Disruption of Fetal Hormonal Programming (Prenatal Stress) Implicates Shared Risk for Sex Differences in Depression and Cardiovascular Disease

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Abstract

Comorbidity of major depressive disorder (MDD) and cardiovascular disease (CVD) represents the fourth leading cause of morbidity and mortality worldwide, and women have a two times greater risk than men. Thus understanding the pathophysiology has widespread implications for attenuation and prevention of disease burden. We suggest that sex-dependent MDD-CVD comorbidity may result from alterations in fetal programming consequent to the prenatal *maternal* environments that produce excess glucocorticoids, which then drive sex-dependent developmental alterations of the *fetal* hypothalamic-pituitary-adrenal (HPA) axis circuitry impacting mood, stress regulation, autonomic nervous system (ANS), and the vasculature in adulthood. Evidence is consistent with the hypothesis that disruptions of pathways associated with gamma aminobutyric acid (GABA) in neuronal and vascular development and growth factors have critical roles in key developmental periods and adult responses to injury in heart and brain. Understanding the potential fetal origins of these sex differences will contribute to development of novel sex-dependent therapeutics.

Keywords

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Conflict of Interest The authors declare that they have no conflict of interest.

1. Introduction

The co-occurrence (or comorbidity) of major depressive disorder (MDD) and risk for cardiovascular disease (CVD) has a substantial population prevalence of approximately 20% (Kawachi et al., 1994b; Barefoot et al., 1996; Everson et al., 1997; Glassman and Shapiro, 1998; Krishnan et al., 2001; Jones et al., 2003; Scherrer et al., 2003) and is a leading cause of morbidity and mortality worldwide (Murray and Lopez, 1997; Ustun et al., 2004). Further, the comorbidity is significantly higher in women than in men (Naqvi et al., 2005; Moller-Leimkuhler, 2007; Goldstein et al., 2011). MDD alone has a higher prevalence in women (almost 2-fold) (Kessler et al., 1993; Kessler et al., 2003; Kendler et al., 2006), and is *an independent risk factor* for the development and progression of coronary artery disease (Kawachi et al., 1994a; Kawachi et al., 1994b; Barefoot et al., 1996; Everson et al., 1997; Musselman et al., 1998), even though the risk for CVD alone is higher in men (Lloyd-Jones et al., 2010). Numerous prospective studies demonstrated significantly elevated risks of coronary heart disease, myocardial infarction, or cardiac death among participants with depression (Glassman and Shapiro, 1998; Rozanski et al., 1999; Rutledge et al., 2006a; Rutledge et al., 2006b; Van der Kooy et al., 2007; Vaccarino et al., 2008). Depression predicts first cardiovascular events even among otherwise healthy people (Vaccarino et al., 2008), and particularly among women (Rutledge et al., 2006a). However, the etiologic pathways underlying this comorbidity are unclear, even though it has major public health implications worldwide.

The comorbidity of MDD and CVD, and in particular the association with significant sex differences, may arise in part from hormone-dependent pathogenic processes initiated during fetal development that result in greater risk in women than men. Fetal origins of MDD and CVD may *independently* result from alterations in the prenatal *maternal* environment, which drive developmental alterations of the *fetal* hypothalamic-pituitary-adrenal (HPA) axis circuitry. Several groups have used model animals to study cellular and molecular mechanisms that may relate to human studies of MDD and CVD (McClellan et al., 2010; Goldstein et al., 2011; Holsen et al., 2011; Carbone et al., 2012a; Holsen et al., 2012; Zuloaga et al., 2012b; Weinstock et al., 1992; Henry et al., 1994; Barker, 1995; Arborelius et al., 1999; Seckl, 2001). These independent bodies of work converge on the hypothesis that maternally-driven disruptions of fetal HPA circuitry during development produce *shared* risk for the adult comorbidity of MDD and CVD, which is significantly higher in females than males.

This review is based on the hypothesis that the key pathways for understanding sex-dependent effects with respect to neuronal and vascular development in HPA circuitry involves the impact of excess maternal glucocorticoids during specific gestational periods on fetal brain development. These mechanisms are shared and influenced by genes and fetal levels of gonadal hormones, growth factors and neurotransmitters such as gamma-aminobutyric acid (GABA). The developmental model is not meant to be an exclusive explanation for sex-dependent comorbidities. However, alternative adult etiologies are reviewed elsewhere (e.g., (Elderon and Whooley, 2013). Brain regions implicated in the stress response circuitry include the paraventricular nucleus in the hypothalamus, central and medial subregions of the amygdala, hippocampus, periaqueductal gray, medial and orbital prefrontal cortices, and anterior cingulate cortex. Many of these brain regions are morphologically or functionally sexually dimorphic (McEwen, 1983; Simerly et al., 1990; Tobet et al., 1993; Filipek et al., 1994; O'Keefe et al., 1995; Giedd et al., 1996; Murphy et al., 1996; Park et al., 1996; Tobet and Hanna, 1997; Gorski, 2000; Goldstein et al., 2001; Chung et al., 2006; Tobet et al., 2009) and implicated in autonomic nervous system (ANS) regulation, the dysregulation of which is a significant risk factor for CVD (Akselrod et al.,

1981; Dalack and Roose, 1990; Musselman et al., 1998). Thus, prenatal stress, or an elevated prenatal glucocorticoid model, may produce shared risk for sex differences in MDD-CVD comorbidity by altering the development of common regulatory pathways, such as the ANS, limbic brain areas associated with stress and anxiety-related behaviors, and/or vascular development within brain areas central to HPA control. This review integrates human clinical literature on HPA and HP-gonadal (HPG) abnormalities and brain activity deficits that occur in depression and risk for CVD with developmental and adult preclinical studies, in order to provide convergent evidence for prenatal stress models as key for understanding sex differences in depressive and anxiety-related behaviors, ANS dysregulation, and the vasculature in stress-relevant central nervous system (CNS) regions.

2. Hypothalamo-Pituitary-Adrenal Axis and Stress

2.1 Anatomy of Stress Circuitry

Brain regions implicated in the stress response circuitry all provide inputs through numerous routes to the PVN, which is the final common motor output for the neuroendocrine hypothalamus. These brain regions include central and medial subregions of the amygdala, hippocampus, periaqueductal gray, medial and orbital prefrontal cortices, and anterior cingulate cortex (see Figure 1). Central to the HPA axis are a group of neurons found in the paraventricular nucleus of the hypothalamus that synthesize and secrete corticotropin releasing hormone (CRH). Secretion of CRH from these neurons and co-secretion of arginine vasopressin into the hypothalamo-hypophyseal portal capillaries of the median eminence regulate secretion of adrenocorticotropic hormone (ACTH) from the anterior pituitary. In turn, ACTH drives the secretion of cortisol in humans and corticosterone in many other vertebrates from the zona fasciculate of the adrenal cortex. At the same time, preautonomic neurons in the PVN activate the sympathetic nervous system (component of ANS) to stimulate the rapid release of epinephrine from chromaffin cells in the adrenal medulla. This rapid neural response to stress is further augmented by the neuroendocrine system since glucocorticoid release also drives adrenal medullary synthesis of the key enzyme responsible for transforming norepinephrine to epinephrine (phenylethanolamine N-methyltransferase, or PNMT). The combination of glucocorticoids and epinephrine secreted into the bloodstream generates diverse responses throughout the body in addition to the glucocorticoid negative feedback responses at the pituitary and brain levels (see Figure 1).

