthes, including the striatum, thalamocingulate, and PFC from the first to the fourth postpartum months, (Kim et al., 2010). In fathers, to date, non-human studies suggest that similar brain regions seem to undergo structural changes in the brains. Male prairie voles exhibiting biparental care show increased *Fos* expression in the MPOA (Kirkpatrick, Carter, Newman, & Insel, 1994), which is critical for paternal behaviors (Rosenblatt & Ceus, 1998). Fatherhood was associated with higher density of the prefrontal cortex of marmoset males (Kozorovitskiy, Hughes, Lee, & Gould, 2006). Based on these parental brain structure studies of human mothers and non-human animal males, it is reasonable to expect that similar structural changes in the striatum and PFC regions occur in human fathers during the early postpartum period. However, it is still unknown whether human fathers may undergo brain anatomical structural changes.

Fathers, although in a lesser degree than mothers, experience mood changes including increased levels of anxiety and distress during the early postpartum period (Kim, Mayes, Leckman, Feldman, & Swain, 2013; Leckman et al., 1999). Highly negative moods such as paternal depression during the postpartum period can have long-term negative cognitive and emotional outcomes in children (Kim & Swain, 2007; Ramchandani & Psychogiou, 2009; Ramchandani, Stein, Evans, & O'Connor, 2005). Studies on parenting behaviors suggest normative gender differences in parental sensitivity (Volling, McElwain, Notaro, & Herrera, 2002). Maternal sensitivity is expressed by emotional warmth and support whereas paternal sensitivity is expressed by providing stimulating interactions (Feldman, 2003; Grossmann, Grossmann, Kindler, & Zimmermann, 2008; Volling et al., 2002). In a previous study with fathers, stimulatory contact (i.e. proprioceptive and stimulatory touch, and exploratory play), but not affectionate contact, was positively associated with increase in oxytocin, a hormone important for parental motivation (Feldman, Gordon, Schneiderman, Weisman, & Zagoory-Sharon, 2010). Therefore, among healthy fathers, paternal intrusiveness, i.e. parent's physical manipulation of infant's body and parent leading the interaction, may capture the typical paternal parenting style more than paternal sensitivity during the early postpartum period. The current study examined whether the neural plasticity may be associated with postpartum moods, and parental sensitivity and intrusiveness in fathers.

In search of an understanding of neuroplasticity related to fathering during the early postpartum period, this longitudinal MRI study examined structural brain changes in human fathers from 2-4 weeks to 3-4 months postpartum. We employed the longitudinal voxel-based morphometry (VBM) method to identify changes in grey matter volumes over the first postpartum months (Mechelli, Price, Friston, & Ashburner, 2005). We also measured paternal mood and infant-related behaviors observed during dyadic interactions. We hypothesized that the striatum and the PFC would show structural increases and that the structural increases important for parenting would be associated with lower levels of negative moods and increased sensitive and/or intrusive parenting behaviors during the early postpartum period.

Methods

Participants

Sixteen biological fathers of full-term and healthy infants were recruited in postpartum hospital wards at the Yale-New Haven hospital. All fathers (age M=36.31, SD=4.92) were right handed, Caucasian, college or above education (M=17.25 years, SD=3.34), and either married or cohabiting. Among the fathers, 7 out of 16 (44%) were first-time fathers. Exclusion criteria included any current psychiatric diagnosis and recent history of prescription medications within 2 weeks of the experiment. Informed consent was obtained from each participant according to the procedure approved by the Yale University School of Medicine Human Investigations Committee.

Procedure

Fathers visited the research center twice to acquire brain imaging data: once between 2 and 4 weeks postpartum (T1) and again 12-16 weeks postpartum (T2). The average interval between two scans was 80.75 (SD= 10.67) days. Depressed mood was assessed at both T1 and T2. At T2, father-infant interactions for paternal sensitivity and intrusiveness data were obtained during a home visit. For videotaped interactions, fathers were asked to interact with their infants for five minutes in as they normally would.

Measures

Beck Depression Inventory (BDI). The measure was used to assess level of depressed mood. All fathers had a score ranging 0-5 which indicates minimal levels of depression at 3-4 months postpartum (Time 2). The mean was 1.93 (SD=1.94).

Sensitivity and Intrusiveness. Father–infant interactions were coded using the Coding Interactive Behavior (CIB) Manual (Feldman, 1998). The CIB is a global rating system for adult–child interactions, with versions for newborns, infants, children, and adolescents with good psychometric properties (for review, see (Feldman, 2012)). It consists of 42 adult, child, and dyadic codes, each rated on a scale of 1 (a little) to 5 (a lot).

Interactions were videotaped at home and coded offline by trained coders. These scales were then aggregated into several composites. The Sensitivity construct used in this study includes the following (averaged) codes (α =0.91): acknowledgement of child communications, vocal clarity, positive affect, gaze, appropriate range of affect, affectionate touch, resourcefulness, consistency of style, adaptation to child signals, and supportive presence. The Intrusiveness (α = 0.84) construct refers to a parental style that overrides the infant's signals and imposes the parental agenda and includes the following codes: parent's physical manipulation of infant's body, interruption of infant's activities, breaking gaze while infant is looking, disregard of infant's signals, and parent leading the interaction. Two of the fathers did not provide the videotaped interactions, thus data of the 14 fathers have been used in the analysis. Overall, inter-rater reliability exceeded 90% on all codes (κ >0.82). The mean for sensitivity was 3.88 (SD=0.92) and intrusiveness was 1.98 (SD=0.87).

Image acquisition

High resolution T1-weighted structural magnetic resonance images (MRI) were obtained (3DMPRAGE; TR=2530 ms; TE=3.66 ms; matrix size 256x256; 176 slices; flip angle = 40°; voxel size was 1.0 mm × 1.0 mm × 1.0 mm) with a Siemens trio 3T scanner (Erlangen, Germany).

Voxel-based morphometry (VBM) longitudinal analysis.

The VBM is automated, thus is not subject to individual bias (Ashburner & Friston, 2005; Mechelli et al., 2005). VBM analyses were performed with VBM8 toolbox for Statistical Parametric Mapping 8 (SPM8) (Wellcome Department of Neurology, London, UK). Using the default preprocessing approach of the VBM8 toolbox for a longitudinal data analysis, the two time point data were first realigned (T2 to T1), then were bias-corrected for the signal inhomogeneity. The bias-corrected images were segmented in the different tissue classes using the segmentation algorithm in SPM8. From the initial data registration was calculated a mean image as baseline image for each subject. A diffeomorphic image registration algorithm (DARTEL) was used for registration to a template generated from the baseline image and applied to all data. Registered grey matter maps were transformed to the stereotactic space of the Montreal Neurological Institute (MNI). In order to preserve the volume of tissue in each structure, grey matter maps were modulated by multiplying the intensity of each voxel in the final images by the local value derived from the Jacobian determinants of the deformations (Ashburner & Friston, 2001). The modulated and warped images were then smoothed with an isotropic Gaussian kernel of 8 mm full-width at half-maximum. The resulting images had a normalized voxel size of 1.5 mm^3. All images were checked for scanner artifacts and anatomical anomalies that would affect the image analyses.

The processed images were analyzed with a repeated-measure ANOVA to test changes between T1 and T2 grey matter changes, controlling for ages of fathers, parenting experience (primiparous or multiparous status), and scan intervals. All reported results were $p < 0.05$, FDR-corrected.

Results

The longitudinal VBM analyses revealed that from T1 (2-4 weeks postpartum) to T2 (3-4 months postpartum), fathers showed an increase in grey matter volumes in striatum (as well as amygdala, hypothalamus and subgenual cortex), lateral PFC, and superior temporal gyrus, $p < 0.05$, FDR-corrected (Table 1 and Figure 1). An increase in certain regional volumes, including in the striatum, amygdala, and subgenual cortex, was negatively correlated with depressed mood at T2, $r(15) = -0.55$, $p <. 0.05$ (Figure 2).

Figure 2. Grey matter increase (red) and decrease (blue) from 2-4 weeks to 3-4 months postpartum in fathers.

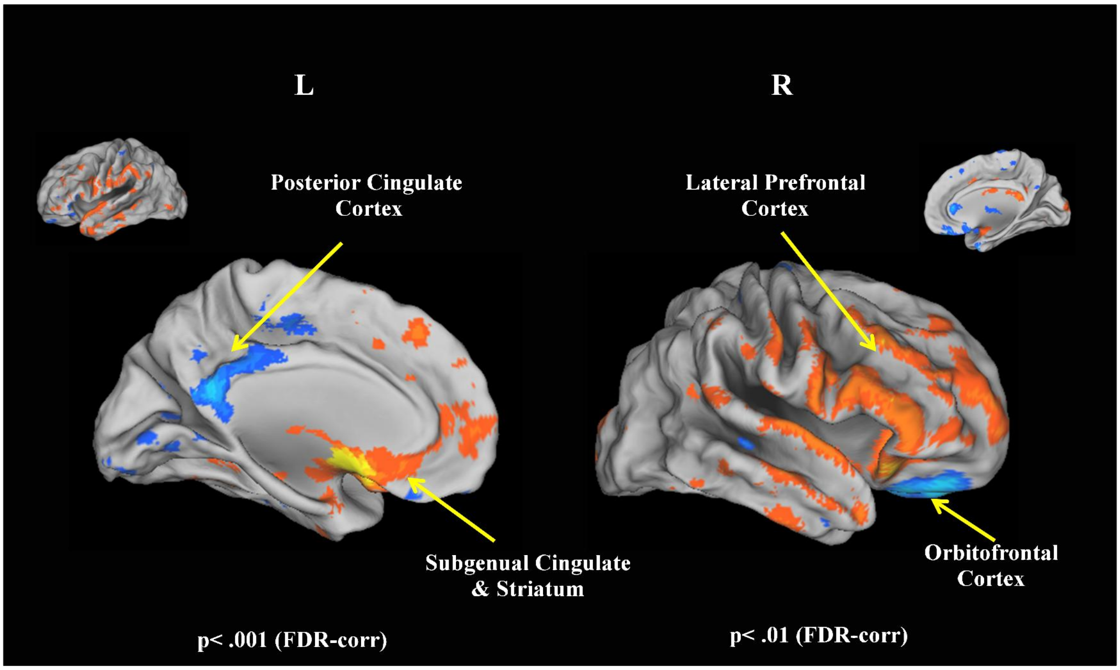

Table 1. Brain regions showing grey matter changes from 2-4 weeks to 3-4 months postpartum in fathers.

