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REVIEW ARTICLE

Neuroendocrinology of Parental Response to Baby-Cry

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This overview attempts to synthesise current understandings of the neuroendocrine basis of parenting. The parent–infant bond is central to the human condition, contributes to risks for mood and anxiety disorders, and provides the potential for resiliency and protection against the development of psychopathology. Animal models of parenting provide compelling evidence that biological mechanisms may be studied in humans. This has led to brain imaging and endocrine system studies of human parents using baby stimuli and concerted psychological and behavioural measures. Certain brain circuits and related hormonal systems, including subcortical regions for motivation (striatum, amygdala, hypothalamus and hippocampus) and cortical regions for social cognition (anterior cingulate, insula, medial frontal and orbitofrontal cortices), appear to be involved. These brain circuits work with a range of endocrine systems to manage stress and motivate appropriate parental caring behaviour with a flexibility appropriate to the environment. Work in this field promises to link evolving models of parental brain performance with resilience, risk and treatment toward mother–infant mental health.

Key words: parent–child relationships, brain imaging, functional magnetic resonance imaging, attachment, parenting, caregiving, cortisol, dopamine, opioids.

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Introduction

Parenting is critical for an infant's survival and development across mammalian species. Despite increased levels of stress as a result of physiological, emotional and economical demands from the baby (1), parents typically find themselves highly motivated to take care of their infants' needs and also find the interactions with infants rewarding (2,3). The present review draws upon recent human and animal brain research using infant stimuli to examine psychological and biological aspects of maternal motivations and behaviours. Using the example of selected maternal brain and endocrine responses to the hunger cry of an infant, we examine the modulatory roles of dopamine (DA), oxytocin (OT), cortisol (CORT) and endogenous opioids (EO). Thus, we propose to build on current bio-behavioural parental brain models (4,5) for a simplified and integrated homeostatic neuroendocrine model.

Neuroimaging methodology primer

Functional neuroimaging methods relevant to the present review include magnetic resonance imaging (MRI) and positron emission tomography (PET). MRI techniques combine non-invasive magnetic fields and radiofrequency signals for millimetre resolution. Voxel-based morphometry detects changes in brain structure as a result of development or the environment. Functional MRI (fMRI) involves blood-oxygenation-level-dependent (BOLD) measurements that reflect changes in neural activity over a time resolution of seconds.

Typically, BOLD signals during different events are measured throughout the brain. Subsequent analyses identify brain regions that show greater activity in response to a condition of interest (e.g. own-baby-cry versus other-baby-cry) and allow correlation of such brain activity with measures of parental behaviours. This technique can also be carried out in rats using such stimuli as nipple suckling, along with direct neurohormone sampling. PET represents another functional brain imaging technique for humans, and measures certain receptor-specific changes in radioactive tracers injected into the bloodstream but with the caveats of radiation exposure and longer minute-scale temporal resolution.

Several caveats of current brain imaging must be considered. First, the BOLD signals of the fMRI data are indirect measures of neural activity, such that the data are susceptible to non-neural changes in the participant's body and environment. Second, imaging data provide information on the association, rather than causality, between brain and behaviour. Third, because of the

limitations of space and movement in the scanner, studies must use simple tasks and stimuli to simulate the performance of parenting behaviours. Finally, differences in parenting brain function are subject to many factors that are not typically controlled, including early-life experiences (6) and postpartum timing and environment (7–9), as is the case for hormonal measures in parents (10,11).

Neuroendocrinology of parenting: responses to baby-cry

An archetypal parenting scenario for a new parent involves perceiving baby-cry, approaching baby, appraising the situation, determining needs such as milk, providing appropriate care such as breastfeeding, and some resolution. We suggest a neuroendocrinological model of parenting, with initial engagement of DA and OT systems, CORT to regulate the closely following stress response, and EO systems for subsequent parenting and reward (Fig. 1). Given the significant gaps in the human neuroendocrine parenting literature, although roles for OT and CORT are relatively well established, more studies are needed to clarify specific roles for DA and EO.