Among the neuroanatomical components of the HPA axis, the PVN stands out for its unique vascularization. It has been appreciated since the 1930's that the PVN and its magnocellular companion, supraoptic nuclei, are more highly vascularized than the surrounding brain regions whether in primates or rats (Ambach and Palkovits, 1974; van den Pol AN., 1982). Surprisingly, little is known about the development of PVN vascularity (Menendez and Alvarez-Uria, 1987). However, our recent studies on PVN development demonstrate that the remarkable vascularity of the PVN in mice develops over the first three weeks of postnatal life and can be regulated by neurotransmitter signaling (Frahm et al., 2012). The timing occurs after most forebrain vasculature is established, and thereby identifies a secondary angiogenic period as a potential critical feature for PVN development. The PVN has been thought to be functionally hypo-responsive over the first few postnatal weeks, and several have tried (with varying levels of success) to associate this with the slow emergence of neuronal connections. This new discovery places vascularization as a potential critical developmental variable that may be essential for the normal 'activation' of the PVN. The issue can be viewed from at least two perspectives with one being the relationship of neural cells to vasculature and the other being the competency of the vasculature itself (e.g., blood brain barrier function), as illustrated schematically in Figure 2. Investigations will be important to test hypotheses that abnormalities of PVN vascularization are risk factors for

HPA dysfunction and contribute to understanding the neural bases for the high comorbidity of depression and cardiovascular disease.

2.2 Functions of Stress Circuitry

A major role for the HPA axis is to integrate potentially stressful stimuli and respond with a neuroendocrine signal that coordinates homeostatic responses throughout the body. Threatening physical or psychological stimuli or stressors are sensed at many levels of the CNS, including the cerebral cortex, and this information is passed to the hypothalamus after processing in limbic regions (Ferguson et al., 2008; Jankord and Herman, 2008). For example, CRH neurons are directly innervated by neurons of the bed nucleus of the stria terminalis, dorsal medial hypothalamus, preoptic area, and nucleus of the solitary tract. These directly innervating regions receive inputs from the ventral subiculum (glutamatergic), medial prefrontal cortex (glutamatergic), and medial and central amygdala (GABAergic) which communicate with the basolateral amygdala. It is thought that much of the negative feedback on the hypothalamus is mediated by glucocorticoid and mineralocorticoid receptors in the ventral hippocampus (the outflow via ventral subiculum) which relay through inhibitory neurons in areas such as the bed nucleus of the stria terminalis and periventricular PVN. In addition to negative feedback mediation by the hippocampus, glucocorticoid receptors are also present in the amygdala, PVN, bed nucleus stria terminalis, and prefrontal cortex (De Kloet et al., 1998; Myers et al., 2012).

2.3 HPA Axis Dysregulation in MDD

There is a long history of work characterizing the HPA system as central to understanding the development of MDD (Nemeroff et al., 1984; Holsboer et al., 1987; Plotsky et al., 1998; Arborelius et al., 1999; Heim et al., 2002; Parker et al., 2003; Raison and Miller, 2003; Barden, 2004; Swaab et al., 2005; Antonijevic, 2006). Depressive symptoms can occur in the context of either endogenously elevated cortisol (i.e., Cushing syndrome (Sonino et al., 1998) or exogenously administered corticosteroids (Kelly et al., 1980), and patients treated with corticosteroids can develop MDD (Ling et al., 1981)). Human studies demonstrate consistent HPA axis abnormalities associated with MDD, such as elevated cortisol levels in plasma, cerebral spinal fluid (CSF), and 24-hour urine, in addition to high CSF CRH levels, blunted responses to CRH administration, and failure to suppress cortisol secretion after administration of a synthetic glucocorticoid, dexamethasone (Carroll et al., 1976a; Carroll et al., 1976b; Carroll et al., 1981; Jarrett et al., 1983; Nemeroff et al., 1984; Halbreich et al., 1985; Holsboer et al., 1985; Banki et al., 1987; Evans and Nemeroff, 1987; Holsboer et al., 1987; Rubin et al., 1987; Nemeroff et al., 1991; Arborelius et al., 1999; Heim and Nemeroff, 2001; Heim et al., 2001; Newport et al., 2003; Oquendo et al., 2003; Raison and Miller, 2003; Barden, 2004). HPA dysregulation has been related to, among other things, age (Nelson et al., 1984a; Nelson et al., 1984b; Bremmer et al., 2007), depression subtype, hypercortisolemia in atypical depression and normal cortisol levels in melancholia (Brouwer et al., 2005), and single versus recurrent episodes of MDD (Poor et al., 2004).

Several studies have examined the utility of HPA reactivity as an indicator of treatment response in MDD. While elevated CRH levels in CSF have been shown to resolve with antidepressant treatment (Nemeroff et al., 1991; De Bellis et al., 1993; Veith et al., 1993), some studies report an incomplete resolution to normal levels, suggesting that HPA dysregulation may be part of the vulnerability to MDD (or a trait) and not only state-related. Although decreases in elevated pre-treatment cortisol levels have been widely reported in patients following antidepressant treatment (Gibbons and McHugh, 1962; Carroll et al., 1976a; Carroll et al., 1976b), a recent meta-analysis found that cortisol levels (blood, saliva or urine) did not change pre-versus post-treatment in over half of MDD cases (McKay and Zakzanis, 2010). An examination of subject characteristics related to changes in cortisol

post-treatment revealed the greatest decreases occurred in those with the melancholic subtype. Time of sample collection, inpatient versus outpatient setting, type of treatment or antidepressant, subject sex, and number of past episodes were not associated with cortisol changes following treatment. However, the length of the current episode was negatively associated with change in cortisol levels (McKay and Zakzanis, 2010). This finding is supported by the hypothesis that the nature of HPA axis dysregulation shifts dramatically from acute (overall hypersecretion of CRH, adrenocorticotropin hormone (ACTH), and cortisol) to chronic (reduced ACTH and hypercortisolemia) phases of MDD (Parker et al., 2003).