Regions			**MNI coordinates (peak within a cluster)**					
	BA	**Side**	**x**	**y**	**z**	**Cluster size**	**z-value**	**p-level (FDR-corr)**
Grey Matter Increase From 2-4 Weeks to 3-4 Months Postpartum								
Putamen, Caudate, Subgenual Cingulate, Pallidum, Globus pallidus, Amygdala, Hypothalamus	25,34,13	L	-15	19	-10	2591	6.53	< .001
Superior, Middle, and Inferior Frontal Gyrus, Superior and Middle Temporal Gyrus, Temporal Pole, Precentral Gyrus	46,45,47,21,9, 44,10,38,22	R	51	33	34	2758	3.70	< .001
Grey Matter Decrease From 2-4 Weeks to 3-4 Months Postpartum								
Orbitofrontal cortex, Inferior, Medial and Middle Frontal Gyrus,	11,47,25	R	9	39	-22	2065	5.28	< .001
Posterior and Middle Cingulate Gyrus, Precuneus	31,23,30,29	L	-3	-52	21	790	4.27	< .05
Inferior and Middle Frontal Gyrus, Insula	44,13,11,45,47	L	-42	25	12	733	4.05	< .05
Inferior Temporal Gyrus, Fusiform Gyrus	20,37	L	-52	-27	-22	646	3.87	< .05
Cerebellum		R	31	-63	-37	685	3.65	< .05

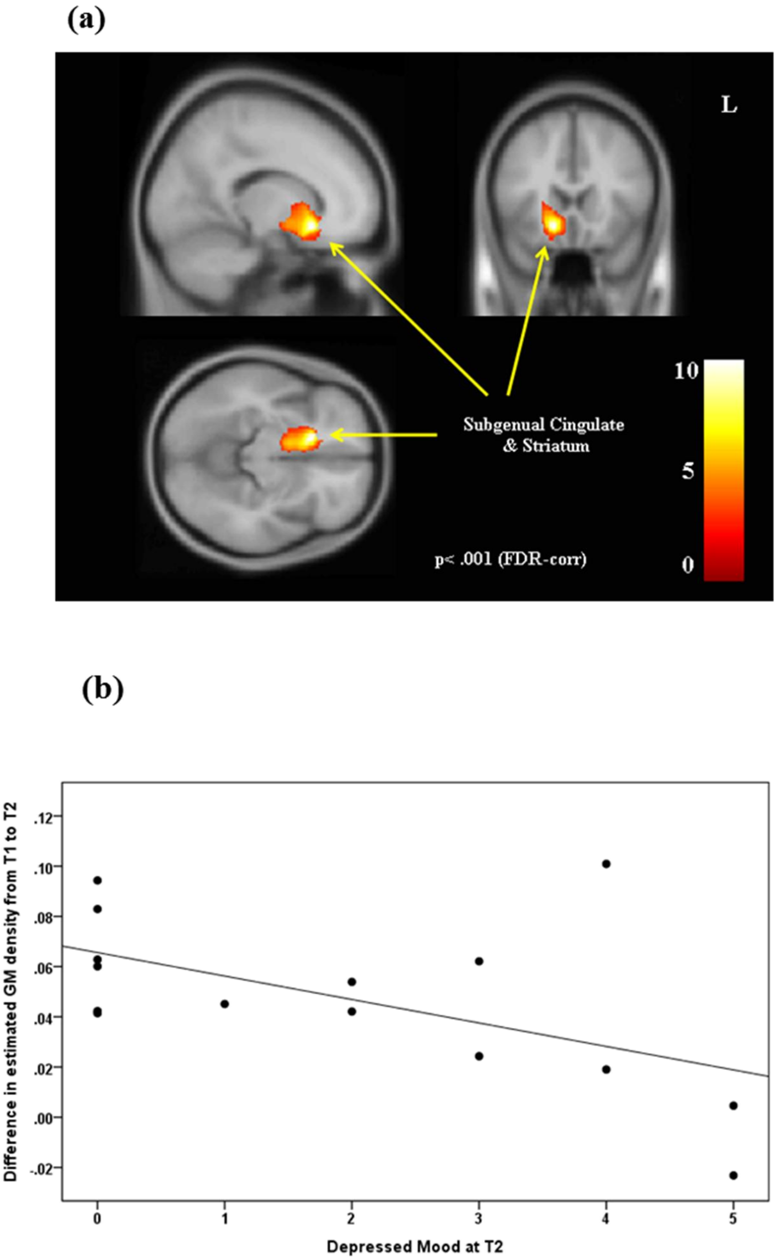

Figure 3. (a) Grey matter volume increase in left striatum, hypothalamus, amygdala and subgenual anterior cingulate cortex in fathers from 2-4 weeks (time 1) to 3-4 months postpartum (time 2); (b) Correlation between grey matter volume increase in this region and depressed mood at 3-4 months postpartum.

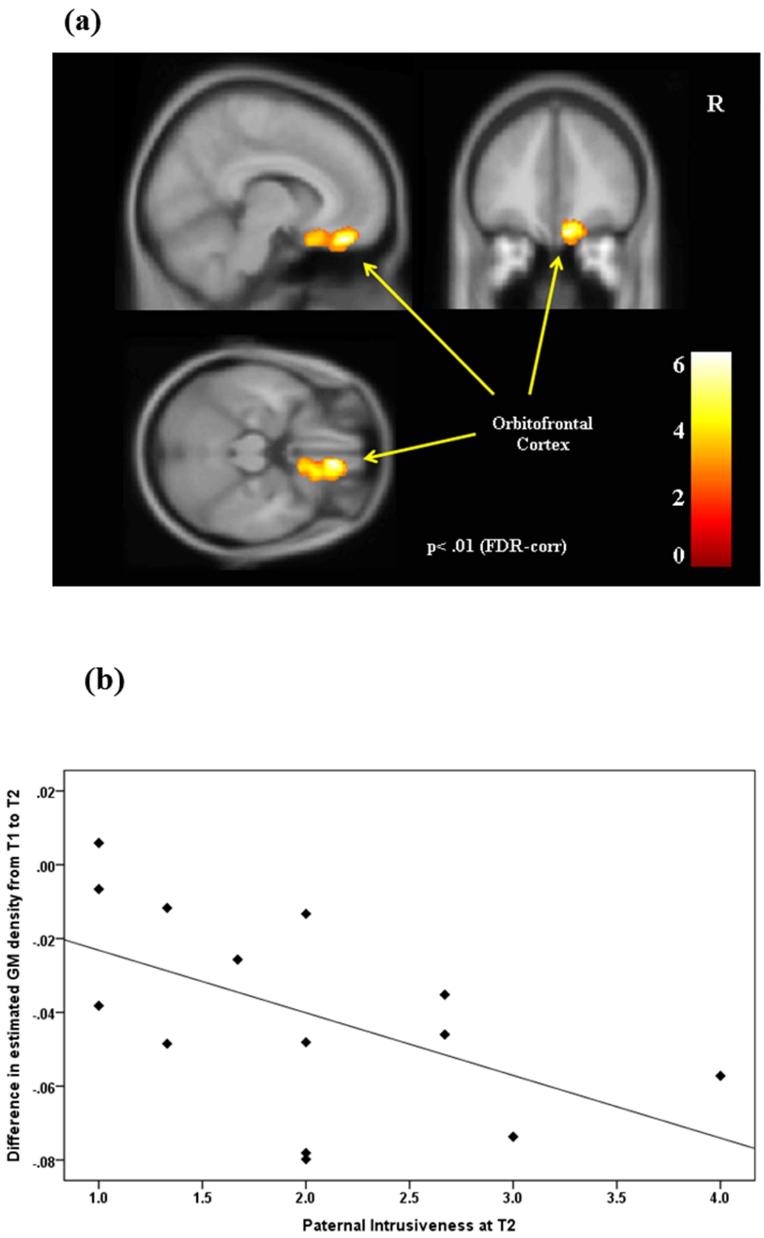

Figure 4. (a) grey matter volume decrease in right orbifrontal cortex (OFC) in fathers from 2-4 weeks (time 1) to 3-4 months postpartum (time 2); (b) Correlation between grey matter volume increase in this region and paternal intrusive parenting behaviors at 3-4 months postpartum

Several brain regions show decrease in grey matter volumes from T1 to T2 including the OFC, posterior cingulate cortex (PCC), insula, and fusiform gyrus, $p < 0.05$, FDR-corrected (Table 1 and Figure 1). The grey matter decrease in the OFC was correlated with higher levels of intrusive parenting behaviors during interactions with infants at T2, $r(14)= -0.55$, $p < 0.05$ (Figure 3). On the other hand, a decrease in the PCC and fusiform gyrus [$r(15)=0.54$, $p< 0.05$; $r(15)=0.60$, $p < 0.05$, respectively] was associated with lower levels of depressed mood at T2. No region was associated with paternal sensitivity.

Discussion

The current study is the first to examine anatomical changes in human fathers' brains from 2-4 weeks to 3-4 months postpartum. On one hand, we found grey matter volume increases in the striatum/subgenual ACC and lateral PFC. On the other hand, the OFC, PCC, insula, and fusiform gyrus show grey matter volume decreases over time. Lower levels of depressed moods at 3-4 months postpartum were associated with grey matter volume increase in the striatum/subgenual cortex and decreases in the PCC and inferior temporal lobe over the first few months postpartum. However, structural decreases in the OFC were associated with higher levels of paternal intrusiveness during father-infant interactions. The findings may shed light on the brain regions that regulate a human father's ability to develop appropriate parental behaviors and postpartum mood regulation.

Consistent with the key brain regions involved in the expression of maternal behaviors in humans and other animals (Barrett & Fleming, 2011; Numan & Woodside, 2010; Rilling, 2013; Rutherford et al., 2011; Swain, 2010), we report that striatum, amygdala and hypothalamus show increases in grey matter volumes from 2-4 weeks to 3-4 months postpartum in fathers (see Supplementary Table 1). This is in accord with our previous report that new mothers show volume increases in the hypothalamus and striatum over the same period (Kim et al., 2010). Non-human studies have underlined the importance of these regions for parenting with lesions in the hypothalamus including MPOA impairing parental motivation (Flannelly et al., 1986; Xerri et al., 1994). In non-human studies, striatum, which includes the globus pallidus and caudate, has been established as an important regulator of behavioral reactivity and salience of infant stimuli together with the amygdala (Numan & Insel, 2003; Numan & Woodside, 2010). Increased activations in the hypothalamus, amygdala and striatum have been shown in response to infant-related stimuli across neuroimaging studies with human mothers (Atzil et al., 2011; Atzil et al., 2012; Barrett et al., 2011; Bartels & Zeki, 2004; Kim et al., 2011; Lenzi et al., 2009). In fathers, watching video clips of own vs. unfamiliar baby also activated the caudate at 2-4 months postpartum (Kuo et al., 2012). Therefore, the volume increase in the striatum, amygdala and hypothalamus that we report in fathers may constitute a mechanism for the functional adaptations that fathers display some months into the postpartum period for parental motivation and detection of the salient infant cues.