Neuroendocrine modulation of parenting motivation and attention

Animal studies using, for example, lesions, electrophysiology and neuroendocrine contributions to behaviours have documented maternal brain circuits that include the hypothalamus, amygdala, striatum, cingulate and prefrontal cortex (12). Such work has encouraged human neuroimaging work with parallel studies, beginning with auditory baby-cues to activate human parental brain circuits. Lorberbaum *et al.* (13) were the first group to study brain activity in mothers, in which they listened to other-baby-cries, highlighting the importance of a thalamocingulate circuit for an emotional response and regulation. Subsequently, researchers have identified a series of hypothalamic-midbrain-limbic-paralimbic-cortical brain circuits that are selectively activated during times when the maternal brain is 'switched-on' by baby-cries (4).

During the early postpartum period, increased levels of anxiety and worries in new parents, typically about their infant's safety and health, may include thoughts of reciprocity, unity and even idealised perfection of the infant, which may elevate anxiety levels (14–16). Perhaps healthy anxiety-producing thoughts that lead to

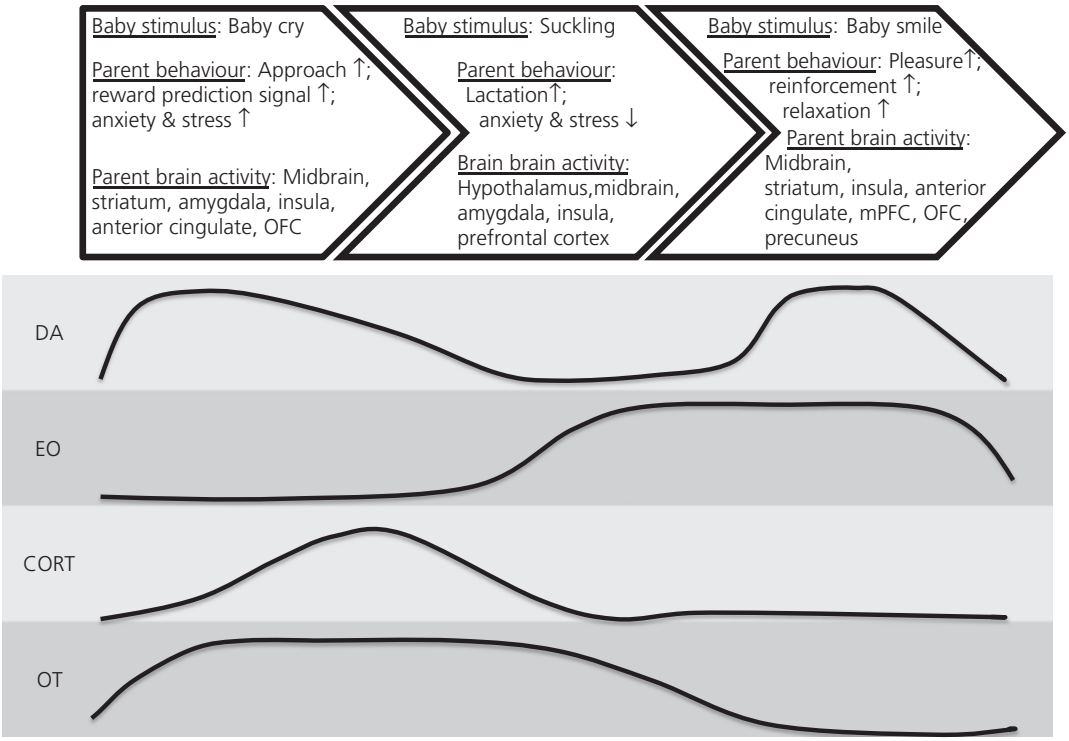

Fig. 1. An integrated neuroendocrine model of parenting. From left to right in time, the baby stimulus, behavioural response, brain activity and associated hormonal shifts of dopamine, endogenous opioids. No strict timeline for events is given. During baby-cry, dopamine may be the first to rise to assist with arousal, motivation and decision-making circuits, including striatum and amygdala. Oxytocin also rises relatively quickly with hypothalamus brain activity to support milk let-down and promote parenting behaviours. Cortisol (CORT) increases with a slower time course to support stress responses and prepare the mother for demanding behaviour depending on the reason for baby-cry and other circumstances. Assuming a simple hunger cry, CORT will start to drop first, with oxytocin next after it has performed lactation-supporting anxiety-reducing functions. Finally, the parent–infant interaction requires regulatory cortical regions of anterior cingulate, medial frontal and orbitofrontal cortices that are modulated by opioids to mediate satisfaction and reinforce caring behaviour. This may be paired with a proposed second rise in dopamine to mediate reinforcement, learning and any extended play or other dyadic interactions. Abnormalities in these neuroendocrine systems, such as in mood, anxiety or substance abuse disorders, contribute to the impaired orchestration of these parental neuroendocrine systems. DA, dopamine; EO, endogenous opioids; mPFC, medial prefrontal cortex; OFC, orbitofrontal cortex; OT, oxytocin.

frequent checking are related to parenting and infant development, (17) via brain systems under the influence of DA (18). In several human fMRI studies, responses to own- versus other-baby stimuli of first-time mothers during this early postpartum period show increased brain activity in several regions, including the orbitofrontal cortex (OFC), midbrain, striatum, cingulate, amygdala and insula (4,5,8,9,19,20). In addition to mediating DA-related anxiety and habitual behaviour and learning (21,22), some of these brain regions also serve to focus attention and promote DA-dependent attention and decision-making (23). For example, baby-cry must be analysed to determine whether it is calling for protection or food. Through reinforcement learning, action–outcome contingencies in response to baby-cries and associated environments can be optimised (24,25). Thus, in Fig. 1, we suggest that dopamine increase is among the first key neuroendocrine responses to baby-cry to focus attention and drive parental behaviour.