Studies have demonstrated more immunoreactive CRH-containing neurons in the human PVN subsequent to hypertension (Goncharuk et al., 2002) as well as for patients with mood disorders (Bao et al., 2005). In the latter case, it was clear that many of the CRH neurons also contained immunoreactive estrogen receptor alpha, providing a potential link for understanding hormone influences in brain regions, such as the PVN, that are associated with MDD and CVD risk. This is not surprising since altered PVN function has been implicated in MDD and CVD in postmortem studies (Mesulam, 1985; Goncharuk et al., 2002; Bao et al., 2005) and, indirectly *in vivo* human functional imaging studies of sex differences in stress response circuitry in healthy adults (Goldstein et al., 2005; Goldstein et al., 2010), MDD subjects (Holsen et al., 2011; Holsen et al., 2013), and ANS function (Holsen et al., 2012).

It is reasonable to ask whether HPA dysregulation is indicative of enduring **trait** characteristics associated with MDD or the clinical **state** that one is in at a given time during an acute episode. The issue of state versus trait (independent of treatment) has not been studied extensively. In remitted MDD patients compared with controls, cortisol levels were reported to be similar (Trestman et al., 1993) or even decreased (Ahrens et al., 2008), although these studies included only small numbers of subjects (n/group ~ 20–30). However, a recent well-powered study examined morning and evening salivary cortisol levels in 308 controls, 579 individuals with remitted MDD, and 701 patients currently in an MDD episode (Vreeburg et al., 2009). Results showed that remitted *and* current MDD subjects demonstrated significantly higher awakening cortisol levels compared to controls (adjusted for sex), providing evidence that elevated cortisol may be a trait characteristic (Vreeburg et al., 2009). This is consistent with our recent brain imaging study of women with recurrent MDD *in remission* who were hypercortisolemic compared with healthy women (Holsen et al., 2013). When tracked longitudinally, baseline cortisol and dexamethasone suppression test abnormalities also predicted vulnerability to relapse, necessity of continued medication to sustain remission, and remission rate following hospitalization in MDD (O'Toole et al., 1997; Zobel et al., 1999; Appelhof et al., 2006; Ising et al., 2007).

2.4 Sex differences in HPA Function and MDD

Despite significant advances in understanding the co-occurrence of MDD and HPA axis dysregulation, there is a paucity of data on sex differences in this comorbidity. This is striking even though: 1) there are well-documented sex differences in MDD incidence and prevalence (Kessler, 2003; Kendler et al., 2006); 2) substantial data support sex differences in HPA-HPG axes functioning during stress in healthy populations (Kudielka and Kirschbaum, 2005; Goldstein et al., 2010; Andreano et al., 2011) and in MDD women (Holsen et al., 2011; Holsen et al., 2013); and 3) there are significant interactions of the HPA axis with the HPG axis, which is *de facto* different between the sexes if based on nothing else than the gonads.

Among the few investigations reporting significant sex differences in HPA axis functioning in MDD, the direction of effects was mixed. Men, but not women, with MDD, demonstrated abnormal plasma ACTH pulsatility (Young et al., 2007b). At baseline, elevated cortisol secretion was documented in depressed men versus depressed women (Bremmer et al., 2007) and non-depressed men (Hinkelmann et al., 2011). However, in contrast, depressed women demonstrated higher 24-hour cortisol secretion versus depressed men (Poor et al., 2004) and non-depressed women (Young and Altemus, 2004). Further, in response to a social stress paradigm, depressed women also exhibited elevated cortisol compared to non-depressed women (Chopra et al., 2009). Conflicting reports on sex differences in cortisol levels may be related to differences in the timing of cortisol assessment (e.g. baseline or under stress) or lack of control for menstrual cycle in women and/or genetic factors.

Recent data suggested an interaction between sex and adrenergic receptor gene polymorphisms in HPA hyperactivity using a dexamethasone/CRH test pre- and post-treatment (Haefner et al., 2008). Specifically, increased ACTH and cortisol responses were seen in males (but not females) homozygous for the *alpha*(2)-adrenergic receptor (ADRA2A) gene, and females (but not males) homozygous for the *beta*(2)-adrenergic receptor (ADRB2) gene (Haefner et al., 2008). Collectively, these findings offer initial evidence of sex differences in the role of HPA axis functioning in MDD pathophysiology *under different genetic conditions*.

By contrast, several reports have found no effect of sex on basal HPA function in MDD (Carroll et al., 1976a; Carroll et al., 1976b; Nelson et al., 1984a; Maes et al., 1987; Dahl et al., 1989; Maes et al., 1989; Maes et al., 1994; Deuschle et al., 1998; Brouwer et al., 2005; Rubin et al., 2006; Vreeburg et al., 2009). However, the majority of these studies did not initially design their studies to investigate sex differences, but rather analyzed the data by sex post hoc. This is problematic since potential confounding (uncontrolled in the initial designs) is typical. For example, the vast majority of studies of MDD oversample women (Maes et al., 1987; Brouwer et al., 2005; Rubin et al., 2006; Young et al., 2007b; Vreeburg et al., 2009; Hinkelmann et al., 2011). Some have matched on sex, whereas some included women using oral contraceptives or estrogen-replacement therapy (Brouwer et al., 2005), which affect plasma levels of cortisol (Kirschbaum et al., 1999). Further, only a few mention "matching for menstrual cycle status" (Maes et al., 1987; Rubin et al., 2006), and those that do generally refer to including similar numbers of women who are pre- or post-menopausal rather than actually controlling for menstrual cycle phase (for example, conducting study visits only within certain phases such as early follicular or late luteal). These methodological confounds present significant challenges to understanding the inconsistencies in the literature on sex differences in human HPA axis dysregulation and MDD comorbidity.

2.5 Postmortem Morphological Changes in HPA in MDD

The importance of HPA axis abnormalities in MDD is underscored by human postmortem studies. It has been reported that there is a 25% decrease in the density of glucocorticoid receptor (GR) mRNA in MDD compared with healthy brains in frontal cortex, dentate gyrus, and subiculum. Such observations showing a down-regulation of GRs suggest that there may be reductions in negative feedback control of the HPA axis, the net result being hypercortisolemia and inability to regulate stress reactivity behaviorally (Webster et al., 2002). This corresponds with the enhanced numbers of arginine vasopressin (AVP) immunoreactive neurons in MDD (von Bardeleben et al., 1989; Muller and Holsboer, 2006). AVP was found to be co-expressed with CRH in some PVN neurons and potentiates the actions of CRH at the anterior pituitary in model animals (Whitnall and Gainer, 1988; Familari et al., 1989). A recent human postmortem study similarly reported increased AVP mRNA in the PVN and supraoptic nucleus in MDD, particularly in brain tissue from patients

with melancholic features (Meynen et al., 2006). This is consistent with an increased number of AVP-immunoreactive neurons in PVN (Purba et al., 1996), particularly those co-localizing with increased CRH in PVN in MDD (Raadsheer et al., 1994a; Raadsheer et al., 1994b). It is also consistent with studies of MDD reporting elevated AVP plasma levels (van Londen et al., 1997; van Amelsvoort et al., 2001; de Winter et al., 2003), positive correlations of plasma AVP with cortisol (De Bellis et al., 1994; Inder et al., 1997; de Winter et al., 2003), and increased ACTH and cortisol in MDD and controls after intravenous administration of AVP (Gispen-de Wied et al., 1992), findings that were not due to medication confounds (van Londen et al., 1997; van Amelsvoort et al., 2001; Meynen et al., 2006).