We also explored relationships between paternal brain structural changes and mood given the importance of postpartum mood for optimal parenting in fathers (Goodman, 2004; Kim & Swain, 2007; Ramchandani et al., 2011) In fathers, volume increases in the striatum and subgenual ACC were correlated with lower depressed mood at 3-4 months postpartum. This is similar to maternal brain activation findings in the caudate in response to baby cries being inversely associated with depressed moods at 18 months postpartum (Laurent & Ablow, 2011). In addition, striatum dysfunction in reward processing has been associated with depression (Pizzagalli et al., 2009). Finally, a meta-analysis of structural brain imaging studies also indicate that decreases in the striatum and subgenual ACC volume are related to depression (Koolschijn, van Haren, Lensvelt-Mulders, Hulshoff Pol, & Kahn, 2009). Thus, grey matter increases, particularly in the striatum and subgenual ACC, may be associated not only with parental motivations but also with the enhanced fathers' ability to regulate his emotion potentially through increased interactions with the infant during the first three months postpartum.

Continuing a review of paternal brain regions with volume increases in the early, postpartum, we detected several findings consistent with those on mothers (Supplementary Table 1), including the lateral PFC and superior temporal regions (Kim et al., 2010). These data are also consistent with data from the biparental primate marmoset males, for which parenting experience was associated with higher density of pyramidal cells in the dendritic spines of the PFC (Kozorovitskiy et al., 2006). In human fathers, lateral PFC were also activated while viewing own vs. unfamiliar infants at 2-4 months postpartum (Kuo et al., 2012). Maternal brain literature consistently suggests that the lateral prefrontal cortex plays a role for the integration and regulation of both emotional and motivational information and for the complex decision processes involved in parental behaviors (Numan & Insel, 2003). Superior temporal regions may perform sensory and emotional information processing (Sander et al., 2005). Indeed, greater responses in lateral prefrontal and superior temporal regions to infant related stimuli were consistently detected across the neuroimaging studies of human mothers (reviewed in (Barrett & Fleming, 2011; Rilling, 2013; Swain, 2010; Swain et al., 2007). Furthermore, in a study comparing fathers' and mothers' neural responses to infant video clips at 4-6 months postpartum, fathers showed greater activation in lateral PFC and superior temporal regions than mothers whereas mothers showed greater activation in amygdala and caudate regions compared to fathers (Atzil et al., 2012). This may highlight the role of the lateral PFC and superior temporal regions in fathering. Our findings in the increased lateral PFC and superior temporal gyrus volumes in human fathers may support the conclusion that these regions serve an important function for the initiation of parenting behaviors in fathers during the early postpartum period.

In contrast, in fathers, several regions show decreases in grey matter volumes over time. This was different from the regions we found for mothers (Kim et al., 2010) in that no region showed decrease in structure over the same postpartum periods (Supplementary Table 1). It is unclear why grey matter volumes may decrease in these regions including OFC, PCC, and insula, where grey matter volumes increased among mothers. One reason for the differences is that fathers experienced less drastic psychological and hormonal changes compared to mothers during the early postpartum period. For instance, fathers show more moderate changes in their moods and develop an attachment to their infants more gradually compared to mothers (Anderson, 1996; Kim et al., 2013). Fathers also tend to spend less time with their infants and have more caregiving responsibilities than mothers. Therefore, the structural reduction in fathers may reflect decreased functions or slower changes in the neural regions due to a lesser degree of mood and psychological changes experienced by fathers.

The other reason for the different findings between mothers and fathers may be that the structural reduction is associated with a synaptic or neuronal pruning process of the neuroplasticity during remodeling of the neuronal connections in these regions (Stoneham, Sanders, Sanyal, & Dumas, 2010), which may further support caregiving behaviors. Activation in the OFC, PCC, and insula in response to infant stimuli has been observed in fathers (Atzil et al., 2012; Kuo et al., 2012). Moreover, a decrease in the OFC volume was associated with higher paternal intrusiveness, a potential indicator of paternal stimulatory interaction styles with infants. Therefore, in fathers, the OFC structural decrease may indicate development and/or specialization of the region for parenting behaviors. It should be noted that these two potential explanations were not directly tested in the current study and more research is needed to interpret the microstructural and functional nature of the grey matter volume reduction. Future research should also examine the relations between neural structure and activity, parenting and infant outcomes in both mothers and fathers – including samples with parents at risk - will be critical to better understand the differences in parental behaviors and neuroplasticity expressed in mothers and fathers.

There may be several factors that are related to changes in fathers' brains. Although endocrine regulation of human paternal behaviors is not well understood, there is evidence that a hormone, vasopressin, may be related to fathers' parenting motivation and changes in brain structure. Male prairie voles, a biparental species, have arginine vasopressin (AVP) receptors in brain regions including the olfactory bulb, hypothalamus, amygdala, and thalamus. Binding of AVP to V1a receptors is critical for parenting behaviors including grooming, crouching over young, contacting, and retrieving pups (Landgraf & Neumann, 2004). In biparental primates, parenting experience was associated with increased V1a receptors in father brain (Kozorovitskiy et al., 2006). The great increase in V1a receptors in the PFC, not in oxytocin or prolactin receptors, drove the enhanced density of dendritic spines on pyramidal neurons of the PFC in the marmoset fathers. Thus, vasopressin may contribute to structural changes in fathers during early postpartum period. The structural changes may also be linked to individual differences in parenting experience. We have controlled for previous parenting experience, first-time vs. experienced father, in our analysis; however, we do not have information on how actively fathers were involved in their child's care throughout the first months. There may have been a wide range of parental involvement during this period among fathers and future work is needed to examine the associations between parenting experience and neural plasticity in fathers. Last, although our findings suggest longitudinal changes in fathers' brain over the first few months, the causal relations between the structural changes and these factors are still unclear. The structural changes may have reciprocal relations with mood regulation, increased experience of interacting with infants, and hormonal changes.

The findings should be considered in light of the following limitations. First, the study has a relatively small sample size, and includes a homogenous sample of Caucasian and middle to high SES background. Due to this characteristic of our sample, the ranges of the depressed moods or parental behaviors were also restricted to a low and normal range. Therefore, the findings of the associations among neural changes and parental moods/behaviors have small effect sizes and need to be replicated by more research with a larger sample of diverse background. Second, because our study is limited to changes during the first few months postpartum, it is unclear whether the structural changes may last beyond the period. In marmoset fathers, the structural increase in the PFC came back to the baseline as the offspring got older and fathers were less involved in parenting (Kuo et al., 2012). Thus, it is possible the structural changes we observed may be temporary to the early postpartum period but other structural changes may occur as the human fathers are continue to be involved in parenting over many years of a child’s life.

In the current study, we found longitudinal changes in grey matter over the first 4 months postpartum in human fathers. This postpartum period marks a critical period for fathers to develop parental sensitivity to their infants. This early parental sensitivity becomes the basis of the father-infant attachment which has long-lasting impact on cognitive functions and social attachment (Feldman et al., 2013; Parke, 2002; Ramchandani et al., 2011; van Ijzendoorn & DeWolff, 1997). Our findings on the plasticity of the paternal brain demonstrate normative changes among human fathers since the sample of our study included healthy fathers of healthy infants who were in supportive environments. However, fathers with genetic and environmental risk factors such as early childhood traumatic experiences or postpartum mental health problems such as depression or posttraumatic stress disorder may show different patterns of structural changes in brain regions that are important for the expression of parenting behaviors. Such abnormal brain structures may be further associated with low parental sensitivity among these fathers. Further research is thus required to identify distinctive changes in the parental brain among at-risk fathers in order to devise more specific and early interventions and treatments.

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Chapter 4

Gender differences in BOLD signals to infant cries and smiles during mind wandering and self-referential tasks in non-parents.

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Introduction

Crying is one of the first signals that allows infants to communicate their needs, and it represents an important cue through which caregivers can modulate their own behaviors of care (for reviews see Newman, 2007; Venuti & Esposito, 2008; Soltis, 2004; Cecchini, Lai, & Langher, 2007). In spite of the morphological variability among species, infant crying is universally present in humans and in other mammals (Furlow, 1996, Newman, 2007; Zeifman, 2001), and it has the intrinsic potential of triggering the adult's response of care and promoting physical closeness (Lorenz, 1971; Seligman, 1971). According to an evolutionary perspective, mammals - including humans - should be provided of a biological "baggage" to support parental care (Lorenz, 1971; Bowlby, 1969). In line with findings from animal models, recent neuroimaging studies, investigating the pattern of cerebral activity in parents in response to infant vocalizations, have shown the involvement of cortical and subcortical structures, which have been found to be critical in promoting approach behaviors and parental motivation of care over time (Barrett & Fleming, 2011; Swain, Kim, & Ho, 2011; Swain, 2008, 2011).

However the sensitivity to infant crying could be influenced by several factors. Some factors can have a positive impact on adult's responses to the infant alerts, such as becoming parents or being exposed to infants (Kim, Feldman, Mayes, Eicher, Thompson, Leckman & Swain, 2011; Seifritz Esposito, Neuhoff, Lüthi, Mustovic, Dammann, von Bardeleben, Radue, Cirillo, Tedeschi & Di Salle, 2003; Mayes, Swain & Leckman, 2005; Fleming, Corter, Stallings, Steiner, 2002; Numan, 2006; Tolman, van Anders, & Volling, 2012). Several studies show that biological changes, normally associated with the transition to parenthood (more visible in mothers, but also present in fathers), modulate the blood-oxygen-level-dependent (BOLD) signal associated to crying, and also parental sensitivity. The human brain could show predispositions to react not only to threat stimuli, but also to all salient biological stimuli, regardless of their valence (Lorenz 1971, Scherer 2011). In this sense, infant crying appears like a privileged processing. In fact, other evidences show a natural responsiveness to baby stimuli in women without children (Montoya, Landi, Kober, Worhunsky, Rutherford, Mencl, Mayes & Potenza, 2012; Brosch, Sander, & Scherer, 2007; Caria, de Falco, Venuti, Lee, Esposito, Rigo, Birbaumer & Bornstein, 2012; Glocker, Langleben, Ruparel, Loughead, Gur & Sachser, 2009; Kringelbach, Lehtonen, Squire, Harvey, Craske, Holliday, Green, Aziz, Hansen, Cornelisse & Stein, 2008). However, others factors could come interfere with adult responsiveness to infant crying, such as for example temperament (Montoya, Landi, et al., 2012), mood disorders (Ablow, Measelle, & Laurent, 2011; Laurent & Ablow, 2012), parental role (Atzil, Hendler, Zagoory-Sharon, Winetraub & Feldman, 2012), attachment style to own parental figures (Fleming, Corter, et al., 2002; Barrett, Hall, Wonch, Ali, Gonzalez, Steiner, 2009; Newman , Harris , Allen, 2011).

