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REVIEW

Using animal models to study post-partum psychiatric disorders

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The post-partum period represents a time during which all maternal organisms undergo substantial plasticity in a wide variety of systems in order to ensure the well-being of the offspring. Although this time is generally associated with increased calmness and decreased stress responses, for a substantial subset of mothers, this period represents a time of particular risk for the onset of psychiatric disorders. Thus, post-partum anxiety, depression and, to a lesser extent, psychosis may develop, and not only affect the well-being of the mother but also place at risk the long-term health of the infant. Although the risk factors for these disorders, as well as normal peripartum-associated adaptations, are well known, the underlying aetiology of post-partum psychiatric disorders remains poorly understood. However, there have been a number of attempts to model these disorders in basic research, which aim to reveal their underlying mechanisms. In the following review, we first discuss known peripartum adaptations and then describe post-partum mood and anxiety disorders, including their risk factors, prevalence and symptoms. Thereafter, we discuss the animal models that have been designed in order to study them and what they have revealed about their aetiology to date. Overall, these studies show that it is feasible to study such complex disorders in animal models, but that more needs to be done in order to increase our knowledge of these severe and debilitating mood and anxiety disorders.

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Abbreviations
BDNF, brain-derived neurotrophic factor; CORT, corticosterone; CRH, corticotrophin-releasing hormone; FSL, Flinders sensitive line; HAB, high anxiety-related behaviour; HPA axis, hypothalamus–pituitary–adrenal axis; HSP, hormone-simulated pregnancy; LAB, low anxiety-related behaviour; LH, learned helplessness; PPD, post-partum depression; PVN, paraventricular nucleus of the hypothalamus

Introduction

The post-partum period represents a time of profound physiological and emotional changes in all maternal organisms in order to ensure the well-being and nurturance of the offspring. These alterations are wide ranging and include the onset of maternal behaviour, lactogenesis, as well as increased calmness and a reduced response to stress. However, in a large subset of mothers, this phase also represents a risk period for the development of several psychiatric disorders. Such post-partum mood and anxiety disorders are particularly damaging because they not only affect the well-being of the mother but also disadvantage the development of the infant as well, increasing their likelihood of developing a psychiatric disorder in later life (Weinstock, 2001; Newport *et al.*, 2002; Davalos *et al.*, 2012). Several post-partum disorders have been described and include post-partum depression (PPD), post-partum anxiety and post-partum psychosis. A number of risk factors have been identified that increase the likelihood of a mother developing such a disorder. However, due in part to a lack of research and the male-orientated preclinical research focus, the underlying aetiology of these disorders remains poorly understood. In contrast, numerous peripartum-associated adaptations have been well characterized and interference with them or assessment of how these changes are affected by manipulations that resemble the identified

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risk factors may help to understand post-partum disorders. In the following review, we first describe normal peripartum-associated changes, then provide a definition of post-partum disorders, including their risk factors and prevalence and, finally, describe animal models that can be used to study these severe illnesses.

Known post-partum maternal adaptations

In all mammalian species, the peripartum period is associated with profound adaptations in maternal neuroendocrinology, behaviour and physiology. As numerous excellent reviews are available (e.g. Neumann, 2003; Brunton *et al.*, 2008; Slattery and Neumann, 2008; Leuner *et al.*, 2010; Bosch and Neumann, 2012; Workman *et al.*, 2012), we only provide a brief description of the main peripartum changes that are relevant for the remainder of the review. Although the majority of these findings have come from rodent studies, the measures that can also be easily assessed in humans have shown patterns similar to those described in rodents.

The hypothalamic–pituitary–gonadal and hypothalamic–pituitary–adrenal (HPA) axes are particularly affected in the peripartum period due to their primary roles in reproductive functions and stress responses respectively. Peripartum-associated alterations in circulating sex steroid levels have been predominantly studied in rodents, but the pattern observed reflects the situation in most mammalian species, particularly for oestrogen (Rosenblatt *et al.*, 1988). Specifically, oestrogen and progesterone, the main female sex steroids, progressively increase during pregnancy to levels 50- and 10-fold higher than observed in virgins, respectively, and rapidly reverse to their pre-pregnancy levels within a few days of parturition. These levels remain low during the first half of lactation and begin to increase when follicular maturation starts again (approximately 10 days in rodents and until a monthly cycle resumes in women – which can take up to 180 days) (Bridges, 1984; Brunton and Russell, 2010). In contrast, the progesterone profile differs between women and rodents, as it remains low throughout lactation in women but increases to levels observed in late pregnancy by the third day of lactation in rats (Grota and Eik-Nes, 1967; Taya and Greenwald, 1982; Rosenblatt *et al.*, 1988; McNeilly, 2001).

The HPA axis also shows profound peripartum plasticity with increased basal levels of plasma glucocorticoids (cortisol in humans and corticosterone in rodents, hereafter referred to as CORT) observed, despite limited alteration in the level of their main secretagogue, adrenocorticotropic hormone (ACTH) (Atkinson and Waddell, 1995). In parallel, the response to a wide variety of stressors is attenuated in rodents and women, particularly in woman who breastfeed (Johnstone *et al.*, 2000; Heinrichs *et al.*, 2001; Kammerer *et al.*, 2002; Deschamps *et al.*, 2003). These adaptations are mediated, at least in part, via alterations in the corticotrophin-releasing hormone (CRH) and vasopressin systems. Thus, increased neuronal vasopressin expression within the paraventricular nucleus of the hypothalamus (PVN) (Walker *et al.*, 2001), together with an enhanced pituitary sensitivity to vasopressin (Toufexis *et al.*, 1999), may contribute to sustain the high basal level of HPA axis activity found in lactation. In contrast, decreased CRH mRNA within the PVN in late pregnancy (Johnstone *et al.*, 2000) and lactation (Fischer *et al.*, 1995), decreased median eminence CRH content in late pregnancy (Ma *et al.*, 2005), together with reduced pituitary CRH receptor binding from mid-pregnancy (Neumann *et al.*, 1998), reflect changes that have been speculated to contribute to maternal stress hyporesponsiveness (Slattery and Neumann, 2008).