2.6 HPA-HPG axes interactions in MDD

Changes in women's reproductive system have been consistently related to mood fluctuations and MDD per se (Rabin et al., 1990; Baischer et al., 1995; Rubinow and Schmidt, 1996; Harlow et al., 2003; Payne, 2003; Roca et al., 2003; Spinelli, 2005; Payne et al., 2009). MDD incidence increases with pubertal onset in females (Angold and Costello, 2006), late luteal menstrual cycle phase (Steiner, 1992), chronic use of oral contraceptives (Young et al., 2007a), the postpartum period (Bloch et al., 2000; Brummelte and Galea, 2010), and postmenopause (Graziottin and Serafini, 2009). Population studies have also demonstrated that ovarian dysfunction precedes the onset of MDD (Harlow et al., 2003). In MDD patients, deficits have been found in estradiol (Young et al., 2000), luteinizing hormone and pituitary function (Young et al., 2000; Meller et al., 2001; Daly et al., 2003; Harlow et al., 2003) suggesting a potential causal relationship.

In fact, inhibition of HPG activity occurring in response to stress was linked to HPA hyperactivity (Halbreich and Kahn, 2001). Given that MDD is associated with increased levels of glucocorticoids, women with persistent MDD had two times the risk of earlier perimenopausal transition, and higher FSH and lower estradiol levels, suggesting an early decline in ovarian function (Young et al., 2000; Harlow et al., 2003). Few studies have focused on hormonal deficits in men with MDD, although deficits in androgens have been reported (Baischer et al., 1995; Rubinow and Schmidt, 1996; Schweiger et al., 1999; Seidman et al., 2001; Weiner et al., 2004). Luteinizing hormone pulse frequency and testosterone secretion in males with MDD were also lower (Schweiger et al., 1999), although not consistently (Rubin et al., 1989)

Low levels of estradiol seen in MDD premenopausal women may lead to decreased inhibitory feedback of the HPA axis (by hippocampus) in the presence of increased HPA drive with unopposed progesterone. In fact, in our functional imaging study in MDD women, gonadal hormone abnormalities (lower estradiol) were significantly associated with hippocampal (and amygdalar) brain activity deficits (Holsen et al., 2011). Decreased inhibitory feedback of the HPA axis may in turn account for elevated levels of cortisol in MDD women compared to MDD men or non-depressed women (Young and Altemus, 2004; Holsen et al., 2013). Additionally, in postmortem studies of MDD, CRH-producing neurons in PVN that co-localized with estrogen receptor alpha (ERα) were enhanced in MDD, again suggesting HPA-HPG interactions in MDD (Bao et al., 2005).

In the preclinical literature, sex differences in stress responsiveness for the HPA axis have been known for a long time (Handa et al., 1994a), and sex differences are reported in response to prenatal stress and resilience (Bowman et al., 2004; Richardson et al., 2006; Heim et al., 2009; García-Cáceres et al., 2010). The mechanisms underlying sex differences in the HPA axis can be tied to either organizational or activational responses to steroid hormones. Organizational actions of steroid hormones are those characterized as being permanent changes that occur in response to gonadal steroid hormone exposure during a

critical period of development, whereas activational actions are transient effects that occur in response to changes or to sex differences in circulating hormone levels. Both actions are found in the control of the HPA axis. Seale et al (2004, 2005a, b) reported organizational effects of gonadal steroid hormones on the HPA axis where testosterone treatment of neonatal females within 24 hours of birth altered the HPA axis phenotype in adulthood to one resembling that of males. This was characterized by reduced corticosterone pulses, reduced corticosterone responses to stress and lower levels of CRH and arginine vasopressin mRNAs in the PVN. Correspondingly, inhibition of aromatase in neonatal males resulted in higher corticosterone levels at baseline and increased responses to stress in adulthood.

Activational effects of steroid hormones on the HPA axis can also be demonstrated. Sex differences in the localization of PVN peptides or receptors have been seen in adults with females having greater levels of ERα than males in the ventromedial hypothalamic nucleus whereas males had greater levels of ERα in the retrochiasmatic area than females (Scott et al, 2000). Correspondingly, estrogen-dependent effects have been reported for a number of genes, such as the kappa opioid receptors, which increased in the PVN following estradiol treatment (Yukhananov and Handa, 1996). The substrate for such influences was made all the more transparent with the reports of high levels of estrogen receptor beta in the PVN (Hrabovszky et al., 1998; Hrabovszky et al., 2004) and by molecular studies showing the ability of this steroid receptor to affect gene transcription in PVN (Handa et al., 2011). Roles for androgen receptors in the PVN have also been noted (Bingham et al., 2006)..

The possibility that MDD risk may be associated with changes in reproductive function, which can further amplify HPA hyperactivity, is also supported by preclinical studies showing that hormones of the HPA axis can profoundly inhibit reproduction in model animals. The simplest connection between the stress axis and the reproductive axis was suggested by the finding of immunoreactive glucocorticoid receptors in gonadotropin releasing hormone (GnRH) neurons (Ahima and Harlan, 1992). This concept was further bolstered by the discovery of specific promoter elements on the GnRH gene that were sensitive to glucocorticoid receptor activation (Chandran et al., 1996). However, the presence of glucocorticoid receptors in GnRH neurons may be species dependent (e.g., not found in ewes (Dufourny and Skinner, 2002)), and later studies have shifted some emphasis to key interactions at the level of the pituitary (Breen and Karsch, 2006).

Another mechanism by which HPA axis may influence reproductive function is via the peptide corticotrophin-releasing hormone (CRH). CRH is the most upstream hypothalamic factor regulating the HPA response to stress, and CRH also inhibits GnRH and gonadotropin secretion in model animal studies (Nikolarakis et al., 1986; Olster and Ferin, 1987) by disrupting the GnRH pulse generator (Li et al., 2010). More recently, CRH receptor mRNA (CRH-R1) was noted in murine GnRH neurons (Jasoni et al., 2005) and GR and CRH-R1 have been demonstrated in kisspeptin neurons of the anteroventral periventricular nucleus (Takumi et al., 2012), a group of upstream neurons that regulate GnRH function. Nonetheless, other more indirect routes for CRH influences on the HPG axis have been suggested, such as through noradrenergic neurons in the locus coeruleus (Traslaviña and Franci, 2012).