Neuroendocrine modulation of suckling and lactation

Provided that the baby-cry calls for milk, the mother may quickly position the infant to breastfeed. Pup-suckling triggers OT, which mediates milk ejection (26). Brain imaging in rats when pup-suckling shows activations in the paraventricular nucleus of hypothalamus, olfactory tubercle, anterior olfactory nucleus, piriform cortex, amygdala, medial preoptic area, ventral tegmentum area, insular cortex and prefrontal cortex (27). Furthermore, exogenous OT administration decreases fear behaviours of lactating rats, at the same time as increasing brain activity in emotion and cognition regulation regions, such as the anterior cingulate, and decreasing brain activity in autonomic, visceromotor and skeletomotor areas enhances neural processing in (and also modulates) emotion regulation brain circuits (28).

In humans, OT plays key roles in social bonding in general (29), as well as specific aspects of maternal brain function (30), including: (i) vaginal delivery (31); (ii) breastfeeding (32); and (iii) parental sensitivity (33–36). First, human mothers who gave birth by vaginal versus caesarean delivery were more sensitive to own- versus other-baby-cry in emotion regulation and limbic brain regions at 2–4 weeks postpartum (37). Furthermore, in response to own-baby-cry, maternal brain activity correlated with depressive symptoms in the left frontal cortex, which is a region of importance to mood dysregulation in psychiatric illness (38). This supports the controversial link between caesarean delivery and depression risk in mothers that may involve OT (39). Second, breastfeeding mothers were reported to be more sensitive to their own infants cry compared to formula-feeding mothers at 2–4 weeks postpartum (40) in emotion response and regulation brain regions, including the superior frontal gyrus, insula, precuneus, striatum and amygdala. Finally, brain activity in the superior frontal gyrus and amygdala predict maternal sensitivity at 3–4 months postpartum among these mothers (40). This fits the findings that intranasal administration of OT increases the links between social memories and reward in mothers (41), increases infant-directed sensitive play behaviours (36). Furthermore, intranasal oxytocin seems to both decrease anxiety and increase empathy circuit activity in parents responding to baby cry (42).

These studies suggest that OT may enhance parenting motivation by enhancing positive emotions and care-related brain circuits, at the same time as also attenuating negative fear and aversion circuits. This may be similar to the way in which exposure to baby faces is associated with maternal hypothalamus activation that correlates with serum OT (43) to contribute to increased reward circuitry and decrease negative social assessment circuits in maternal brains (44). This is also agreement with decreasing amygdala activation to fearful faces in healthy (45), as well as anxious (46), humans with OT administration.