Further evidence for PVN plasticity, in terms of a reduction in excitatory – and enhancement of inhibitory – inputs, is also well documented. In more detail, expression of α_{1D}-adrenoreceptor mRNA in the hypothalamus of lactating rats was found to be reduced by almost 40% in comparison to virgins (Toufexis *et al.*, 1998), whereas i.v. injection of naloxone, an opioid antagonist, was shown to prevent the pregnancy-related attenuation in stress-related CORT secretion (Douglas *et al.*, 1998). In addition to their role in lactogenesis and maternal behaviour, the neuropeptides, oxytocin and prolactin, have also been shown to effect stress responsivity in the peripartum period. Thus, oxytocin and oxytocin receptor expression in the PVN (Zingg *et al.*, 1995; Figueira *et al.*, 2008), as well as central oxytocin release (Neumann and Landgraf, 1989; Neumann *et al.*, 1993), are increased in the peripartum period and have been implicated in the stress and anxiolytic phenotype observed in this period (Neumann, 2003; Brunton *et al.*, 2008). Expression of prolactin and its receptor is also enhanced in lactation, and infusion of an antisense oligonucleotide to decrease receptor expression was shown to increase anxiety and stress-related ACTH levels in lactating dams (Torner *et al.*, 2002). Moreover, breastfeeding has been demonstrated to increase plasma prolactin and oxytocin levels in women (Chiodera *et al.*, 1991; Nissen *et al.*, 1996), which is likely to be mirrored within the brain (Neumann and Landgraf, 2012). Breastfeeding mothers have been shown to display a reduced CORT response to an acute stressor compared with non-breastfeeding mothers (Heinrichs *et al.*, 2001), and high circulating prolactin levels in breastfeeding women have been associated with hypo-anxiety (Asher *et al.*, 1995). All of these changes appear to act in concert to reduce PVN activation to stress exposure, as a marked reduction in stress-induced *c-fos* expression was observed in this region in late pregnancy compared with mid-pregnancy (Windle *et al.*, 2010). A similar pattern between pregnant and lactating rats was also detected in extrahypothalamic regions compared with virgins, including the medial amygdala and lateral septum, which are both regions that can influence PVN activity (da Costa *et al.*, 1996).

It is also interesting to note that central monoamine levels are altered across the peripartum period, given the monoamine theories of depression and the fact that all approved antidepressants act on these transmitter systems (Slattery *et al.*, 2004). Thus, dopamine, noradrenaline and 5-HT levels are 30–88% lower in the prefrontal cortex, whereas noradrenaline levels are higher in the CA1 and CA3 regions of the hippocampus, of pregnant rats when compared with virgins (Macbeth *et al.*, 2008). Dopamine and GABA levels were shown to be altered even during lactation in the medial prefrontal cortex, with basal levels being higher in rats at early lactation (from day 1 to day 3) compared with virgins

(Arriaga-Avila *et al.*, 2013). However, the studies performed so far have been limited to specific brain regions and neurotransmitters, which impede our understanding of the overall changes across pregnancy and lactation. On the contrary, hippocampal morphology is known to undergo post-partum re-organization, with changes in dendritic structure and spine density observed in the CA1 and CA3 regions of the hippocampus (Pawluski and Galea, 2006; 2007). Moreover, it has recently been demonstrated that hippocampal neurogenesis is altered during the peripartum period, with a decrease in cell proliferation observed during the first post-partum weeks. Interestingly, this phenomenon has been correlated with the presence of the pups and the high basal plasma CORT levels observed at this time (Leuner *et al.*, 2007; Levy *et al.*, 2011). Besides decreased cell proliferation in the dentate gyrus of primiparous and multiparous rats during the early post-partum period, cell survival in the dentate gyrus was also shown to be decreased in primiparous rats, regardless of pup exposure. This gives rise to the hypothesis that these effects are not ascribable to pregnancy or pup exposure alone (Pawluski and Galea, 2007). These changes finally converge to result in alteration of brain circuitries required to enable the 'peculiar' peripartum behavioural phenotype of the mother – since care of young generally does not occur in virgins of most species (except humans). Maternal behaviour may be described as the behavioural set that mothers display in order to feed, protect, warm and take care of the litter (Fleming and Rosenblatt, 1974). However, as well as the display of behaviours directly addressed to care for the offspring, pregnant and lactating females also show altered emotional and cognitive phenotypes. Indeed, rodent mothers, when exposed to unfamiliar intruders in the home cage during the maternal defence test, are more aggressive than virgin females (Neumann *et al.*, 2001; Bosch and Neumann, 2012). Moreover, the previously mentioned changes in cell survival and proliferation were reported to correlate with behavioural readouts in rats when tested for spatial performance with dams showing impaired learning after delivery, whereas spatial-retention ability was improved 2 weeks later compared with nulliparous rats (Darnaudery *et al.*, 2007). Additionally, pregnant rats have been shown to perform better than virgins when tested for spatial memory during the first two trimesters of pregnancy (Galea *et al.*, 2000). These studies showing that maternal memory is impaired in the last trimester of pregnancy and after birth in the rat (Galea *et al.*, 2000; Darnaudery *et al.*, 2007) mirror those from human studies, revealing that verbal recall memory (but not recognition or working memory) is diminished during human pregnancy and after parturition (Glynn, 2010).

The decreased activity of the HPA axis during the peripartum period already mentioned may relate to the enhanced calmness that characterizes the maternal period (Altemus *et al.*, 1995). Indeed, several studies reported that anxiety-related behaviour is decreased in lactating rodents (Fleming and Luebke, 1981; Neumann, 2001; Wartella *et al.*, 2003; Hillerer *et al.*, 2012). In contrast, in mid- to late pregnancy, there are findings showing increased anxiety-related behaviour compared with virgin rats (Pawluski *et al.*, 2011).

All of the changes described earlier are essential to ensure the proper development and nurturance of the offspring. However, there is growing evidence that these changes may also be vital for the well-being of the mother, considering that the previously described peripartum-associated plasticity involves systems whose dysregulation is known to participate in the aetiology of mood disorders such as depression and anxiety, that is, the monoaminergic systems and the HPA axis [for the interested reader, we recommend the following reviews, which explore the role of these systems in mood disorders (Slattery *et al.*, 2004; Swaab *et al.*, 2005; Ising *et al.*, 2007; Krishnan and Nestler, 2008; Slattery and Neumann, 2008; 2010b; Neumann and Landgraf, 2012)].