As an additional factor, crying baby will not necessarily find an adult ready to assist him\her, but probably an adult who is engaged in other activities, or even just immersed in their own thoughts. There are not studies that have investigated whether and how the brain activation in response to infant crying could affect performances while adults are busy in other behavioral tasks (self-oriented or externally-oriented), or whether being focused on cry-unrelated activities could have repercussions on the adult responsiveness to infant signal. Typically, fMRI studies have focused on the interactions between BOLD signals and measures oriented to investigate critical dimensions for parental responsiveness, such as data from socio-psychological assessments, observations of child-caregiver interactions, feelings elicited by infant cues through self-reports (Kim, Leckman, Mayes, Feldman, Wang, & Swain, 2010b; Kim, Feldman et al., 2011; Kim, Leckman, et al., 2010a; Noriuchi, Kikuchi, & Senoo, 2008). However, in real life parents must ensure an appropriate response regardless of the situation in which they are involved (i.e. externally-oriented activities or absorbed in their own thoughts or even simply asleep).

In our previous study (2nd chapter) we investigated in a sample of healthy adults (with and without children) their cerebral response in association to exposure to the infant crying, while they were awake and at rest, and engaged in their own thoughts (mind-wandering) (De Pisapia, Bornstein, Rigo, Esposito, de Falco, Venuti, 2013). In the last years many studies have shown a consistent pattern of activations in a network of brain regions underlying spontaneous cognition, a form of self-relevant mentalizing (mind-wandering), typical of the so called resting state. Activity in this consistent cerebral network, named the default mode network (DMN), has been attributed to different mental states, such as thinking about something not related to the environment (i.e. mind wandering), during self-referential processing, retrieval of autobiographical memories, mental imagery, envisioning of the future, and taking another person's perspectives (Buckner, Andrews-Hanna, et al., 2008; Greicius, Krasnow, Reiss, & Menon, 2003; Gusnard & Raichle, 2001; Gusnard, Akbudak, Shulman, & Raichle, 2001; Fox & Raichle, 2007; Raichle, MacLeod, Snyder, Powers, Gusnard & Shulman, 2001; Raichle & Snyder, 2007; Greicius, Srivastava, Reiss, & Menon, 2004; Svoboda, McKinnon, & Levine, 2006). Interestingly, the DMN tends to be deactivated during goal-directed activities, which require externally oriented attention. In our previous study (De Pisapia, Bornstein, et al., 2013), we found that women, while resting and simultaneously listening to baby cries, showed a greater deactivation than men in the medial prefrontal cortex (MPFC) and posterior cingulate cortex (PCC), two midline nodes of the DMN. Gender differences were found regardless of parental status. An interpretation of these findings is that the burst of the baby's cry could elicit in women an higher promptness to disengage cognitive resources from internally focused thoughts to the sudden signal processing. Given the previous results, the aim of the present study was to investigate in a more homogeneous sample (only adult without children), and using a multifaceted paradigm, the modulation of BOLD signals in association to the infant crying during various tasks. These tasks required the activation (during mind wandering and self-referential tasks about own personality traits), or the deactivation of the DMN (during the counting task).

Additionally, in the previous study (De Pisapia, Bornstein, et al., 2013) our control stimuli consisted of infant crying of children with atypical development and white noise, which did not allow to discriminate whether or not such sensitivity, shown by women, was linked specifically to infant crying or to a more general propensity of women towards emotional vocalizations. In the present study, control conditions included other human emotional sounds of children and adults (crying and laughing), as well as non-human and non-emotional sounds (noise).

Our main goal in this follow-up study was therefore to further explore – behaviorally and with neuroimaging - the gender differences during listening to baby cry, and to investigate whether the more intense deactivation of the female brain compared to males was specifically linked to that stimulus, or it could repeat also for other baby sounds (baby laugh), other emotion sounds (adult cry) or even a complex noise (control sound).

Methods and Materials

Behavioral Study 1

Subjects

We recruited 23 healthy non-parents adults (12 females, age 22,91 ± 2,95 years; 11 males, mean 23,00 ± 2,83 years) through the University of Trento by local fliers and oral communication. Inclusion criteria were to be non-parents, within an age range of 18 and 30 years, and without a personal and family history of neurological or mental disorders. The sample was of Italian heritage (or language). Participants gave informed consent to participate. The study was approved by the ethical committee for experiments involving humans at the University of Trento.

Stimuli

Auditory stimuli: We considered four sound categories, 20 baby hunger cry (BC) and 20 baby laugh (BL) (both in the first year of life), 20 female adult cry (AC) and 20 control sounds episodes. Human vocalization excerpts were selected from file sounds in a public online databases (Sounddogs sound library *www.sounddogs.com*, Soundcloud sound library *www.soundcloud.com*). First we selected five seconds from the original cry and baby sounds (sample rate 44100, mono stereo), and the resulting sounds were noise corrected, normalized, and matched each other for volume using Auditory 2.0.4 (Audacity®, the Free, Cross-Platform Sound Editor). Control sounds (CS) were built with the aim to generate noise sounds with the similar temporal modulation of the baby's cries. The rational was to have a better baseline condition for the baby's cry than a mere white noise condition, which would not take into consideration the morphological feature effect of the temporal pattern expressed by infant crying (Lorberbaum, Newman, et al., 2002). First we generated a white noise stream of five seconds, the same duration of the human sounds. In order to get the same temporal modulation present in infant crying, the white noise was matched for the intensity modulation, and matched for frequency and volume of the baby's cry (Cool Edit Pro Version 1.2, Syntrillium Software, Phoenix, AZ). Each control sound was perfectly matched to one specific infant crying and as resulting we obtained 20 control sounds.

Visual stimuli: Depending on the session (with or without active tasks) and the experimental task (self-referential, and syllabic counting) we prepared three types of strings with and without meaning. Visual stimuli were personality adjectives with neutral valence (PA, 40 items), neutral personality adjectives of three and four syllables (SA, 40 items), and 80 strings without meaning. Neutral personality adjectives about personality traits (personality task), were extracted by a cohort of adjectives previously evaluated by 12 individuals for positive and negative quality, using a 7-point scale ranging from -3 (extremely negative) to 3 (extremely positive) passing through 0 (neutral). In order to avoid to use positively and negatively connoted adjectives , we selected only adjectives assessed as neutrals. For the session that did not provide for any active task by the participant (resting state session), we created a cohort of strings without meaning, balanced for length of adjectives. Finally, for syllabic counting task we extracted from the cohort of adjectives those consisting of three and four syllables.

Behavioral Study Procedure

The investigator helped the participant in assuming the correct position in front of the screen, and wearing the headphones. In the pre-experimental phase the investigator explained briefly what was required by the experimental task. After participants underwent to three blocks of training (4 trials), one for each session, in which appeared all the conditions and tasks. From that moment began the actual experiment. Each participant underwent three experimental sessions, and the order of session sequence was counterbalanced among participants. At the beginning of each session appeared the fixation point (baseline condition), in the direction of which the participant had to direct the gaze. After 4000 msec. the experimental target sound stimulus appeared in a unpredictable way, which could consist in one of the four category sound stimuli (BC, AC, BL, CS, duration 5000 msec.). Simultaneously, the visual stimulus compared at the center of the screen, which could consist in one of the four types visual stimuli (NA, fSA or tSA, and STR), depending on which of the three experimental tasks were ongoing.

Session 1 : This session provided for a self-oriented task (resting state session). Experimental block provided for a simultaneous presentation of two stimuli, namely an auditory stimulus from one of four sound categories (BC, BL, AC, and CS) and a visual stimulus from the string category (STR). Participants were free to think about whatever they wanted, taking care to maintain the gaze oriented toward either the fixation point or the visual stimulus.

Session 2: This session provided alternatively in an unpredictable way for two decision tasks, a goal-oriented (syllable counting) and a self-oriented task (personality), both unrelated with the simultaneous sounds. Experimental block provides for simultaneous presentation of two stimuli, namely an auditory stimulus (from one of BC, BL, AC, and CS categories) and a visual stimulus either from one of two adjective categories (PA, or SA), depending on the ongoing task. In the *personality task* participants had to decide whether the adjective, shown on the screen, described one's own personality trait (PA), through a dichotomist response, yes or no. In the *syllable counting task* participants had to decide whether the adjective, shown on the screen, were composed by three or four syllables. Response times (RTs) were collected pressing a button box response. For each block, at the top of the screen appeared every time the label of the ongoing task, and the association between dichotomist responses and left and right buttons. Each session was composed of 80 blocks.

Experimental design

Participants were tested in 6x2 factorial design in the behavioral study (4x2 factorial design in the fMRI study). First factor (within-participants) was considered the sound:six level (four level), factor, referring to the relative distance (sound categories) between each sound category (BL-CS, AC-BL, AC-BC, AC-CS, BC-BL, BC-CS (BC, AC, BL, CS). Second factor (between-participants) was the gender: two level (male, female). Dependent variables were behavioral measures RTs (blood oxygenation level dependent BOLD signal associated with all sounds and experimental tasks). Additionally, we considered a supplementary two level, within-participants factor in second session, taking into account the two different tasks inside the same session (syllabic counting/personality tasks).

fMRI Study 2

Subjects

We recruited 22 healthy non parents adults (10 females, age 20,5 ± 4,04 years; 12 males, mean 25,25 ± 2,77 years). Modality of recruitment and inclusion/exclusion criteria were the same as for behavioral study 1.

fMRI Study Procedure

Firstly, the investigator gave participants a detailed explanation about the experimental task and the technical characteristics of the magnetic resonance imaging, followed by a training session as the previous study 1. Each participant underwent a medical interview to assess their mental and physical suitability with the magnetic resonance imaging. Then, MRI operators of the research center accompanied the participant in the room of the MRI machine, who was helped to correctly place the necessary equipment for noise reduction, the headphones (Serene Sound, Resonance Technology, Inc.) and earplugs. I addiction, participants were equipped with microphone and button box response (Lumina), enabling them to communicate and interact with the experimenter, and respond to task trials during scanning sessions. Through a camera was possible monitor inside the scanner all the time. The experimental phase started only after the verification of appropriate functioning of the various devices. As first step started the sequence for the anatomical image acquisition, which not required any kind of task, and the participants were free to stay at rest keeping your eyes closed. Then, the investigator informed of the beginning of the experimental session. Participants underwent three fMRI scanning sessions, and the order of scanning sessions was counterbalanced across participants. For this study we used the experimental design of the previous behavioral study 1. See previous sections about methods and procedures for a detailed description of stimuli, tasks and sessions.