3. Brain circuitry linking MDD, HPA-HPG and ANS

3.1 Rationale

The comorbidity between MDD, HPA-HPG-axis dysregulation and CVD risk is not surprising from a brain circuitry point of view, given that depression is a disorder that involves hypothalamic nuclei (such as PVN and ventromedial nucleus), central medial amygdala, hippocampus, anterior cingulate cortex (ACC), and medial and orbitofrontal

cortex (mPFC, OFC) (Dougherty and Rauch, 1997; Mayberg, 1997; Drevets et al., 2002; Sheline et al., 2002; Rauch et al., 2003), regions that are dense in glucocorticoid and sex steroid hormone receptors (MacLusky et al., 1987; Clark et al., 1988; Handa et al., 1994b; Kawata, 1995; Tobet and Hanna, 1997; Donahue et al., 2000; Ostlund et al., 2003) and can relay information that regulates cardiac function through the ANS. The overlap between these circuitries has been historically noted from behavioral and endocrinological findings. However, with the advent of magnetic resonance imaging (MRI) technology, there is a greater focus on the investigation of shared brain circuitry implicated in the regulation of mood, endocrine, and cardiac functioning. This technology allows for hypothesis-driven *in vivo* exploration of this shared circuitry.

Over the past 5 years, there has been a rapid increase in studies examining the relationship between endogenous and exogenous glucocorticoids and brain activity in stress responsive brain regions using a variety of functional MRI (fMRI) paradigms. These studies typically examine healthy control subjects, generally comprising mixed-gender samples with age ranges between 18–35 years. Amygdala and hippocampal activity in response to stimuli of high negative emotionality was positively associated with pre-versus post-scan (Root et al., 2009) and diurnal rises in salivary cortisol (Cunningham-Bussel et al., 2009). This relationship between hyperactivation in the amygdala and increased diurnal cortisol was supported by evidence indicating that when categorized by level of endogenous cortisol, individuals with high cortisol demonstrated greater amygdala activity than those with low cortisol levels (van Stegeren et al., 2007; van Stegeren et al., 2008). Of interest, the increase in amygdala activation in a high cortisol condition was blocked by administration of a noradrenergic antagonist (van Stegeren et al., 2007; van Stegeren et al., 2008).

Cushing syndrome (CS), associated with chronic hypercortisolemia, also appears to be associated with hyperactivity in arousal regions. Adolescents with CS, compared with age- and gender-matched controls, demonstrated increased activation of the amygdala and hippocampus during successful encoding of emotional faces, despite similar memory performance (Maheu et al., 2008). Further, adults with CS showed hyperactivation in the anterior hippocampus, medial frontal gyrus, ACC, caudate, and superior parietal lobule during identification of emotional facial expressions. Accuracy in CS patients was lower and correlated with brain activity, suggesting these differences could be partially explained by compensatory recruitment of these regions (Langenecker et al., 2012). However, in general, these findings point to a pattern of significantly enhanced activation in the presence of heightened endogenous cortisol levels in healthy controls and Cushing syndrome patients. These relationships between brain activity and HPA response are not surprising given the shared neural circuitry regulating stress and HPA (as well as HPG) responses (see Figure 1).

In cortical stress response circuitry regions, however, somewhat contrasting results emerged with some reporting lower and some reporting higher cortical activity in prefrontal and ACC regions in association with cortisol response to stress (Pruessner et al., 2008; Root et al., 2009). Although several of these studies included sex as a covariate in the analyses, only one focused specifically on sex differences (Wang et al., 2007). Taken together, these findings suggested a complicated picture of endocrine effects on brain activity in subcortical and cortical arousal regions which may be better clarified if studies were specifically designed to investigate sex effects.

Not all subjects can be classified as natural cortisol "responders" to specific stimuli. (Wust et al., 2000a; Wust et al., 2000b; Muehlhan et al., 2011) Thus, one methodological alternative has been to experimentally administer exogenous cortisol (i.e., hydrocortisone). In general, amygdala and hippocampus appeared to be most sensitive to cortisol, demonstrating significant decreases in activation in comparison to placebo (Lovallo et al.,

2010). Striking sex differences in the neural response to cortisol (versus placebo) during fear conditioning (circuitry associated with stress response (Lebron-Milad et al., 2012) have been observed, with increased activation in the ACC, OFC, and mPFC in response to the conditioned (versus unconditioned) stimulus in females and decreases in these same regions in males (Stark et al., 2006; Merz et al., 2010).

3.2 HPA-HPG Alters Stress Response Circuitry Activation

Although studies on the HPA hormone-brain relationships occasionally reported controlling for menstrual cycle phase in women (Stark et al., 2006), gonadal hormone relationships with brain activity in functional neuroimaging studies have primarily involved cognitive tasks with fewer reports using emotional tasks as the endpoint. We recently demonstrated that activation in stress response circuitry regions was modulated across menstrual cycle in healthy women in response to stressful images, with greater activation in anterior hypothalamus, amygdala, hippocampus, ACC, and OFC during the early follicular phase compared with late follicular/midcycle (Goldstein et al., 2005). Further, in imaging studies of healthy women, hyperactivity of the amygdala and hippocampus was found during late luteal compared with early follicular menstrual cycle phase (Andreano and Cahill, 2010). Importantly, estradiol levels were negatively associated with amygdala activation (Andreano and Cahill, 2010). A direct comparison between males and females showed a consistency with these patterns, with greater hyperactivity in men than women in a number of subcortical and cortical stress response regions (especially the latter), particularly when women were scanned during their late follicular/midcycle compared to when the men were compared to the same woman scanned during the early follicular menstrual cycle phase (Goldstein et al., 2010). The results suggested that gonadal hormones modulated subcortical arousal by prefrontal circuitry in the healthy brain (Goldstein et al., 2005; Goldstein et al., 2010).

Inhibitory responses to negative (versus neutral) emotional stimuli targets during the luteal phase (versus follicular) were associated with greater activation in the medial OFC (Protopopescu et al., 2005), ACC, dorsolateral prefrontal cortex, and putamen (Amin et al., 2006), although not consistently (Dreher et al., 2007; Rupp et al., 2009a). Discrepancies may have been related to differences in menstrual phase definition, with follicular phase defined as days 4–8 (Dreher et al., 2007), 8–12 (Protopopescu et al., 2005), or 10–12 after the start of menstruation (Rupp et al., 2009a), and luteal phase defined as 19–23 days following the start of menstruation (Rupp et al., 2009b), 6–10 days post luteinizing hormone surge (Dreher et al., 2007), or 1–5 days before menses onset (Protopopescu et al., 2005). Although healthy control women in these samples had regular cycles, this variation in phase definition across studies could have had significant effects on interpreting the changing circulating estradiol and progesterone levels, leading to substantial differences reported in these studies in brain activity across the menstrual cycle.