Post-partum mood disorders

Although decreased anxiety and stress reactivity are common peripartum changes, the post-partum period also represents a period of susceptibility to develop mood and anxiety disorders, which can be divided into four main groups. The most common, and least severe, is 'post-partum blues', which affects between 30 and 75% of mothers within the first 2 weeks after delivery. The 'blues' are characterized by changeable mood with crying and other symptoms, including feeling of confusion and sleep disturbances often observed. Post-partum blues often resolve spontaneously within 2 weeks without negative consequences for the mother or child (Seyfried and Marcus, 2003). PPD is more serious for both the mother and the offspring (O'Connor *et al.*, 2002; Deave *et al.*, 2008) and represents an episode of major depression with a specific temporal manifestation, which is still under debate. Currently, the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders sets the first 6 months post-partum as the period at risk for developing PPD, which occurs in 10–22% of mothers, often as a result of a long-lasting 'blues' episode (O'Hara and McCabe, 2013). The majority of the symptomology associated with PPD is indistinguishable from other depressive episodes (Cooper *et al.*, 1988); however, a distinguishing feature is the loss of interest in the infant, which can often present as the mother finding infant stimuli aversive (Adamakos *et al.*, 1986; Bifulco *et al.*, 2004). Psychological and/or pharmacological treatment is often required for these disorders amid several concerns regarding the use of antidepressants during breastfeeding (O'Hara and McCabe, 2013). However, given the importance of breastfeeding, particularly during the first 6 post-natal months, it is preferable that women continue with their medication. This is also due to the fact that there is little transfer of newer antidepressants to the infant via the milk and that they do not appear to be associated with serious adverse events, although longer term studies are required (Chad *et al.*, 2013). Moreover, pharmacological treatment may improve maternal mood, which, in turn, positively affects the infants (Gentile, 2005). Maternal anxiety during the post-partum period may also be pathological (Lonstein, 2007), when there is no specific reason for its appearance, or when the intensity and duration of the symptoms are disproportional to the situation that elicits the episode (Correia and Linhares, 2007) and is often observed in woman with PPD (Ross *et al.*, 2003). However, there is evidence to suggest that it can exist as a separate disorder and it has been speculated that it may even display a higher prevalence than PPD (Wenzel *et al.*, 2005). Therefore, it is important to consider and study these two

pathologies separately. Mothers with post-partum anxiety show bidirectional parenting styles, with one subset showing reduced coping and reactivity to the infant and a second group showing a highly protective maternal style, often termed 'helicopter parenting' (Bridges, 2008). Post-partum psychosis is probably the most serious post-partum illness and has a prevalence of between 0.1 and 0.5% in mothers. It has been hypothesized to be a feature, or even be a subset, of bipolar or schizoaffective disorder and it may culminate with suicide or infanticide; thus, mothers must be hospitalized for their own and their child's well-being (Appleby *et al.*, 1998).

Although described separately, there is substantial overlap in the symptomology of these disorders (with the 'blues' not actually representing a psychiatric disorder), and therefore, they can be considered as continuum with overlapping symptomology in terms of diagnosis and treatment. Although the direct causes for these disorders unfortunately still remain unclear, predisposing and risk factors have been identified, which are discussed next.

Risk factors for the development of post-partum mood and anxiety disorders

The main predictor for depressive, anxiety or psychotic diseases after delivery is an antenatal episode of the illness (Rich-Edwards *et al.*, 2006; Grant *et al.*, 2008; Topiwala *et al.*, 2012). However, other environmental factors have been shown to increase the likelihood for the development of a post-partum psychiatric disorder, including drug abuse (Beck, 2006; Friedman and Resnick, 2009) and low socioeconomic status (Soderquist *et al.*, 2009). Marital problems have also been described as moderate risk factors for the development of PPD (Beck, 2001), whereas obstetric pregnancy-related complications, such as Caesarean section or instrumental delivery, are classified as low risk factors (Warner *et al.*, 1996; Johnstone *et al.*, 2001). One of the most convincing, and translational, risk factors is chronic psychosocial stress during the peripartum period (Robertson *et al.*, 2004), which is in agreement with the fact that women exhibit a higher susceptibility to stress-related illnesses, such as mood and anxiety disorders than men, in general (Kessler, 2003). In keeping, emotional support during pregnancy has been shown to negatively correlate with depression (Beck, 1996). Finally, the dramatic fluctuations in sex steroid levels and in the HPA axis activity, which occur across the peripartum period, may play a role in these post-partum psychiatric disorders (Bloch *et al.*, 2000; 2005; Hillerer *et al.*, 2012).

Animal models to study post-partum psychiatric disorders

In the next section, we describe the preclinical approaches that have been taken to model such post-partum disorders. These have been predominantly performed in rodents, but wherever possible, comparisons to human findings are provided. Such complex psychiatric disorders are unlikely to be mimicked in their entirety in an animal model. However, assessment of manipulations that resemble the known risk factors, or to systems that are known to alter during the peripartum period, is likely to lead to a greater understanding of the aetiology of post-partum psychiatric disorders.

Pseudo-pregnancy models: assessing the role of fluctuating hormones in post-partum disorders

The prevalence of mood disorders is higher in women compared to men, which has led to the speculation that circulating gonadal steroids may play an important role in these disorders (Fernandez-Guasti *et al.*, 2012). The fact that mood disorders are particularly prevalent during the post-partum period gives further support for this hypothesis (O'Hara *et al.*, 1983; Abou-Saleh *et al.*, 1998; Marcus, 2009). In addition, other phases characterized by large hormonal fluctuations, or even withdrawal-like states, such as the pre- and post-menopausal periods, respectively, are also times of increased susceptibility to psychiatric disorders, thus strengthening the hypothesis of a pivotal role of hormones in the aetiology of such diseases (Johnson, 1987; Halbreich and Kahn, 2001). Moreover, it was shown that the cortisol response to ovine CRH administration was higher in woman with a history of PPD, compared with controls, when they received supra-physiological doses of gonadal steroids (Bloch *et al.*, 2005) and that such women show more labile mood after withdrawal from the steroids (Bloch *et al.*, 2000).

The rapid decline in oestrogen levels after delivery has been particularly implicated in the development of post-partum mood disorders in susceptible women (Vaha-Eskeli *et al.*, 1992; Fink *et al.*, 1996; Hendrick *et al.*, 1998). However, many studies have attempted to repeat these findings and their conclusions are inconsistent at best (see Abou-Saleh *et al.*, 1998; Gentile, 2005). Although some studies have indicated that administration of a high oestrogen bolus shortly after parturition could reduce the risk of relapse of a psychiatric disorder (Sichel *et al.*, 1995) and depressive symptoms (Gregoire *et al.*, 1996) in mothers, the majority of such studies have a number of limitations, and better designed clinical trials are required to examine the putative beneficial effect of oestrogen in more detail (Gentile, 2005). Moreover, high post-partum oestradiol levels are known to hinder breastfeeding, which discouraged its potential use as therapeutic agent (Kochenour, 1980). Contrastingly, treatment with progesterone in females even appears to be detrimental. Thus, studies have found an association of progesterone treatment with higher PPD scores than placebo (Lawrie *et al.*, 2000; Dennis *et al.*, 2008). Moreover, Wagner (1996) reported that subdermal progesterone implantation, for contraceptive purpose, was associated with major depression and a broad spectrum of anxiety-related disorders in women who had no prior psychiatric history. Thus, animal models employing hormone-simulated pregnancy (HSP; also called pseudo-pregnancy) have been utilized to determine how the dramatic hormonal fluctuations affect behaviour and physiology

in more detail. This approach allows the investigation of the specific consequences of hormonal withdrawal, although it clearly does not mimic the complete situation in the post-partum period. In addition to the advantage of HSP being a suitable method to focus upon the involvement of sex steroid withdrawal in the aetiology of post-partum mood disorders, HSP may also exacerbate pathological manifestations that may otherwise be difficult to approach with studies performed with intact animals.