fMRI scanning

Functional images were acquired through a whole-body scanner equipped with a Bruker MedSpec MRI magnet 4 Tesla (T) and Siemens Sonata gradients of 40 mT/m, a system with 8-channel coil for signal reception. Functional images T2*-weighted were obtained with a standard technique called Echo Planar Imaging (EPI), acquiring 37 slices of the brain volume with the following parameters: slice thickness = 3 mm, FOV = 192 mm, flip angle = 75 °, TR (Repetition Time) = 2200 ms, TE (echo time) = 33 ms, matrix 64x64, voxel size 3x3x3mm. The total acquisition time was about 43 minutes, the number of volumes for each of the three sessions was 334. We also acquired for each participant, 3D anatomical images with high resolution T1-weighted (MPRAGE, 176 axial slices, slice thickness = 1 mm, FOV = 256 mm, EN (Inversion Time) = 1020 ms, flip angle = 7 °, TR = 2700 ms, TE = 4.18 ms.

fMRI data processing

All performed analyses of collected fMRI data were carried out with BrainVoyager QX version 2.8 (Brain Innovation, Maastricht, the Netherlands) running on a Windows operating system. Every analysis was done separately for each session. Before analysis, we did not need discard the first volumes because each scan session was preceded by 4 dummy scans to eliminate the magnetic saturation effect. As first, preprocessing steps of functional images provided for 3D motion correction using trilinear interpolation and linear trend removal, realigning of each volume to the first volume of the session to correct artifacts due to movements of the head. Then, the realigned functional 2D images were co-registered with the 3D anatomical image. In order to improve the co-registration process, 3D anatomical image was previously corrected for inhomogeneity (2 cycles), and brain tissue was segregated from head tissue. Functional 2D images were translated and rotated into the AC-PC plane, and eight landmarks for the borders of the cerebrum were definied. Finally images were normalized into a Talairach space, and a 8-mm full-width at half-maximum gaussian smoothing was applied. Four predictors, one for each block condition (BC, BL, AC, CS) in all tasks (session 1: resting state; session 2: personality task, and syllabic counting), were convolved with the hemodynamic response function (HRF). For the statistical analysis of the activation blocks defined by experimental paradigm, we defined a general linear model (GLM), fitted in with all predictors in order to create a whole brain statistical map for each subject. Our aim was investigate the activity modulation of the same regions considered in the previous study (De Pisapia, Bornstein, et al., 2013), namely nodes of the default mode network (Buckner, Andrews-Hanna, & Schacter, 2008). For the resting state session, which did not required any active task, ROIs analysis were carried out using the same masks from the previous study: medial prefrontal cortex x=3 y=49 z=20 (mPFC), posterior cingulate cortex x=-1 y=-46 z=25 (PCC), left and right superior temporal cortex x=49 y=-14 z=7, x=-42 y=-20 z=7 (STC). In the second session participants underwent to one self- and one external-oriented task. Then, regions of interest were defined, for the following ROIs analysis, using coordinate regions evidenced in a peer-reviewed DMN meta-analysis (van der Meer, Costafreda, Aleman, & David, 2010). In specific, we created spheres based on coordinate regions involved in self-referential personality task (personality versus baseline), and the considered coordinates were MPFC x=-12 y=45 z=29, PCC x=-2 y=-57 z=21, cuneus x=-4 y=-61 z=25, and temporal pole x=-40 y=22 z=-18. A false discovery rate (FDR) or Bonferroni adjusted for multiple comparisons analysis was done in all analysis, and on resulting map was applied a t-test analysis for contrasts of interest.

Results

Behavioral data analysis and statistical tests (study 1)

Response times (RT) were submitted to a two-factor repeated measures ANOVA two-tailed. Factors used in the analysis were the relative measures of RTs (within), and gender (between).

Syllabic counting task: Analysis did not reveal any significant effect of the main factor, the type of sound. Gender factor was not found significant. Instead, analysis of the interaction sound distance * gender showed a significant effect (F (1,21) = 3.271, p < .009). Post-hoc paired t-test, comparing female (F) versus male (M), revealed that women were significantly slower with BC than AC (F: AC-BC =-86.04 ±82.78 msec.; M AC-BC =198.42 ±96.63 msec.; t(21) = -2,25, p< .03), BL than AC (F: AC-BL=-113.72 ±80.86 msec.; M: AC-BL=187.59 ±103.29 msec.; t(21) = -2.32, p< .03), and BC than CS (F: BC-CS=88.63 ±206.42 msec.; M: BC-CS=-100.38 ±209.38 msec.; t(21) = 2.18, p< .04) (figure 1b).

Self-referential task: Analysis did not reveal any significant effect for all factors and their interaction (figure 1a).

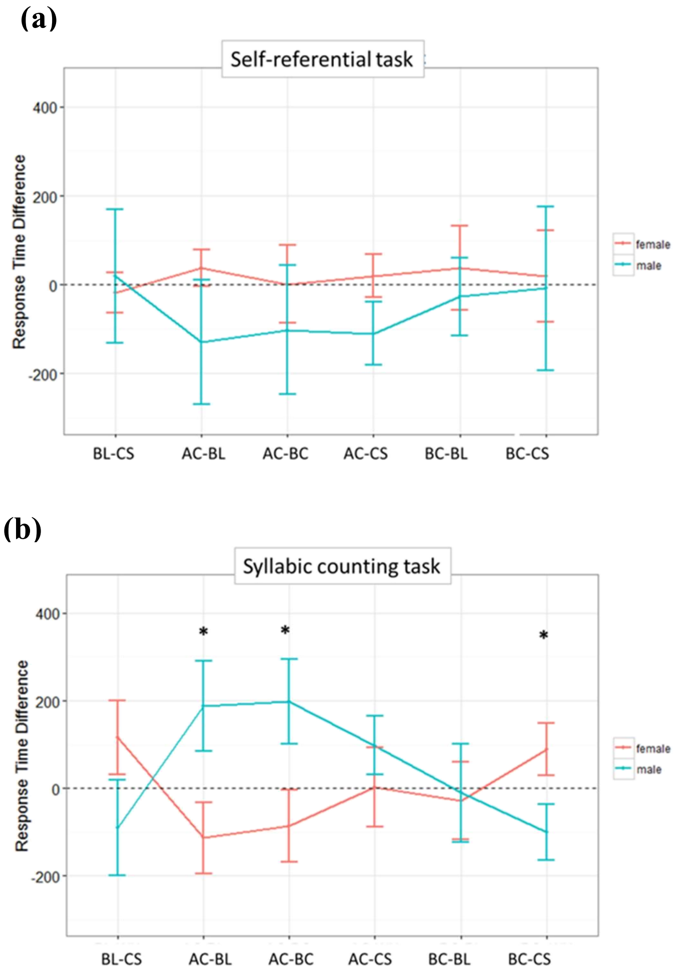


Figure 1:
Reaction Time (msec.). Plots represented the participants' performances in syllabic counting (b) and self-referential (a) tasks, while they were listening to adult cry (AC), baby cry (BC), baby laugh (BL), and the noise control sound (CS). Gender differences were found in the following contrasts: AC>BL (p=.03), AC>BC (p=.04), BC>CS (p=.04) while participants were engaged in the self-oriented task.
p<.05 (*)

fMRI data analysis and statistical tests (study 2)

(Session without active tasks: Passive listening to sounds)

ROI analysis

For all regions of interest we carried out two factor ANOVA with repeated measure. Different sounds and gender represented namely within- and between-participants factors

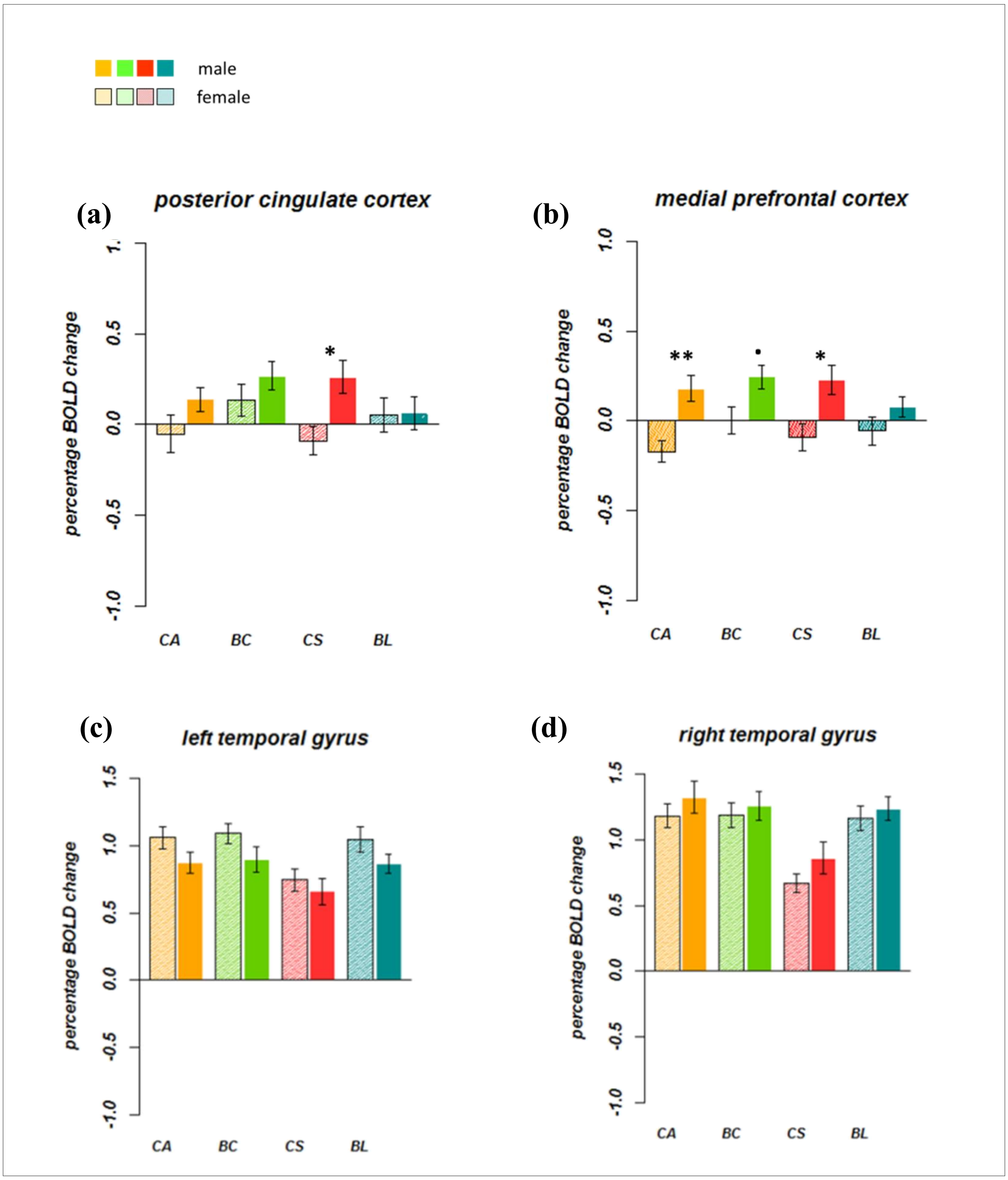
In MPFC region (figure 2b), analysis did not reveal significant main effect and interaction between sounds and gender, but did reveal gender effect (F(1,19)= 5.319, p=.03). Women showed lesser activation in this region in association with all sounds (meanF= -0,080, meanM= 0,182 SE=0.136). A direct group comparison in contrast of interest (BC, BL, AC, CS) active significant effect in response to AC (meanF= -0,172, meanM= 0,179, t(60)=2.72, p= 0.014), and CS (meanF= -0,093, meanM= 0,227, t(60)=2.10, p= 0.049). Other contrasts though maintaining the same trend did not reach the significance. However analysis evidenced a trend to significance in association with [BC-baseline] condition (meanF=0.004, meanM=0.245 SE=0.134 t(60)=1.80 p=0.08). All factors and their interactions were not found significant in PCC (BA 23) (figure 2a) and bilateral STC (figure 2c, 2d).