Experimental studies of effects of exogenous gonadal hormone regulation of neural responses to emotional stimuli demonstrated that compared with placebo, progesterone administration during the early follicular phase was related to increased amygdala reactivity to emotional face processing, increased amygdala-dorsal ACC connectivity, and decreased amygdala-fusiform gyrus connectivity (van Wingen et al., 2008b). In contrast, testosterone administration increased hippocampus and inferior temporal gyrus activation during memory formation and retrieval of male faces in middle-aged women (van Wingen et al., 2008a). Compared with placebo, testosterone increased amygdala responsiveness to levels equivalent to those observed in young women (van Eijndhoven et al., 2009) and reduced functional connectivity between the amygdala and OFC (van Wingen et al., 2010). Thus, administration of exogenous gonadal hormones exerted significant influence on amygdala

responsiveness in general and coupling between the amygdala and other limbic and cortical regions during evaluation of emotionally salient cues.

A few studies recently demonstrated compelling evidence of links between HPA-HPG hormone dysregulation and brain activity deficits in MDD. Cortisol administration to currently depressed women resulted in increased hippocampal activation during encoding of neutral (versus negative or positive) words in comparison to healthy control women, a trend not observed during placebo and not in men (Abercrombie et al., 2011). Further, premenopausal women with recurrent MDD displayed hypoactivity in a number of regions involved in the stress response circuitry that were significantly associated with gonadal hormone deficits (Holsen et al., 2011), i.e., decreased estradiol and increased progesterone levels in MDD women during late follicular/midcycle phase of the menstrual cycle. Finally, hypoactivation to positive stimuli in the nucleus accumbens and hyperactivations in the amygdala and lateral OFC in response to negative stimuli during the luteal phase (versus late follicular) were reported in women with premenstrual dysphoric disorder compared with healthy controls (Protopopescu et al., 2008). Taken together, findings from these studies indicated complex interaction between HPA (cortisol) and HPG (progesterone, estradiol) dysregulation and brain activation during emotional processing (respectively) in women with mood disorders, providing support for mechanisms implicating neuroendocrine systems associated with sex differences in depression.

3.3 Mood, Endocrine and ANS Share Brain Circuitries

Historically, emotions and visceral function have been intimately associated, the latter of which is controlled by the ANS, coordinated to a large extent by the hypothalamus (Papez, 1995). Subsequently, a more complex network has been implicated including some highly sexually dimorphic brain regions of interest, such as amygdala (Zola-Morgan et al., 1991; Kluver and Bucy, 1997), hippocampus, cingulate cortex (Mac, 1949; Papez, 1995), medial PFC, and periacqueductal gray (Price and Drevets, 2010). In fact, MDD has been characterized by some authors as maladaptive stress-induced neuroplastic alterations in the medial prefrontal cortico-amygdalo/hippocampo-hypothalamo-brainstem circuits (Krishnan and Nestler, 2008; Murray et al., 2011). Vagal dyscontrol of the solitary nucleus and motor nucleus of the vagus in the brainstem, which are innervated by preautonomic neurons of the PVN, can affect heart and cardiovascular function (Swaab et al., 2003); (see Figure 3).

Linking ANS activity to various metabolic abnormalities and MDD has gained popularity in the brain imaging literature (Licht et al., 2008; Dao et al., 2010; Henry et al., 2010). The time interval between two R-waves during the recording of heart rate (HR) by electrocardiogram is referred to as the R-R interval. Fourier or autoregressive analysis of the cyclical oscillations in the R-R interval (or R-R variability; RRV) produces power spectra, portions of which reflect different autonomic influences on heart rate and blood pressure. Sympathetic activity causes a slow increase in HR and is thus reflected in the low-frequency (LF) range of 0.04 to 0.15 Hz. Parasympathetic or vagal activity causes a rapid decrease in HR and is associated with the relatively high-frequency (HF) range of 0.15 to 0.40 Hz (Malik et al., 1996). The spectral components of the RR-intervals have been defined as heart-rate variability (HRV) or RRV, and reflect sympathovagal balance (Malik et al., 1996).

Research suggests that increased sympathetic and decreased parasympathetic activity (cardiac regulation from the CNS through the vagal nerve) in response to stress may represent a unique window to visualize underlying biological mechanisms involved in MDD and its comorbidity with CVD. Decreased RRV is associated with the incidence of cardiac events and coronary disease (Tsuji et al., 1996; Liao et al., 1997), atherosclerosis (Huikuri et al., 1999), mortality in men (Dekker et al., 1997), and MDD (Gorman and Sloan, 2000;

Nahshoni et al., 2004; van der Kooy et al., 2006; Licht et al., 2008; Lane and Wager, 2009); (Licht et al., 2010), and with the comorbidity of MDD and CVD risk (particularly in women), demonstrated in our recent study (Goldstein et al., 2011). Specifically, MDD has been associated with parasympathetic cardiac dysregulation (Yeragani et al., 1991; Gorman and Sloan, 2000; Nahshoni et al., 2004; van der Kooy et al., 2006; Holsen et al., 2012), operationalized primarily as the high frequency component of the R-R interval variability.

Recent studies have investigated the abnormal brain circuitry correlates of ANS dysregulation, although primarily in healthy participants. The investigations on heart rate reactivity and RRV in association with emotional tasks (Lane et al., 2001; Simpson et al., 2001; Kuniecki et al., 2003; Critchley et al., 2005; O'Connor et al., 2007; Ahs et al., 2009; Lutz et al., 2009; Mujica-Parodi et al., 2009; Wager et al., 2009a; Wager et al., 2009b) reported activation of CNS regions implicated in ANS control, including hypothalamic nuclei, brainstem regions, and amygdala, and medial prefrontal cortex (mPFC), orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), and insula. This circuitry was activated regardless of sample size or whether assessed using pulse oximetry or an electrocardiogram.

Reviewing the literature in healthy populations, Lane and Wager (Lane and Wager, 2009) defined a medial-prefrontal-brainstem network implicated in ANS control in tandem with endocrine, emotion, and behavior (see Figure 3). In an elegant series of studies by Wager and colleagues (Wager et al., 2009a; Wager et al., 2009b), two main pathways mediated brain-heart rate (HR) relationships in response to stress: increases in the pregenual ACC [mediated by connections with periaqueductal gray (PAG)] and decreases in ventromedial PFC (vmPFC)/medial OFC (mOFC). Ventromedial PFC/mOFC was particularly important in mediating anxiety and HR associations (Wager et al., 2009a). We extended this work to investigate brain CNS-ANS associations in stress response circuitry in women with recurrent MDD, demonstrating that hypoactivations of stress response circuitry in anterior hypothalamus, hippocampus, ACC, and OFC were significantly associated with a loss of parasympathetic cardiac regulation in premenopausal MDD women (Holsen et al., 2012), controlled for menstrual status and potential medication confounds.