Galea *et al*. (2001) established a HSP model in rats, in which ovariectomized animals received daily s.c. injections for 16 consecutive days of a low oestradiol benzoate (2.5 μg) in combination with high progesterone (4 mg) dose. From day 17 to day 23, the oestradiol benzoate dose was increased (50 mg) to mimic the levels observed in pregnancy. The control group was injected with sesame oil throughout the whole experiment. Depressive-like behaviour was assessed in this study using the forced swim test; the most commonly used preclinical test to assess depression-like behaviour/antidepressant action (Slattery and Cryan, 2010). Three days after hormone withdrawal, animals displayed more immobility behaviour in the forced swim test, suggesting that HSP withdrawal results in a depressive phenotype (Galea *et al*., 2001), a finding that was confirmed by Stoffel and Craft (2004). Interestingly, when oestradiol administration was continued, the depressive-like phenotype was absent, suggesting that oestradiol withdrawal is behind the depressive-like phenotype. These changes were not the result of general alterations in locomotor activity, which can often be a confounding factor in the swim test, as HSP animals even showed higher locomotion than animals that continuously received oestrogen or the controls in the open-field test (Galea *et al*., 2001). Moreover, HSP withdrawal also decreased sucrose consumption 2 days after withdrawal compared with the last days of HSP, although in this instance oestrogen supplementation was unable to reverse this deficit (Green *et al*., 2009). Sucrose consumption/preference is a test commonly used to assess anhedonic-like behaviour, a core symptom of depression, in rodents due to its high reward value (Cryan and Slattery, 2007). More recently, Schiller *et al*. (2013) examined the effect of low- or high-dose oestradiol withdrawal on depression-like behaviour in ovariectomized rats on intra-cranial self-stimulation responding and forced swim test behaviour. The results demonstrated that withdrawal from the high dose caused anhedonic-like behaviour, as indicated by reduced self-stimulation responses and depressive-like behaviour in the forced swim test. Oestrogen withdrawal after HSP was also shown to affect cell death in the hippocampus. Specifically, hormonal withdrawal was accompanied by increased hippocampal cell death as assessed 4 days after withdrawal (Green and Galea, 2008).

Navarre *et al*. (2010) investigated the effect of a HSP protocol, similar to that described previously, and normal pregnancy on sucrose preference. Interestingly, HSP animals displayed decreased sucrose preference compared with the control group when exposed for the first time to the sucrose solution, whereas intact mothers did not differ from the respective virgin group on post-partum day 2. The fact that the preference differed only on the first day of testing suggests that hormonal withdrawal may induce deficits in the behavioural response to novelty, although baseline differences in sucrose preference may have contributed to these findings (Navarre *et al*., 2010).

In contrast to the findings of Galea *et al*. (2001), HSP in mice was reported to lead to decreased immobility in the forced swim test. However, this was assessed 7 days after withdrawal and the mice showed increased escape failures in a learned helplessness (LH) paradigm (Suda *et al*., 2008), a widely used model of depression (Cryan and Slattery, 2007), where such a deficit is indicative of a depressive-like phenotype. This is one of the few studies investigating post-partum disorders to assess multiple behavioural and molecular consequences simultaneously. Thus, the authors suggested a number of candidate genes whose transient modulation may underlie the behavioural phenotype, which included brain-derived neurotrophic factor (BDNF) and the 5-HT transporter (Suda *et al*., 2008). Taken together, these studies suggest that oestrogen withdrawal leads to a depressive-like phenotype, particularly with respect to anhedonia, and alterations in hippocampal cell death. Therefore, HSP represents a valid approach for studying certain aspects of post-partum psychiatric disorders. It would be of interest to determine the behavioural consequences of progesterone withdrawal in such models, which, to the best of our knowledge, has not been performed to date.

HPA axis-based approaches

As previously mentioned, profound changes in the HPA axis function around birth have been documented in several species and include stress hyporesponsiveness and elevated basal activity (Allolio *et al*., 1990; Neumann *et al*., 1998; Shanks *et al*., 1999; Carter *et al*., 2001; Heinrichs *et al*., 2001; 2002; Kammerer *et al*., 2002; Douglas *et al*., 2003; Neumann, 2003). In more detail, plasma CORT was reported to be elevated in mice and rats from mid-pregnancy to mid-lactation (Atkinson and Waddell, 1995; Douglas *et al*., 2003; Hillerer *et al*., 2011). In rodents, circulating CORT begins to decline around lactation days 15–18, probably as a consequence of the reduced necessity for maternal behaviour as the offspring become more independent and begin to ingest solid food (Voogt *et al*., 1969). Mood disorders are often characterized by altered HPA axis activity (Ising *et al*., 2007). Indeed, a subgroup of depressed patients show disturbed CORT diurnal rhythms and increased resistance to the feedback action of glucocorticoids (Herbert, 2013). More pertinently, mothers suffering from PPD have been reported to show an attenuated physiological morning rise in CORT (Taylor *et al*., 2009) and a lack of correlation between ACTH and CORT release elicited by maximal treadmill exercise, such as observed in healthy individuals (Jolley *et al*., 2007).

Therefore, animal models, designed to interfere with the HPA axis function during the post-partum period, have been extensively utilized to determine whether these normal alterations in HPA axis function, and/or their perturbation, may be associated with post-partum mood and anxiety disorders. These studies fall into two main categories; direct manipulation via exogenous CORT administration and repeated stress paradigms.

CORT-based models

Brummelte and Galea (2010) designed a paradigm with which to study the effects of chronic hyper-CORT levels during lactation on the behavioural phenotype of the dam. Specifically, animals received daily CORT injections (40 mg·kg^{-1}) from the day after parturition until lactation day 26, to maintain the high levels found in pregnancy. In this study, maternal care was scored from lactation day 2 to day 8, depressive-like behaviour was assessed on lactation days 24–25 in the forced swim test and, finally, anxiety-like behaviour was tested in the open-field test. Dams that received CORT injections were characterized by deficits in maternal care as they spent less time nursing their pups and a depressive-like phenotype as indicated by increased immobility in the forced swim test compared with control (sesame oil) mothers. Although performance in the open-field test did not differ between the groups, it is possible that performing the swim test on the two prior days may have masked any behavioural difference (Brummelte *et al.*, 2006). In a study of CORT administration during pregnancy and/or lactation at low (10 mg·kg^{-1}) or high (40 mg·kg^{-1}) doses, both low and high CORT injected throughout pregnancy and lactation were demonstrated to reduce nursing behaviour from lactation day 2 to day 8 (Brummelte and Galea, 2010). However, differences in depressive-like behaviour were only observed in dams treated post-partum with the higher CORT dose (Brummelte and Galea, 2010). These findings on maternal behaviour and depressive-like behaviour were reproduced in a more recent study (Workman *et al.*, 2013). In keeping with these findings from rodents studies, female marmosets injected with CORT concentrations designed to mimic the circulating levels observed following stress exposure showed decreased maternal behaviour, as indicated by reduced pup carrying (Saltzman and Abbott, 2009).