(Session 2 with active tasks: self-referential personality traits and syllabic counting)

First, we considered differences in the cerebral activity amongst the personality task and the syllabic counting (figure 3), with the aim to make a comparison of the DMN involvement in both tasks. We found greater activity in personality task than the syllabic counting task (F(1,19)=50,75, p=0.000 Bonf<0.05) in midline structures, as PCC (BA 31), MPFC (BA 9), and also in right inferior parietal lobe IPL (BA 40), and in left middle

Figure 2: ROI analysis in the resting state session. Anatomical ROIs were defined using the coordinates from our previous study (De Pisapia, Bornstein et al., 2013). Women showed greater cerebral deactivation in the Medial prefrontal cortex (b), Posterior Cingulate cortex (a), two nodes of the DMN, while they were listening to the adult cry (AC), baby cry (BC), baby laugh and the noise control sound (CS)(FDR <.05). As in our previous study, analysis in the left and right temporal gyri (c,d) did not reveal any gender differences (FDR <0.05).

p<.01 (**), .05 (*) and .1 (.)



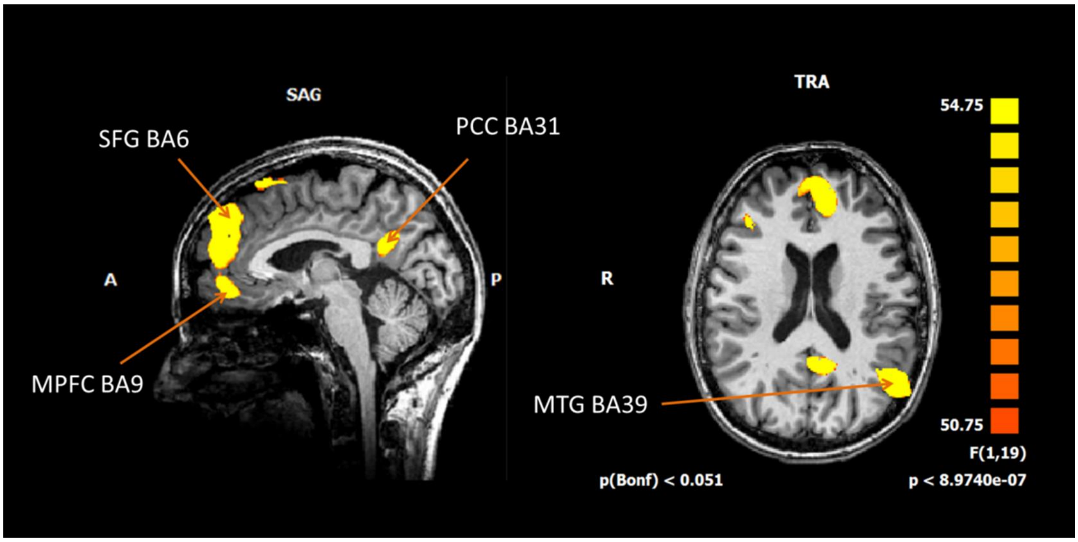
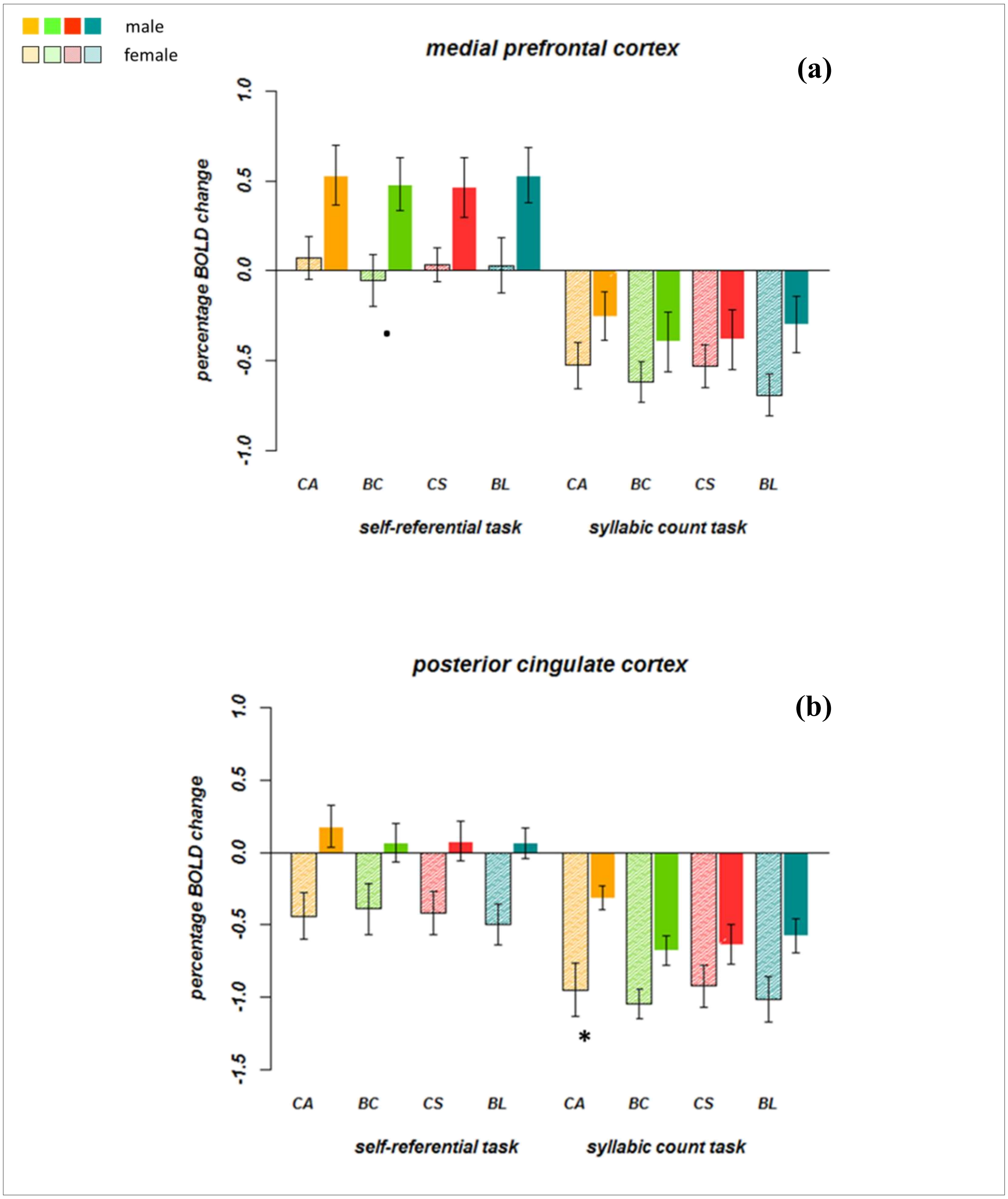


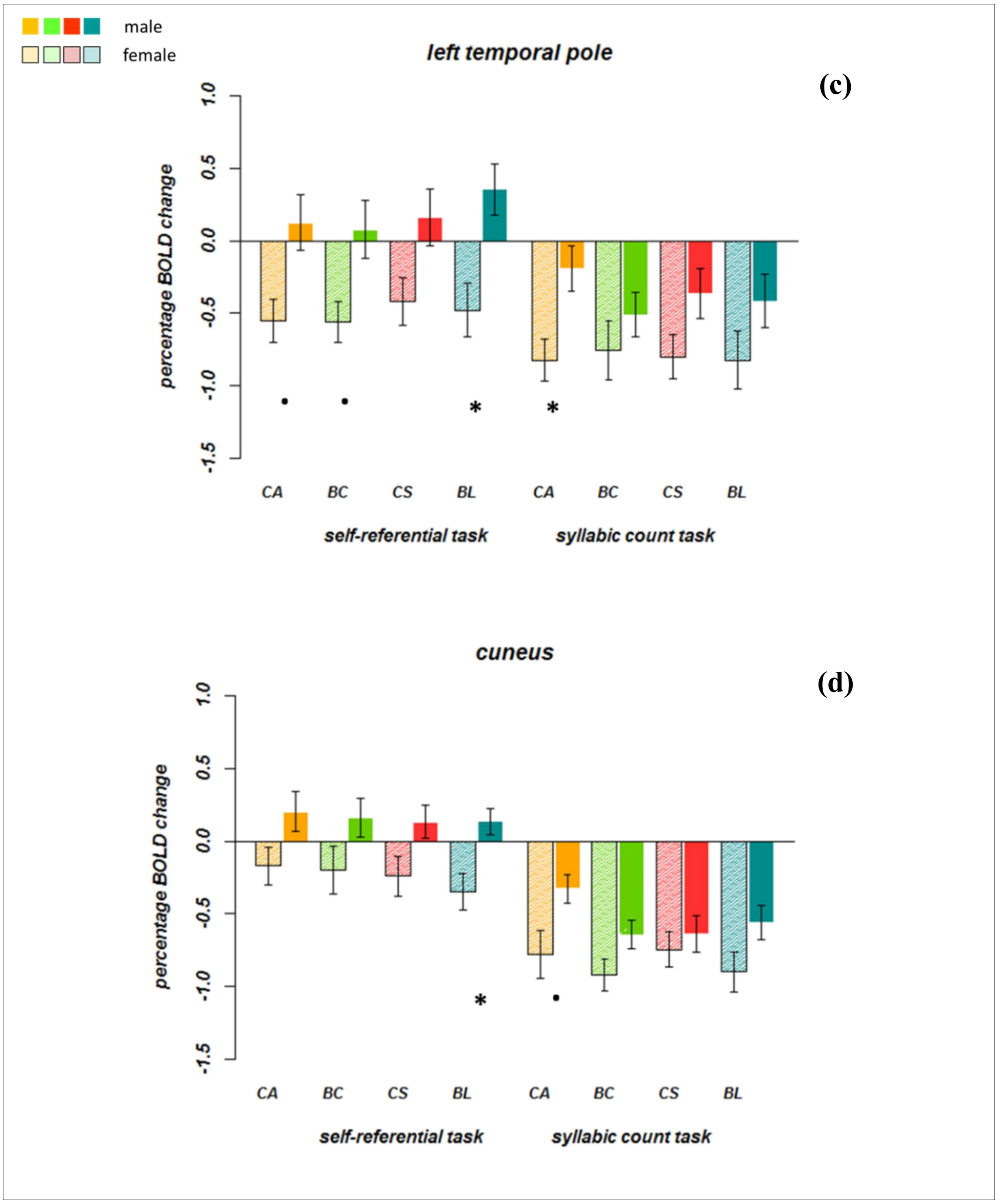
Figure 3. Areas that showed greater activation in the self-referential task than the syllabic counting task (Bonf. >.05). Self-oriented task involved a cerebral network which was compatible with the DMN. Abbreviations: MPFC= medial prefrontal cortex, SFG= superior frontal gyrus, PCC= posterior cingulate cortex, MTG= middle temporal gyrus.