Findings that implicated limbic brain regions in ANS regulation were not surprising given that they are critical in the regulation of mood. Experimental evidence for the fact that limbic regions, such as hippocampus and amygdala, impact changes in autonomic tone date as far back as 1956 (Anand and Dua, 1956; Schwaber et al., 1982). These regions also affect autonomic regulation through their projections to the anterior hypothalamus and the control of the HPA and HPG circuitries. Further, paralimbic regions, such as the orbitofrontal cortex and anterior cingulate gyrus, also regulate autonomic tone, demonstrated in human studies (Mesulam and Mufson, 1982) as well as stimulation studies in monkeys (Kaada et al., 1949; Hoffman and Rasmussen, 1953). Previous work demonstrated that menstrual status significantly affected RRV (Dart et al., 2002; McKinley et al., 2009), and most studies have not controlled for menstrual status in female participants. Sex differences in RRV (Zhang, 2007) were reported in one study, and thus we are currently investigating sex differences in shared brain circuitries regulating mood and cardiac dysregulation. Increased sympathetic activity and decreased vagal activity have been proposed as biomarkers of the severity of depression (Kemp et al., 2010) and thus understanding this comorbidity and associated sex differences will be key to understanding the nature of MDD and associated risk for CVD.

3.4 Sex differences in shared mood, endocrine and ANS circuitries

Circuitry shared by mood, endocrine and ANS regulation includes the most highly sexually dimorphic regions in the brain (see Figure 4). Thus, we have argued that an understanding of the disruption of this circuitry during fetal development may provide critical clues to understanding the fetal programming of sex differences in their comorbidity. On the human

level, *in vivo* imaging and postmortem studies demonstrated sex differences in these regions at the gross brain volume level in brain imaging studies or nuclei level in postmortem work. *In women*, relative to cerebrum size, findings demonstrated greater relative volumes of hippocampus (Filipek et al., 1994; Giedd et al., 1996; Murphy et al., 1996; Goldstein et al., 2001), ACC (Paus et al., 1996; Goldstein et al., 2001), and OFC (Goldstein et al., 2001). *In men*, there are greater volumes (relative to cerebrum size) of the amygdala (Giedd et al., 1996; Goldstein et al., 2001), hypothalamus (Swaab and Fliers, 1985; Allen et al., 1989; Goldstein et al., 2001), and paracingulate gyrus (Paus et al., 1996; Goldstein et al., 2001). Thus, women tend to have relatively larger volumes of hippocampus, OFC and ACC, whereas men have relatively larger amygdala and hypothalamic volumes (see Figure 4). Recent findings offer additional evidence that even structural brain volumes in women may show some variation at different points in the menstrual cycle, as demonstrated with hippocampal gray matter volume increased and dorsal basal ganglia gray matter volume decreased during follicular compared with luteal phase (Protopopescu et al., 2008). Further, estradiol, progesterone, and testosterone levels in young adults were associated with 13%, 13%, and 2% of the variation in superior parietal gyrus, medial temporal pole, and inferior frontal gyrus gray matter volumes, respectively (Licht et al., 2010), suggesting significant activational associations between gonadal hormone levels and neuroanatomic variation in humans.

4. Towards Determination of Mechanisms

Together, studies on HPA, HPG, stress behavior, and ANS circuitries suggest a shared biologic substrate underlying comorbidity of MDD and CVD that has developmental origins and is sex-dependent. A growing body of data is consistent with a prenatal stress model that involves excess maternal glucocorticoids impacting sex-dependent development of fetal stress circuitry implicating disruptions in GABA and growth factors with consequences for mood, endocrine function, ANS and vascular abnormalities (as illustrated in Figure 5).

4.1 Impact of Sex Differences in Brain Development

Sex differences in brain development are driven by synergies of hormone influences and selective gene transcription. Although recent work has identified direct genetic contributions to sexual differentiation of the brain (De Vries et al., 2002; Arnold, 2011; Majdic and Tobet, 2011), the primary driver of this process has always been noted at the level of gonadal hormone regulation. This is initiated when the testes begin to secrete testosterone at the beginning of second trimester, at which time both androgens and estradiol (which increases by the conversion of testosterone to estradiol by the enzyme aromatase) masculinize the male brain. This has been demonstrated in animal studies (McEwen, 1983; Tobet et al., 1985; Simerly et al., 1990; Tobet et al., 1993; Handa et al., 1994b; O'Keefe et al., 1995; Park et al., 1996; Gorski, 2000; Chung et al., 2006). Findings in humans indirectly suggest that this too may, in part, contribute to understanding sexual dimorphisms in adulthood (Goldstein et al., 2001), although the role of estradiol in humans is less clear as neither aromatase (Grumbach and Auchus, 1999; Maffei et al., 2004) or estrogen receptor (Smith et al., 1994) deficient individuals are lacking in sexual interest. In animals, nuclei of the corticomedial amygdala, PVN, ventromedial hypothalamic nucleus, hippocampus, OFC and ACC express high concentrations of gonadal and/or adrenal hormone receptors compared with other brain regions (Handa et al., 1994b; Pacak et al., 1995; Koob, 1999; Solum and Handa, 2002; Tobet, 2002; Ostlund et al., 2003; Lund et al., 2004a; Lund et al., 2004b; Suzuki and Handa, 2004; Lund et al., 2006). These brain regions have been implicated in regulating HPA and ANS functions and are abnormal in MDD patients. The hypotheses in this review are, in part, based on the premise, supported by work on sex differences in another disorder with fetal origins (schizophrenia) (Goldstein et al., 2002), that normal

sexual dimorphisms during fetal development go awry in brain regions associated with mood, HPA and ANS functions, and that mechanisms involved in understanding normal sexual dimorphisms, such as the roles of gonadal and adrenal hormones (in association with genes) (Handa et al., 1994c; Majdic and Tobet, 2011) will contribute to understanding sex differences in risk for comorbid MDD and CVD risk in adulthood. Work with model animals has been a primary driver of this notion.