Moreover, assessment of CORT effects on hippocampal cell proliferation showed that dams injected with low and high CORT doses post-partum and with the high dose exclusively during pregnancy or throughout pregnancy and lactation were characterized by reduced cell proliferation and reduced density of newly generated cells in the granule cell layer area and in the subgranular zone of the dentate gyrus (Brummelte and Galea, 2010). Moreover, a recent study demonstrated that post-partum CORT administration reduced dendritic complexity and increased the density of mushroom spines of hippocampal CA3 arbours (Workman *et al.*, 2013).

Therefore, to date, high CORT levels have been shown to impair maternal behaviour and hippocampal plasticity, although more studies are required to verify this and to determine its impact on other parameters.

Stress-based models

Repeated/chronic psychosocial stress during pregnancy represents one of the most prominent risk factors for the development of post-partum mood disorders and numerous studies have investigated the effect of stress exposure on the dam. However, the vast majority of studies in which maternal stress is employed are used almost exclusively to examine the consequences of early life stress (e.g. gestational and/or preweaning) on the offspring given the association between early trauma and increased risk for anxiety and depression disorders, schizophrenia and substance abuse in later life (see Weinstock, 2001; Meaney *et al.*, 2002; Heim *et al.*, 2004). Indeed, maternal stress may affect the offspring both directly and indirectly when maternal physiology and/or behaviour is altered. There is also the complication that different stressors are effective in male and female rodents, which is particularly true of social stress paradigms that are believed to more accurately mimic the human situation (Cryan and Slattery, 2007; Reber, 2012). For example, although resident–intruder paradigms work well in male rodents, in order to be effective in females, lactating dams, with their increased level of aggression, have to be employed (Neumann, 2001; Neumann *et al.*, 2005). Physical stressors, such as repeated restraint stress or chronic mild stress paradigms, have been shown to be effective stressors during the peripartum period (Hillerer *et al.*, 2011).

One of the most examined systems after peripartal stress exposure is the HPA axis for obvious reasons. Although these studies consistently reveal changes in the normal peripartum-associated adaptations, these differ depending upon the stressor and species used. Mice that were subjected to a chronic mild stress paradigm throughout pregnancy were shown to have elevated CORT (and oestrogen levels) when assessed at mid-pregnancy; however, this increase was no longer significant in lactation compared with controls (Misdrahi *et al.*, 2005). Exposure to a psychosocial stress model designed in our laboratory, which combined alternating days of restraint stress and days of overcrowding with unknown females between pregnancy days 4 and 16 – resulting in chronic social instability as well, prevented the lactation-associated plasma basal hyper-CORT levels in mid-lactation in rat dams (Hillerer *et al.*, 2011). Interestingly, this alteration in CORT was not accompanied by a difference in ACTH levels, which is in keeping with the findings of mothers with PPD who lack the CORT awaking response and show an imbalance in stress-induced ACTH and CORT levels (Jolley *et al.*, 2007; Taylor *et al.*, 2009). Although our stress paradigm did not affect lactation-associated stress hyporesponsiveness, repeated strobe-light stress throughout pregnancy and in lactation resulted in an enhanced CORT response to stress in the afternoon compared to the morning (Leonhardt *et al.*, 2007). Further, rats exposed to repeated restraint stress between pregnancy day 10 and day 20 were observed to exhibit enhanced acute stress-induced ACTH and CORT secretion in lactation (Smith *et al.*, 2004). Therefore, it appears that depending upon the stress paradigm employed, different effects on peripartum-associated HPA axis adaptations can be observed.

Repeated stress has also been shown to affect maternal care, with repeated restraint stress between pregnancy day 4 and day 14, decreasing both maternal aggression and pup retrieval in mice (Maestripieri *et al.*, 1991). The latter effect was also observed following a chronic mild stress paradigm throughout the whole pregnancy period, in which mice were exposed to a variety of mild stressors, such as cage tilt and alterations in the light/dark cycle (Pardon *et al.*, 2000). Basic maternal care in the home cage was not affected by this paradigm but chronic stress exposure has been shown to bidirectionally affect kyphotic nursing, the most active form of nursing in rodents. Thus, repeated restraint stress, as well

as exposure to CORT (see previous discussion), has been shown to decrease this form of nursing (Smith *et al.*, 2004; Brummelte and Galea, 2010). Exposure of dams to a daily chronic social stress paradigm, composed of placing a similar-sized male into the dam's home cage between postnatal day 2 and day 16, was also shown to result in reduced maternal care compared with non-stressed dams (Nephew and Bridges, 2011; Murgatroyd and Nephew, 2013). Further, Kurata *et al.* (2009) subjected dams to an inescapable shock on post-natal day 3 and assessed the number of escape attempts 24 h later and classified dams as non-LH or LH. Interestingly, LH dams were shown to have reduced levels of active nursing behaviour until mid-lactation, which suggests that the LH paradigm may be a useful model to study PPD. Similar findings have also been observed in gorillas and baboons, where highly perceived levels of stress are associated with decreased care of the infants (Bahr *et al.*, 1998; Brent *et al.*, 2002). In our psychosocial stress paradigm, however, stressed dams displayed increased kyphotic nursing in the early lactation phase (Hillerer *et al.*, 2011). Repeated/chronic stress was reported to increase both anxiety- and depression-like behaviour in the post-partum period. In our model, chronic stress exposure prevented lactation-associated anxiolysis (Hillerer *et al.*, 2011) and, similarly, alternation of restraint and novel environment stress from early-to-late pregnancy increased anxiety-related behaviour on post-natal day 6 (Maestripieri *et al.*, 1991). Moreover, exposure to repeated restraint stress performed during the last week of pregnancy was shown to increase anxiety behaviour in the dam when tested 26 days after the last stress exposure (Darnaudery *et al.*, 2004). Repeated restraint stress has also been shown to increase depressive-like behaviour in the dam up to post-partum day 22 (Smith *et al.*, 2004; O'Mahony *et al.*, 2006) but not afterwards (days 35 and 36 post-stress) (Darnaudery *et al.*, 2004). However, others have reported unaltered depressive-like behaviour when pregnant animals were tested on day 3 post-stress (Pawluski *et al.*, 2011), suggesting that the time of testing may be of importance. Of note, the $GABA_A$-δ receptor subunit may be particularly involved in a depressive-like phenotype in lactation, as this receptor subunit undergoes substantial plasticity in the peripartum period. Mice lacking the receptor only display depressive-like behaviour, in both the forced swim test and the sucrose preference test, during the post-partum period, suggesting a specific temporal association between this receptor subtype and PPD. Interestingly, these mice also display poor maternal care (Maguire and Mody, 2008). However, whether stress modulates this receptor in the peripartum period is currently unknown. Finally, repeated restraint stress throughout the last week of pregnancy has been shown to prevent the increase in spatial memory observed in mothers 16 months later (Lemaire *et al.*, 2006). This not only suggests that stress during pregnancy has long-lasting consequences for the mother but that more studies should address which such long-term consequences may arise.