temporal gyrus MTG (BA 39), superior frontal gyrus SFG (BA 6), middle frontal gyrus MFG (BA 6), inferior frontal gyrus IFG (BA 47). In addition, analysis showed a significant effect of sounds (F(3,57)=5,80, p=0.002 FDR<0.05) in bilateral STG and right IFG. In the comparison between the groups, we focused on regions involved in self-referential task (own personality characteristics). We defined anatomical ROIs using as reference a meta-analysis report of neuroimaging studies about self-reflection (van der Meer, Costafreda, Aleman & David, 2010): MPFC (BA 9), PCC/precuneus (BA 23/30), cuneus (BA 18/23), and the left temporal pole (BA 38). Furthermore we investigated the modulation of cerebral activity for each region of interest in both tasks.

Figure 4: ROI analysis in the self-referential/syllabic counting session. As reference of anatomical ROIs we used a meta-analysis report on self-reflection in neuroimaging studies (van der Meer , Costafreda, Aleman and David (2010). Women showed greater deactivation in all ROIs then man. At this moment, the analysis reached the significance in the posterior cingulate cortex (b), cuneus (d), and left temporal pole (c) (FDR<.05). However the same tendency was found in the medial prefrontal cortex (a) (FDR<.05). Such sensitivity in women was not oriented to a specific sound, but appeared to be a trend in association to all of the sound.

p<.05 (*) and .1 (.)





ROI analysis

In MPFC region (figure 4a), the main effect (task) was significant(F(1,19)=106 p=0.000 FDR<0.05), but all the other factors and their interactions did not reach the significance. Although not reaching the significance, we observed a tendency in women to show lesser activation in [BC>baseline] contrast during the self-referential concomitant task (meanF=-0.053, meanM=0.482, SE=0.281 t(20)=1.91 p=0.072). Similarly, in PCC region (figure 4b) we found a significant main effect (F(1,19)=54.71 p=0.001 FDR<0.05), whereas the other factors did not reach the significance. Post-hoc analysis revealed a strong deactivation in women in [AC-baseline] contrast (meanF=-0.844 meanM=-0.387, SE=0.214 t(20)=2.13 p=0.05) during the concomitant syllabic counting task. In cuneus (figure 4d) the ROI analysis showed a significant main effect (F(1,19)=87.70 p=0.000 FDR<0.05) and a trend on gender differences (F(1,19)=2.88 p=0.106 FDR<0.05). We found greater deactivation in women in all conditions, but only the [BL-baseline] contrast was found significant in the self-referential task (meanF=-0.350 meanM=0.136 SE=0.203 t(20)=2.4 p=0.027), whereas the [AC-baseline] contrast showed a tendency toward the significativity (meanF=-0.781 meanM=-0.328 SE=0.250 t(20)=1.81 p=0.086) in the syllabic counting task. Finally, the analysis which focused on the left temporal pole (figure 4c) showed a significant main effect (F(1,19)=43.93 p=0.000 FDR<0.05), a strong tendency to the significance in the interaction between task conditions and gender factor (F(1,19)=3.53 p=0.076 FDR<0.05), and a weak trend in gender factor (F(1,19)=2.98 p=0.100 FDR<0.05). In the personality task women showed greater deactivation in association to the [BL-baseline] contrast (meanF=-0.479 meanM=0.355 SE=0.345 t(20)=2.42 p=0.026), but also [BC-baseline] and [AC-baseline] contrasts (meanF=-0563 meanM=0.079 SE=0.341 t(20)=1,88 p=0.075 ; meanF=-0.557 meanM=0.123 SE=0.339 t(20)=2.01 p=0.059).

Discussion

Our purpose in this study was to better understand in a sample of non-parents the neurocognitive processes during listening to infant crying. As a follow-up to our previous study (De Pisapia, Bornstein, et al., 2013), here we focused on the effect of the outbreak of infant crying sounds in cognitive processes activated during concurrent activities, internally and externally oriented processing, both unrelated to sounds of the infant crying.

During *resting state,* we found that women tend to show - in response to crying stimuli and noise - a greater deactivation than men in the medial prefrontal cortex (MPFC), but not in posterior cingulate cortex (PCC). These results are in partial agreement to our previous fMRI resting-state study (De Pisapia, Bornstein, et. al., 2013), in which we found higher activity in the male group in the DMN nodes (MPFC and PCC) during the listening to the typical baby cry in comparison to the female group. Instead, in the present study we found significant gender differences only in the MPFC. Interestingly, this deactivation in women was not specific for infant stimuli, in fact it took place also during listening to adult cries and noise. There was a tendency for infant crying, but no effect for the infant laughing. In line with our findings, Seifritz and colleagues (2003), showed the same gender differences in relation to the involvement of anterior cingulate cortex (ACC) in response to infant vocalizations, without discriminate between infant crying and laughing. Despite of the convergence amongst our and Seifritz studies about such tendency in women, regardless the parental status, to deactivate medial anterior brain regions during the listening to infant vocalizations (De Pisapia, Bornstein, et al., 2013; Seifritz, Esposito, Neuhoff, Lüthi, Mustovic, Dammann, Von Bardeleben, Radue, Cirillo, Tedeschi, Di Salle, 2003), general findings about gender differences are not very clear. For example, Sander and colleagues (2007) showed that infant vocalizations elicited in non-mother women a stronger activation in the anterior cingulate cortex (ACC). In addition, noise sounds, derived from infant vocalizations, elicited greater cerebral activation in the PCC in all participants (Sander, Frome, & Scheich, 2007). Studies with parents typically involved only mothers, and did not investigate cerebral activations in regions attributable to the default network (Swain, 2011). However, parental experience and gender can modulate the activation in limbic regions underlying alarm and preoccupation (Purhonen, Kilpelainen-Lees, Paakkonen, Ypparila, Lehtonen, & Karhu, 2001; Seifrits, Esposito, et al., 2003). This could be reflected as a different involvement of the DMN. The responsiveness to infant cues could change over time in connection with the experience. For example, an event-related potentials (ERPs) study showed in mothers higher levels of arousal and alertness in contrast to women without children during the listening to unexpected stimuli, like baby crying, and also neutral word (Purhonen, Kilpelainen-Lees, et al., 2001). With this in mind, the presence of mothers in our previous study (De Pisapia, Bornstein, et al., 2013) may underlie the variability of results that we have found. The presence of mothers might have amplified a natural sensitivity to relevant stimuli, already present in women without children.

We now report our comments concerning the execution of the task (syllabic count and self-referential)

Behavioral results. In the *syllabic count task* in the behavioral study, we found that women were significantly slower (RT) than men while they listened to infant vocalizations in contrast to the adult crying, and the infant crying in contrast to the control noise. Conversely, we did not find any gender differences in participants' performances in the *self-referential task*, in which findings in literature reported an increase of cerebral activity of the DMN (Buckner, Andrews-Hanna, et al., 2008). Behavioral data in this study evidenced a modulation on women's performances in association with the infant cues during the concomitant externally oriented task. This gender differences in performance emerged when comparing matched infant to non-infant sounds (infant versus no-infant sounds), but no difference was found when comparing matched non-infant stimuli or matched infant stimuli to each other (infant versus infant, and non-infant versus non-infant). At this point, results suggested that infant vocalizations could elicit an automatic attention shift in women when they are engaged in externally oriented task, probably accompanied by a greater deactivation of the DMN. However such attention shifting could be one of the factors that can affect performances in association to the listening of infant vocalizations. In literatures there is a lack of studies that recollect RTs in their investigations of responsiveness to infant crying. However recently a behavioral study showed that adults (without children) were faster in motor tasks, after soon the listening to infant crying respect to other sounds. There was no evidence of gender differences. Authors suggested that the baby's cry could elicit an immediate modulation in motor performance over time (Parsons, Young, Parsons Stein & Kringelbach, 2011). Authors used long sounds (4.5 minutes), whereas the sound duration in the present study was very shorter (five seconds). Here we focused on the early effect of infant sounds, in term of only a few seconds. The sound durations of stimuli represent a critical aspect, because in the most of neuroimaging studies that focused on parental responsiveness to baby cues there is great variability respect to the duration of sounds, and this factor may partly explain the variability on results (Kim, Feldman, et al., 2011; Lorberbaum, Newman, et al., 2002, Parsons, Young, et al., 2011; De Pisapia, Bornstein, et al., 2013; Sander, Frome & Scheich, 2007)

Neuroimaging results. We found that the female group showed in both tasks more cerebral deactivation in the DMN regions involved in self-referential tasks: MPFC, PCC/precuneus, cuneus (Cu), and left temporal pole LTP (for a meta-analysis see van der Meer, Costafreda, et al., 2010). In our *self-referential task*, the female group showed a higher tendency to deactivate the LTP and Cu while they were listening to all emotional stimuli, with a stronger effect in association to the infant laughing. Furthermore, results evidenced higher deactivation the MPFC in association with infant crying, whereas no gender differences were evidenced in PCC. In agreement with literature, we found the deactivation of DMN in all of the participants during the syllabic counting, which required the shift from self-referential task to the externally oriented task (Gusnard, Akbudak, et al., 2001; Raichle, MacLeodet, et al., 2001). Furthermore, women showed higher deactivation than men in all of the condition sounds. However, gender differences reached significance in association to the listening to adult crying, in association to which PCC, LTP and Cu (but no MPFC) showed stronger deactivation. Once again, findings evidenced higher deactivation in women. In line with participants' performances in the present study, we expected to find in women more cerebral deactivation in the midline regions of DMN in response to infant stimuli, during the concomitant syllabic counting task, and lesser during the self-referential task. However, gender differences emerged mainly in the self-referential task, in which women showed cerebral deactivations in Cu, LTP, and MPFC while they were listening to emotional sounds, and the baby laughing in particular. Interesting, BOLD signals in MPFC – in the self-referential task - showed a tendency to decrease in response to infant crying in women. Even if such trend was generalized to all stimuli, the infant vocalizations seemed to have more saliency.