Further work is required to understand the coordinated responses of structures such as the insula and amygdala (47) with oxytocin (48), which may together orchestrate competing systems toward sensitive baby-care in the initial phases of the baby-cry response. In Fig. 1, we show OT rising soon after baby-cry to regulate milk let-down and related parenting behaviours during the potentially stressful episode.

Neuroendocrine modulation parental stress

Prolonged exposure to baby-cry is stressful, placing demands on the mother to act, and triggers the hypothalamic-pituitary-adrenal (HPA) axis (49). Subsequent CORT has a complex association with maternal behaviours in humans (50). During the first few months postpartum in normal mothers, high salivary CORT levels relate to responsive behaviours, positive attitude and vocalisation toward infants during the mother–infant interaction (51). Accordingly, high CORT levels are also found among new mothers who rated infant odours more favourably (50).However, at 6 months postpartum, maternal CORT is inversely associated with sensitive maternal behaviours, including gaze to infant's face and vocalisation toward infants and OT (33,52). Along the same lines, chronically-elevated CORT levels as a result of high early-life stress may interrupt the activation of maternal brain circuits in response to infant cues. Indeed, high CORT levels among mothers who had frequent changes in their caregivers as children were associated with negative emotions and less responsive parenting (10).

Cortisol is also in complex relationships with OT-related responses. When suckling rapidly, adrenocorticotrophic hormone (ACTH) and corticosteroid secretion is stimulated in rats (53), On the other hand, plasma CORT decreases in human mothers (54), potentially through the suckling-induced OT (55) that can inhibit ACTH secretion (56). In Fig. 1, we suggest that CORT will rise after dopamine to assist with the stress responses needed for immediate concerns, as well as extended periods of caring behaviours.

Neuroendocrine modulation of post-cry parental care

Once baby-cry ceases, and lactation has occurred, the infant–mother dyad may enjoy a moment of rewarding happiness. In animal models, components of the reward system are critical for parenting. This can be probed in humans by showing happy baby visual stimuli in human neuroimaging studies. Indeed, human mothers showed a greater activity of response in the midbrain, periaqueductal grey and striatum, OFC, medial prefrontal, anterior

cingulate cortex, anterior insula and precuneus to their own- versus other-baby pictures (20,44) or videos (19,57). Furthermore, orbitofrontal cortex responses to own-baby visual stimuli correlate with ratings of pleasant mood, excitement and love that mothers may experience when viewing the stimuli (19,58).

These hedonic maternal response and behaviour-mediating brain circuits behaviours may be modulated by EO in a narrow physiological range by providing satisfaction feedback to augment reinforcement (59). Furthermore, DA (as discussed above) and EO reward systems may subserve dissociable components of rewards that may be applicable for understanding the maternal brain: a behavioural reinforcement learning component ('wanting') and a hedonic experience component ('liking'), respectively (60). In an animal study, microinjections of an opioid-stimulating drug to nucleus accumbens increased the hedonic liking impact of sucrose on behaviour and incentive salience signals in firing to the cue associated with the reward, although they did not alter firing signals to the learned reward prediction signals as part of reinforcement learning; conversely, microinjection of a DA-stimulating drug enhanced only the motivation component but did not alter hedonic impact or the learned prediction signal (61). Thus, the EO system may play a central role in the hedonic experience of a mother who, perhaps after breastfeeding, sees her baby smile, such that subsequent sensitive interactions may then be reinforced.

Although the association between the EO and maternal brain responses remains unknown in humans using direct hormone measurements, neuroimaging studies suggest that central opioid system activations (62) overlap with central maternal activations (4,5) in the mesocorticolimbic circuitry. Using PET techniques, μ-opioid neurotransmission induced by the analgesic cognitive expectations, known as placebo effects, are enhanced in the orbital frontal cortex, dorsal and rostral anterior cingulate cortex, nucleus accumbems and midbrain (63,64). Furthermore, analgesic placebo effects are mediated by the co-activation of DA and opioid neurotransmission in the ventral striatum (including the nucleus accumbens) (63), highlighting the potential interactions between DA and EO in the mesolimbic reward circuitry.