Taken together, manipulation of the HPA axis via CORT administration or chronic stress paradigms has repeatedly been shown to affect maternal behaviour and emotion. However, unlike HSP, the outcome appears to be heavily reliant upon the model employed and, therefore, makes comparison across the different studies more complicated.

High-fat diet-based models

It is now well established that obesity shares biological underpinnings with disorders of the HPA axis at several levels (Bornstein *et al.*, 2006); for example, obesity has been well documented to interfere with basal and stress-induced HPA activation (Kyrou *et al.*, 2006). Thus, basal plasma CORT negatively correlates with waist-to-hip circumference ratio in obese women, whereas the stimulation of CORT secretion via administration of an ACTH analogue was augmented, suggesting an increased sensitivity of adrenal responses in obese woman (Marin *et al.*, 1992). Studies have also reported that obese subjects show paradoxically low levels of plasma CORT, which may be linked with changes in CORT clearance (Marin *et al.*, 1992; Andrew *et al.*, 1998) and metabolism (Stewart *et al.*, 1999). During the peripartum period, maternal obesity, overweight or even excessive weight gain during pregnancy have been shown to negatively affect several pregnancy outcomes. More specifically, the risk for hypertensive disorders, diabetes, obstetric complications and delayed lactogenesis is increased in obese women (Hernandez *et al.*, 2012; Scott-Pillai *et al.*, 2013). Moreover, maternal obesity also compromises offspring development and increases the likelihood of psychiatric disorders later in life (Rodriguez *et al.*, 2012; Volpato *et al.*, 2012; O'Reilly and Reynolds, 2013). Although less studied, there is also evidence for interplay between excessive body weight and mental illnesses across the peripartum period, particularly from human studies. Bogaerts *et al.* (2013) reported that in obese women, post-partum weight retention 6 months after delivery was correlated with pre-pregnancy body mass index and maternal trait anxiety in the first trimester of pregnancy. A positive correlation between pre-pregnancy and 4 month post-partum body mass index with maternal depression and anxiety symptoms in the first post-partum year has also been reported (Carter *et al.*, 2000). Therefore, recent attempts have focused upon the development of animal models to study this multifaceted peripartum co-morbidity. A study from Purcell *et al.* (2011) revealed that rat dams fed from the beginning of pregnancy with a high-fat diet (60% fat) decreased the time the mothers spent in active nursing. In our laboratory, we designed an animal model to study the effects of obesity on HPA axis-associated peripartum adaptations in the rat. To address this, animals were fed continuously on a high-fat diet (45% fat) starting two weeks before pregnancy and left undisturbed until testing. To date, we have been able to reveal that this diet prevents the lactation-associated basal hyper-CORT and anxiolytic phenotypes (C. V. Perani *et al.*, unpubl. data). Thus, more studies assessing the effect of high-fat diet/obesity in animal models may help to increase our understanding of post-partum psychiatric disorders, particularly those in relation to obese mothers.

Selective breeding models and strain differences

Maternal depression and anxiety are both associated with alterations in maternal behaviour towards her child. Therefore, a number of researchers have explored whether animals

bred for high or low anxiety-related behaviour (HAB and LAB, respectively) or depressive-like behaviour, namely the Flinders sensitive line (FSL) and Wistar-Kyoto strain, display altered maternal behaviour. HAB mothers, both rats and mice, display enhanced maternal behaviour, including care and aggression, even in aversive environments (Neumann *et al.*, 2005; Bosch, 2011; Kessler *et al.*, 2011). In contrast, FSL dams have repeatedly been shown to display reduced attention and nursing behaviour towards their pups (Lavi-Avnon *et al.*, 2005a,b; 2008), behaviour that may be influenced by the pups themselves. Pup interaction is usually rewarding for the dam, particularly during the early lactation period, when dams even prefer pups over cocaine (Mattson and Morrell, 2005), and it could be shown via a microdialysis study that the increased dopamine release observed in the nucleus accumbens of Sprague-Dawley dams following pup interaction was absent in FSL dams (Lavi-Avnon *et al.*, 2008). Moreover, FSL dams were shown to have a decreased conditioned place preference for a pup-associated box than Sprague-Dawley dams. However, for both these parameters, the reduced interaction of FSL dams with the pups may be a confounding factor (Lavi-Avnon *et al.*, 2008). Furthermore, the deficit in maternal behaviour observed in FSL dams became more pronounced when the dams were given limited bedding material in the first post-partum week. In contrast, Wistar-Kyoto rats showed increased pup-directed behaviour under both undisturbed and stress conditions (Braw *et al.*, 2009). In general, these findings are in keeping with the maternal phenotype observed in mothers, since anxiety has been linked with 'helicopter parenting' and depression with decreased interest in the child. Thus, they suggest that further investigation into both basal and stress-induced changes in maternal behaviour in these animal models of depression and anxiety may help to shed light on the aetiology of post-partum mood disorders.

In addition to these selectively bred lines, researchers have also assessed differences in mouse strains, with C57/BL6 and BALB/c strains being the most commonly assessed. Although these strains differ in their anxiety and maternal phenotype, the majority of the research has focused upon the outcome for the offspring (see Tarantino *et al.*, 2011). However, determination of the underlying causes for their differing maternal styles could provide valuable insights in the aetiology of post-partum psychiatric disorders.

Pup separation models

As stated earlier, pup separation is a widely used paradigm to assess the impact of early life stress on the development of the offspring. However, separation from the pups also represents a form of stress for the dam and has been shown to influence maternal behaviour and emotion. The duration of the separation of the dam from her pups plays a crucial role in the outcome for her maternal care. Thus, short separation periods (15 min) were shown to increase in maternal behaviour, whereas longer separations (3 h) lead to reduced maternal behaviour. Interestingly, the long separation of the dam from her pups (between post-natal day 2 and day 14) was also associated with increased immobility behaviour in the forced swim test, suggesting that these dams also displayed increased depressive-like behaviour (Boccia *et al.*, 2007). This phenotype may be long lasting, as a separate study revealed that dams subjected to 3 h pup separation displayed increased anxiety and depressive-like behaviour 4 weeks after weaning, as well as increased plasma CORT levels, increased hypothamalic CRH mRNA and decreased hippocampal expression of mRNA for glucocorticoid receptors (Maniam and Morris, 2010). However, these findings were in relation to mothers who had experienced 15 min pup separation and, therefore, caution is required in their interpretation. Of note, given the previous section, high-fat diet exposure was able to reverse the behavioural and CRH expression consequences of long-term pup separation (Maniam and Morris, 2010). Finally, it has been shown that removal of the litter within 24 h of delivery results in increased depressive-like behaviour when compared with dams that were allowed to keep their litter and undergo a normal lactation (Pawluski *et al.*, 2009). Thus, pup separation is also associated with alterations in maternal behaviour that resemble those observed in post-partum mood and anxiety disorders and may therefore represent valid models for their study. In an interesting aside, these findings also suggest that care should be employed when using early life separation paradigms to assess long-term consequences for the offspring, since changes in the mother may play a role.