§ § §

There are only a few studies that have reported evidences on gender differences at the level of DMN. Differently from our results in the present and previous studies, other reports showed that women tend to have a higher activation in the ACC and PCC than men, a difference which might facilitate men in externally cognitive tasks (Gusnard, Akbudak, et al., 2001; Raichle, MacLeodet, et al., 2001), and women in introspective tasks (Jiménez, Mancini-Marie, Lakis, Rinaldi, & Mendrek, 2010). While great deactivation of this network reflected the promptness to respond to external stimuli, strong activation reflected more involvement in self-reflection tasks. Despite all of this, the observed trend in our study, and findings from our previous work (De Pisapia, Bornstein, et al, 2013), evidenced in women lesser activation of DMN in the presence of auditory stimuli. This is an important point for interpretations, because a trend of higher deactivation of the DMN regions that we found in women, is in contrast with other findings that evidenced gender differences in DMN activations, in which women showed greater activity in these same regions than men (Jimenez, Mancini-Marïe, Lakis, Rinaldi & Mendrek, 2010; Bluhm, Osuch, Lanius, Boksman, Neufeld, Théberge, & Williamson, 2008). So, if gender differences that we observed were attributable to a mere gender differences at the level of DMN, our data should have been more in line with literature, even if only as a tendency. In contrast, all of our results in this study showed an opposite pattern of DMN involvement (deactivation) in association to the occurrence of sounds.

Several previous studies suggest a different sensitivity to emotional auditory stimuli between women and men. For example, it was suggested that women elaborated the prosodic information in early stages of sound processing, and that the emotional prosody influenced more rapidly the subsequent verbal processing. (Schirmer, Kotz, & Friederici, 2002). In women, emotional stimuli appeared to be more salient and catch greater attention than neutral stimuli (Schirmer, Striano, & Friederici, 2005). Hormones, like estrogen, could play a role in such sensitivity in detecting changes in the prosodic information, and in the priority of the emotional event processing (Schirmer, Escoffier, Li, Li, Strafford-Wilson & Li, 2008). In addition, women seemed to be more responsive to the noise sounds, resulting in greater activation of the primary auditory cortex, which - as hypothesized by authors of the study - was probably caused of the activation of the dorsal PFC and the posterior part of middle frontal gyrus underlying attention processes (Ruytjens, Georgiadis, Holstege, Wit, Albers & Willemsen, 2007). Thus, our observed deactivation in women might reflect this inclination, to the benefit of the emotive stimulus processing such as crying and laughter. As alternatively interpretation, the more involvement of DMN in women (Bluhm, Osuch, et al., 2008) could have promoted greater expertise in self-referential task, which could manifest itself through lesser involvement of the DMN in the present study for the benefit of the elaboration of concurrent sounds.

Given that our study is still in progress, there are a number of limitations. On limitation is that we have not - due to technical problems - behavioral measures during the scanning sessions. Consequently it was not possible investigate the interactions between the BOLD signals and behavioral measures. Another limitation concerns the fact that the sample is small and unbalanced for gender.

A important future direction of this study is to extend it to an investigation on parents. In fact, results of this present study do not allow to understand whether the observed gender differences in our previous study were independent of the parental status of participants. It is possible that part of the variability between groups (women, men) might have been impacted by the greater contribution given by mothers in the female sample.

In summary, the current study shows that behaviorally women are penalized by concomitant infant sounds during externally oriented activities. In terms of brain activations, women appear to be more receptive to infant related, emotionally meaningful and even a complex form of noise (as described before) sounds, and thus not specifically in response to baby cries. This interpretation is motivated by the fact that on association to the onset of sounds women showed greater deactivation of the DMN, a neural network which was found activated when our attention is internally-oriented in self-referential thoughts, than men.

Chapter 5

General conclusions

In this research project we focused on the effects of biological factors and cognitive processes - and their interaction - from adult responsiveness to baby signals. We investigated, using the functional magnetic resonance imaging (fMRI), factors in human adults (parents and no parents) that may affect the mechanisms underlying the complex adult-child relationship, along two parallel lines of research about the neurobiology of parenting. A first line of research investigated the neural mechanisms underlying blood-oxygen-level-dependent (BOLD) signals in association to infant vocalizations (infant crying and laughing). The second line investigated the anatomical brain change occurring during the early postpartum period in new fathers and its relation with emergent fatherhood. Focus of our investigations has been directed toward the first caregiver-child interactions, which constitute the starting point from which it will develop the attachment bond (Bowlby 1969, Trevarthen and Aitken, 2001; Ainsworth, Bell, Stayton, 1974; Bornstein, Tamis-Lemonda, Hahn, & Haynes, 2008; Bornstein, 2002). During the very first interactions, within which mother and child develop mutual knowledge, several factors coming into play may reflect both the ontogenetic development of the individual (i.e. environmental factors, personal experience) and phylogenetics (i.e. biological predispositions). Such factors can have positive or negative impact on adult's responsiveness to the infant alerts, and generally to the infant vocalizations, such as becoming parents or being repeatedly exposed to infants (Kim, Feldman, Mayes, Eicher, Thompson, Leckman & Swain, 2011; Seifritz Esposito, Neuhoff, Lüthi, Mustovic, Dammann, von Bardeleben, Radue, Cirillo, Tedeschi & Di Salle, 2003; Mayes, Swain &

Leckman, 2005; Fleming, Corter, Stallings, Steiner, 2002; Numan, 2006; Tolman, van Anders, & Volling, 2012)) or individual temperament (Montoya, Landi, Kober, Worhunsky, Rutherford, Mencl, Mayes, and Potenza, 2012).

In the *first line of research* we investigated the effect of the outbreak of infant sounds in cognitive processes already activated by concurrent activities, internally and externally oriented processing, both unrelated to sounds of the infant crying and laughing. The rational was that in life, when the baby cries it will not necessarily find an adult ready to assist him\her, but probably an adult engaged in other different activities, or even just lost in their own thoughts or asleep. Findings in these current studies showed that women tended to be more receptive to the sounds, all sounds, regardless of both the emotional meaning conveyed and the source of sounds, while they were engaged in self-reflection. We found in women a higher deactivation of the default mode network (DMN) than in men, in association to the onset of infant sounds - and also to emotional sounds in general - while they were engaged in self-oriented tasks, as mind wandering and self-referential judgment. Interestingly, several studies reported that DMN typically showed great cerebral activity when our attention is internally-oriented in self-referential thoughts (Buckner, Andrews-Hanna, et al., 2008; Greicius, Krasnow, Reiss, & Menon, 2003; Gusnard & Raichle, 2001). Furthermore, reports in literature showed that emotional stimuli appear to be more salient and catch greater attention than neutral stimuli in women (Schirmer et al., 2005, 2007, 2008). Hormones, like estrogen, could play a role in such priority of the emotional event processing (Schirmer, Kotz, & Friederici, 2002; Schirmer, Escoffier, Li, Li, Strafford-Wilson & Li, 2008). In our studies gender differences might be more attributable to this different way of processing emotional cues. Thus, the observed deactivation in women might reflect this inclination, to the benefit of the emotive stimulus processing such as crying and laughter. In women such sensitivity to the sounds, while not being a specific mechanism in response to infant crying, is however to the benefit of a higher sensitivity to emotional vocalizations of infants. Responsiveness to infant cues represents a crucial aspect in parenting, because the attachment behavior of the very young child is manifested through his/her vocalizations, which catch the adult's attention and elicit behaviors of care. Future lines of research should also investigate in parents the effect of concurrent infant-unrelated activities on the responsiveness towards infant vocalizations. Furthermore, Jimenez and colleagues (Jimenez, Mancini-Marïe, Lakis, Rinaldi & Mendrek, 2010;) in reporting greater involvement of DMN in women than men, suggested that such difference which might facilitate men in externally cognitive tasks, and women in introspective tasks (Gusnard, Akbudak, Shulman, & Raichle, 2001; Raichle, MacLeod, Snyder, Powers, Gusnard & Shulman, 2001; Bluhm, Osuch, Lanius, Boksman, Neufeld, Théberge, & Williamson, 2008). Future studies should investigate if the deactivation of the DMN that we found in women may be due in part to a greater expertise in self-reflection. In our present studies, such feminine expertise could have allowed or favored the processing of sounds while continuing to carry out self-referential tasks.

The *second line of research* investigated the phenomena of brain plasticity occurring at the first early postpartum period in new fathers. We found an increase in grey matter (GM) volumes in striatum - including amygdala, hypothalamus and subgenual cortex - lateral PFC, and superior temporal gyrus, from 2-4 weeks postpartum to 3-4 months postpartum. Furthermore we found a decrease in GM volumes the orbitofrontal cortex (OFC), posterior cingulate cortex (PCC), insula, and fusiform gyrus. The findings suggest that parenting experience in early postpartum period may be associated with structural increase in neural regions for parental motivation and mood regulation in human fathers (Barrett & Fleming, 2010). The structural increase in these regions associated with low levels of depression and a normal level of preoccupation about the baby, may be related to better mood regulation, which may facilitate paternal sensitivity toward a baby. The efficiency in processing infant-related information may explain the structural decrease in neural regions for emotional and social information processing over the first three months postpartum. For example the decrease in these regions is associated to a good father-child relationship and low level of intrusiveness. Fathers are becoming ever more involved in the care of the baby and nowadays fathers are playing an important role inside the family management. There is a lack in literature regarding the neurobiology associated to the paternal responsiveness and parental behaviors. In mothers, increased activations in the striatum, thalamocingulate circuits and prefrontal cortex (PFC) in responses to infant pictures or cry sounds are associated with sensitive parenting behaviors (Barrett & Fleming, 2010; Swain, Lorberbaum, Kose, & Strathearn, 2007). Recent findings reported that increased GM volumes in the striatum during the first few months postpartum was associated with mothers' more positive thoughts and feelings about their own baby (Kim, Leckman, Mayes, Feldman, Wang, & Swain, 2010). Rodent and primate studies suggest that similar neural regions may also be important for sensitive parenting and parent-child emotional bonding in fathers. For example, parenting experience was associated with the greater density of the PFC in male marmosets (Kozorovitskiy, Hughes, Lee, & Gould, 2006). The findings may shed light on what brain regions may be linked to a human father's ability to develop appropriate parental behaviors and parent-infant attachment. Future investigations should be aimed on the study of relations between the brain plasticity in fathers during the early postpartum period and the degree of their active involvement in infant care during the first month. Findings in this present study were based on healthy fathers with normal mood and low level of anxiety. Future directions should investigate paternal brain plasticity in samples with greater variability.

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