Additionally, EO contributes to maternal euphoria and the inhibition of stress-related HPA reactivity to protect the foetus in the late-gestation (65) and lactation phases (65). Overall, EO serve as mediator of social rewards, affiliation, motivation and attenuation of separation-induced pain and anxiety (66), such that a phenomenological resemblance between narcotic addiction and social attachment has been proposed: both display an initial attachment phase, a tolerance-development phase and similar symptoms upon withdrawal (67). This is consistent with the idea that exogenous opiates may commandeer maternal motivation to seek and care for their baby (68). Indeed, the sensitive and powerful interactions between EO and DA in central reward circuitry render narcotic addictions very difficult to treat, potentially by intertwining addiction with primal social attachment needs. In Fig. 1, we illustrate EO as rising with the satisfaction of attending to baby, presuming the cessation of baby-cry, breastfeeding behaviours. We speculate that EO levels may remain elevated to support the pro-social sensitive parenting behaviours that may follow.

Summary, discussion and new directions

Human parent brain responses to baby stimuli were reviewed to be largely in agreement and to build upon largely subcortical animal models, including reward circuits (midbrain, nucleus accumbens, amygdala, OFC, anterior cingulate cortex, insula) and social cognition regions (medial prefrontal cortex, superior temporal gyrus, OFC). A selection of the emerging complex literature is discussed to support modulatory roles for the key neurohormones (DA, OT, CORT and EO). Evidence for the importance for OT and CORT in human parental response to baby-cry is well established in human mothers. However, there are many gaps in the literature with respect to DA and EO in humans. Future approaches combining brain imaging and endocrine measurements (e.g. plasma or salivary CORT and OT) and/or acute endocrine manipulation [e.g. exogenous CORT and OT (intranasal OT spray)] may reveal how these hormones interact with each other to modulate parental brain and behaviour. In addition, more ethologically valid stimuli are required to better simulate a real parenting situation, such as interactive audiovisual stimuli that may be personally tailored or involve decision-making, and such studies may prove to be enlightening.

Also, joint consideration of brain circuit and endocrine regulation may be particularly important for understanding special populations of parents, such as mothers under the influence of exogenous endocrine modulators or suffering from endocrine dysregulation that comprises part of a psychiatric condition. For example, mothers with substance abuse problems may have alterations in their brain circuitry and EO systems (69) that render them vulnerable to maladaptive maternal behaviours in the post-partum period. This could be studied in a somewhat controlled fashion in women with opiate addictions who are treated with controlled doses of methadone or buprenorphine maintenance to prevent miscarriage, with the aim of understanding how these substances affect striatum-dependent maternal responses, reward and affiliation processes, as well as how any adverse effects can be mitigated.

Thus, combining brain imaging approaches with psychological measures and interventions in parents may begin to address significant public health issues of other peripartum mental health problems, such as postpartum depression, anxiety and low socioeconomic status, by developing specific mechanistic models that could provide more effective management strategies. In the first study of brain activity in clinically depressed mothers, frontal executive function regions were less sensitive to a standard face-matching task (70). Furthermore, there was an inverse relationship between depression and the amygdala response to negative faces, as well as a significantly reduced left dorsomedial prefrontal cortical face-related activity in response to fear and anger faces. Also, very recently and in the first study of clinically depressed mothers using own-baby-cry, the brain response was essentially eliminated by depression in a distributed network of paralimbic and prefrontal regions, which displayed an inverse correlation between response and depression severity, including function in prefrontal areas and the striatum (71). Taken together with known variations in frontal cortex activity in mothers as a function of depression symptoms (37), it appears that postpar-

tum depression affects the cortical–amygdala connections that are important for mood regulation and motivation, thus impairing parenting. Neuroendocrine brain systems under the influence of anxiety and other adverse circumstances around parenthood, such as poverty (72,73), also remain to be studied.

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