Potential avenues for studying post-partum mood and anxiety disorders

Although the following sections deal with topics that are not specifically animal models for assessing post-partum mood disorders, they suggest potential avenues of approach that could be employed for their study. This is because of their known involvement in peripartum-associated changes, as well as in depression- and anxiety-related behaviour and stress coping.

Neuropeptide-based approaches

As stated earlier, activation of the oxytocin and prolactin systems is necessary for the manifestation of maternal repertoire and the late-pregnancy and lactation-associated calmness/anxiolysis (Neumann *et al.*, 2000; Heinrichs *et al.*, 2001). Moreover, there is evidence for their involvement in post-partum mood and anxiety disorders, as prolactin levels in women just prior to delivery were shown to negatively correlate with anxiety ratings (Asher *et al.*, 1995). With respect to oxytocin , plasma levels are known to increase during healthy mother–infant interactions (Strathearn *et al.*, 2009) and this may be impaired in mothers suffering from post-partum mood disturbances (Hornstein *et al.*, 2006). Moreover, low plasma oxytocin levels at mid-pregnancy predicted PPD symptoms assessed two weeks after delivery (Skrundz *et al.*, 2011). Therefore, several animal studies have directly manipulated these systems to understand their specific contribution to peripartum-associated adaptations, as well as to assess how natural variations in behaviour and/or stress exposure affect them.

Champagne *et al.* (2001) reported that rat dams that display high frequency of licking and grooming of the pups had higher levels of oxytocin receptor in distinct brain regions known to play a central role in the regulation of maternal behaviour, such as the bed nucleus of the stria terminalis, the medial preoptic area and the central amygdala compared to those showing low licking and grooming mothers. Interestingly, exposure of the high licking and grooming mothers to intermittent stress (restraint) during pregnancy resulted in oxytocin receptor expression comparable to those of low licking and grooming mothers, a change that was paralleled by a decrease in licking and grooming behaviour (Champagne and Meaney, 2006). A similar finding was observed in our psychosocial stress paradigm, in which stress exposure prevented the peripartum-induced rise in oxytocin mRNA expression in the PVN, as well as increasing anxiety-related behaviour (Hillerer *et al.*, 2011). Of note, HAB mothers, who display high levels of maternal care, have increased oxytocin release during maternal defence and their lactation-associated anxiolysis can be partially prevented by administration of an oxytocin receptor antagonist (for full details, see Bosch, 2011). Moreover, chronic central oxytocin infusion results in attenuated stress-induced fos activation (Windle *et al.*, 2004) and an anxiolytic phenotype in ovariectomized virgin rats (Windle *et al.*, 1997), and even in HAB virgins (Slattery and Neumann, 2010a). Down-regulation of prolactin receptor expression via centrally administered antisense oligonucleotides, also leads to increased anxiety-related behaviour in lactating dams (Torner *et al.*, 2002). In keeping, 5 day continuous central prolactin infusion was shown to exert an anxiolytic effect in virgin rats as assessed on the elevated plus maze testing and to blunt stress-induced increase in ACTH and CORT (Torner *et al.*, 2001; Donner *et al.*, 2007).

Taken together, these findings suggest that it is likely that maladaptive adaptations of the central oxytocin and prolactin circuitry may participate in the underlying aetiology of post-partum mood disorders. Thus, studies that chronically manipulate these systems and determine the consequence on a variety of peripartum-associated adaptations may help us gain a better insight into the underlying aetiology of post-partum mood and anxiety disorders.

Neurogenesis-based approaches

Neurogenesis has been implicated in both the pathogenesis of stress-related disorders, as well as in mediating the beneficial effects of antidepressant treatment (Santarelli *et al.*, 2003; Gass and Henn, 2009; Snyder *et al.*, 2011). Interestingly, neurogenesis exhibits profound sex differences and these are particularly prominent during the peripartum period (Shingo *et al.*, 2003; Pawluski and Galea, 2006; 2007; Levy *et al.*, 2011; Hillerer *et al.*, 2012). Thus, the high levels of prolactin that are present in early pregnancy has been linked with increased subventricular zone neurogenesis, leading to increased cell numbers in the olfactory bulb (Larsen and Grattan, 2010), whereas the high levels of CORT in lactation are associated with decreased hippocampal neurogenesis (Leuner *et al.*, 2007). Interestingly, bromocriptine administration, which prevents the increase in prolactin, abolishes the increase in olfactory bulb neurogenesis and impairs maternal behaviour. Moreover, exposure to female pheromones in early pregnancy, which also suppresses the prolactin system, increased post-partum anxiety and attenuated the normal levels of neurogenesis observed in early pregnancy in mice (Larsen and Grattan, 2010). However, whether there is a causal link between these findings remains to be determined. The altered stress response observed in peripartum period gives rise to the intriguing possibility that stress during the peripartum period may affect neurogenesis in a fashion different from that observed in male and female (virgin) rodents. Thus, it has repeatedly been demonstrated that exposure to a variety of chronic or repeated stressors decreases cell proliferation and survival in males, and cell survival in females (Lucassen *et al.*, 2001; Pham *et al.*, 2003; Hillerer *et al.*, 2013). Such stress-related alterations in neurogenesis have been posited to play a crucial role in the aetiology of anxiety and depression (Snyder *et al.*, 2011). Interestingly, repeated restraint stress during pregnancy was shown to increase hippocampal cell proliferation at late pregnancy, but the same effect was observed in virgin rats, so the specificity of this finding to the peripartum period is unclear (Pawluski *et al.*, 2011; 2012). However, to date, no studies have been performed assessing the role of stress on neurogenesis in lactation, which would be of interest in relation to post-partum mood and anxiety disorders considering the findings from the previously mentioned studies that clearly showed how CORT administration during pregnancy and/or post-partum affects cell proliferation in the dentate gyrus (Brummelte and Galea, 2010) and dendritic complexity in the hippocampus (Workman *et al.*, 2013). Further, even early life environment can affect peripartum-associated hippocampal plasticity when the offspring become pregnant (Brummelte *et al.*, 2006; Akbari *et al.*, 2007). Moreover, sex-related differences in the neurogenesis response to stress that have been extensively reported (Westenbroek *et al.*, 2004; Barha *et al.*, 2011; Hillerer *et al.*, 2013) strengthen the hypothesis that neuronal plasticity mechanisms may participate to increase the susceptibility for the development of post-partum mood disorders.

Genetic association studies

As psychiatric disorders display strong heritability, there have also been a number of studies in recent years that have attempted to correlate genetic variations with post-partum mood disorders. The majority of these studies have focused upon genes that have already been implicated in major depression, such as the 5-HT transporter, BDNF, and the glucocorticoid and CRH receptors. Thus, it has been shown that the 5-HT transporter polymorphism is associated with a higher prevalence of PPD, especially if exposed to stress during pregnancy, although the results differ as to whether the long or short allele is the risk variant (Sanjuan *et al.*, 2008; Binder and Nemeroff, 2010; Pinheiro *et al.*, 2012; 2013; Comasco *et al.*, 2013). A more recent study also revealed that a polymorphism in the tryptophan hydroxylase 2 gene, the rate-limiting enzyme in the synthesis of 5-HT, was associated with PPD (Fasching *et al.*, 2012). However, this gene also increased the risk of depression independent of the peripartum period, suggesting that it may be related to increased risk of depression *per se* rather than specifically to PPD. Engineer *et al.* (2013) revealed that single-nucleotide polymorphisms in both the glucocorticoid receptor and the CRH receptor 1 genes were associated with increased risk of depression

Table 1

Summary of the animal models to study post-partum psychiatric disorders and their main effects on dam HPA axis activity and behaviour

	Parameter assessed				
Model type	**Maternal behaviour**	**Anxiety**	**Depression**	**Basal CORT**	**Stress-induced CORT**
Exogenous CORT	↓ (Brummelte *et al.*, 2006; Saltzman and Abbott, 2009; Brummelte and Galea, 2010; Workman *et al.*, 2013)	↔ (Brummelte *et al.*, 2006; Brummelte and Galea, 2010; Workman *et al.*, 2013)	↑ (Brummelte *et al.*, 2006; Brummelte and Galea, 2010; Workman *et al.*, 2013)	n/a	n/a
Repeated stress	↑ (Maestripieri *et al.*, 1991; Hillerer *et al.*, 2011) ↔ (Pardon *et al.*, 2000) ↓ (Smith *et al.*, 2004; Kurata *et al.*, 2009; Nephew and Bridges, 2011; Murgatroyd and Nephew, 2013)	↑ (Maestripieri *et al.*, 1991; Darnaudery *et al.*, 2004; Smith *et al.*, 2004; Hillerer *et al.*, 2011) ↓ (Pawluski *et al.*, 2011)	↑ (Maestripieri *et al.*, 1991; Smith *et al.*, 2004; O'Mahony *et al.*, 2006) ↔ (Darnaudery *et al.*, 2004; Hillerer *et al.*, 2011; Pawluski *et al.*, 2011)	↑ (Misdrahi *et al.*, 2005) ↔ (Misdrahi *et al.*, 2005; Pawluski *et al.*, 2011) ↓ (Hillerer *et al.*, 2011)	↑ (Smith *et al.*, 2004; Leonhardt *et al.*, 2007) ↔ (Hillerer *et al.*, 2011)
HSP	n/a	↔ (Galea *et al.*, 2001)	↑ (Galea *et al.*, 2001; Stoffel and Craft, 2004; Suda *et al.*, 2008; Green *et al.*, 2009; Navarre *et al.*, 2010; Schiller *et al.*, 2013) ↓ (Suda *et al.*, 2008)	n/a	n/a
High-fat diet	↓ (Purcell *et al.*, 2011)	↑ (C. V. Perani, unpublished)	n/a	↓ (C. V. Perani, unpublished)	n/a
Pup separation	↑ (Boccia *et al.*, 2007) ↓ (Boccia *et al.*, 2007)	↑ (Maniam and Morris, 2010)	↑ (Boccia *et al.*, 2007; Pawluski *et al.*, 2009; Maniam and Morris, 2010)	↑ (Maniam and Morris, 2010)	n/a
Selective breeding	↑ (Neumann *et al.*, 2005; Braw *et al.*, 2009; Bosch, 2011; Kessler *et al.*, 2011) ↓ (Lavi-Avnon *et al.*, 2005a,b; 2008)	↑ (Neumann *et al.*, 2005; Bosch, 2011; Kessler *et al.*, 2011)	↑ (Lavi-Avnon *et al.*, 2005a,b; 2008; Braw *et al.*, 2009)	n/a	n/a

n/a, not assessed.

during both pregnancy and the post-partum period. The Val66Met BDNF polymorphism, which affects the secretion of the protein, has also been studied in relation to PPD, but again the findings to date are inconsistent (Figueira *et al.*, 2010; Comasco *et al.*, 2013). Interestingly, this polymorphism has also been researched in mice bred to carry these human BDNF gene variants. Here, the researchers could demonstrate that female mice homozygous for the Val66Met polymorphism were more anxious before puberty and during the oestrous phase than control (wild-type) mice (Bath *et al.*, 2012). Therefore, given the hypothesized involvement in sex steroids with post-partum mood and anxiety disorders, it would also be of interest to determine the behavioural, neuroendocrine and physiological phenotype of these mice across the peripartum period. Finally, recent studies in pigs have implicated two candidate regions in the porcine genome that are associated with increased maternal infanticide (Quilter *et al.*, 2007; 2008). Interestingly, these regions are close to candidate regions from human studies that have been implicated in post-partum psychosis and bipolar disorder.

Therefore, back-translation of such genetic association studies into preclinical models may help to increase the strength of their association with post-partum psychiatric disorders and provide greater understanding of the underlying aetiology behind their association with such illnesses.

Conclusions

In this review, we have summarized the animal models that have been used to date to study post-partum psychiatric disorders. These models fall into two main categories; namely those that attempt to isolate certain peripartum- and/or psychiatric disorder-related changes, such as HSP and pup separation, and those that attempt to mimic risk factors for the disorders, such as stress. These models have shown that it is possible to represent certain facets of post-partum mood and anxiety disorders in basic research (for an overview, see Table 1). However, most of the studies described earlier only assess specific readout parameters, which make it difficult to draw detailed conclusions about their impact on multiple maternal characteristics. Therefore, future studies should attempt to study multiple parameters using the same models in order to reveal the concerted effect of the manipulation on physiology and molecular consequences for the dam, which may correlate with the observed behavioural phenotype. Such a research direction will lead to a greater understanding of the aetiology of post-partum mood and anxiety disorders and, hopefully, in the longer term, lead to treatment options that are specifically tailored for this specific period of a woman's life.

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Conflict of interest

The authors report no potential conflicts of interest.

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