4.2 Changes in GABA Implicated in MDD

There is a long history of study on the role of GABA in brain sexual differentiation (e.g., (Davis et al., 1996; McCarthy et al., 2002; Tobet et al., 2009). Sex-dependent disruption of the development of sexually dimorphic brain regions implicated in MDD may involve GABA signaling pathways (Gao and Bao, 2011; Stratton et al., 2011; Tobet et al., 2013). GABA has been implicated in the development of MDD in *ex vivo* and *in vivo* studies, particularly its role in understanding the efficacy of antidepressant medications. MDD patients have consistently shown reduced plasma, cerebrosprinal fluid (CSF), and cortical levels of GABA as compared to healthy controls (Chang et al., 2003; Pilc and Nowak, 2005; Kalueff and Nutt, 2007; Sanacora and Saricicek, 2007), findings that have been in part replicated in model animal studies (Alcaro et al., 2010). The majority of GABA studies in MDD have focused on its therapeutic role, including interactions with serotonin and neuronal systems targeted by selective serotonin reuptake inhibitors (SSRIs) (Taylor et al., 2003), although GABAergic pharmaceuticals in and of themselves have shown low efficacy in MDD patients. Polymorphisms in GABAergic genes have been identified in MDD patients (Liu et al., 2007) as has altered levels of GABA in first-degree unaffected relatives of MDD patients (Petty, 1994). Postmortem findings demonstrated that mRNA levels of GABA receptors in frontopolar cortex were lower in MDD suicide cases than controls (Merali et al., 2004; Choudary et al., 2005). Sex differences in GABA in MDD cases have also been reported previously (Sanacora et al., 1999), although few have focused on this issue and designed studies to avoid confounding the associations among sex, hormones, medications, and GABA. In fact, earlier studies reported that GABA levels decreased in the mid-follicular menstrual cycle stage among healthy women (Halbreich et al., 1996), although this was not replicated at the level of cortical GABA levels and gonadal hormones (Epperson et al., 2006).

There have been a number of preclinical studies indicating a role for GABA using model animals (reviewed (Cryan and Slattery, 2010; Luscher et al., 2010)). Although animal findings based on the forced swim test (a model of depressive-like behaviors) did not identify significant associations with GABA$_A$, alpha 1, or GABA$_A$, alpha 3 (Verkuyl et al., 2004), knockout mice for GABA$_A$ gamma2 subunits may provide a substantially better model (Shen et al., 2010; Shen et al., 2012). Further, examining the metabotropic GABA$_B$ receptors, knockout mice for GABA$_B$ R1 subunit displayed antidepressant-like activity and GABA dysfunction (Cryan and Kaupmann, 2005). Given the pivotal role of the PVN in HPA axis outflow, it is perhaps not surprising that GABA may play role(s) in prenatal stress models, not only for PVN neuronal development but also PVN vasculature, suggesting potential links between MDD and CVD risk. As we recently demonstrated, PVN development is regulated by glucocorticoids and GABA, with females being particularly vulnerable to GABA disruption in PVN neuronal (McClellan et al., 2010; Stratton et al., 2011) and vascular development (Frahm et al., 2012).

It is important to note that there are other neurotransmitter connections that can be drawn across multiple disorders (Gao and Bao, 2011; Blier and El Mansari, 2013). As reviewed above, there are substantial reasons for focusing on GABA, but these are not meant to be exclusive of other mechanisms, some of which are reviewed further below.

4.3 Glucocorticoid Excess during Development Programs Adult Function

The hypothesis that glucocorticoid excess leads to the propensity for adult disorders has been tested in a number of studies over the last two decades (Reynolds, 2012). This work received a great deal of attention when Barker and colleagues in the 1980's proposed a fetal programming model of CVD (Barker, 2012). Preclinical studies using a number of different model animals demonstrated the impact of prenatal stress on a host of HPA-related outcomes, including hypothalamic and hippocampal structure and function (Takahashi et al., 1992; Matsumoto and Arai, 1997; Weinstock, 1997), with lasting effects on the HPA axis by programming a "hyperactive" system vulnerable to ANS deficits, hyperglycemia and hypertension (Weinstock et al., 1992; Henry et al., 1994; Barker, 1995; Arborelius et al., 1999; Seckl, 2001). Evidence from model animal and human studies suggested that a variety of prenatal stressors altered fetal cardiac function and parasympathetic regulation of the heart (Manning, 1995; Schifrin, 1995); (Prechtl, 1984; Lee et al., 1998). Inflammation (which has been associated with prenatal stress models) has been postulated as one pathway linking autonomic dysregulation to atherosclerosis, through what Tracey and colleagues called the vagal anti-inflammatory reflex (Tracey, 2002).

Exactly how glucocorticoid excess in development programs elevations in blood pressure in adulthood is still under investigation (Edwards et al., 1996). In observational studies of humans though, higher blood pressures were observed among adolescents exposed to corticosteroids antenatally (Doyle et al., 2000). Explanations have included, for example, long term changes in glucocorticoid receptors (Levitt et al., 1996) or reduction in endothelial nitric oxide (NO) production (Wallerath et al., 1999). Further, hypotheses focused on placental compromise are critical in the pathway between maternal excess glucocorticoids and fetal response and are currently under investigation (O'Regan et al., 2001; Howerton et al., 2013).

CRH is produced in large quantities by the healthy placenta in late pregnancy and contributes to the initiation of parturition (Frim et al., 1988; Giles et al., 1996). Placental 11-beta-hydroxysteroid dehydrogenase (11-beta-HSD, type 2 isoform) is produced to protect the fetus from overexposure to glucocorticoids. Investigators have proposed that the generalized placental response when compromised is to produce increased quantities of CRH. In preclinical studies, even a reduction of protein intake during rat pregnancy decreased 11-beta-HSD activity (Edwards et al., 1993; Edwards et al., 1996; Langley-Evans et al., 1996a; Langley-Evans et al., 1996b; Churchill et al., 1997; Langley-Evans, 1997; Seckl, 2001). Thus, conditions producing a maternal prenatal stress response may result in placental compromise, which may be related to studies in humans demonstrating a significant association between reduction in placental 11-beta-HSD, type 2 isoform and MDD in adulthood (Poor et al., 2004).

In fact, pregnancy conditions associated with placental compromise and fetal vascular adverse outcomes were related to disproportionate elevations in circulating CRH levels, including fetal growth restriction (Goland et al., 1993; Petraglia et al., 1995; Giles et al., 1996), inflammation in general (Petraglia et al., 1995), preeclampsia and other hypertensive states in pregnancy (Warren et al., 1995), and preterm delivery (Wolfe et al., 1988; Warren et al., 1992), pregnancy complications that have been associated with adult risk for MDD and CVD. Chronic villitis and uteroplacental ischemia evoked enhanced placental CRH release. Furthermore, vascular compromise, assessed by umbilical artery velocimetry, was associated with increased CRH concentrations in the fetal compartment (Giles et al., 1996). Unlike in the hypothalamus, placental CRH and cortisol participate in a feedforward loop (Robinson et al., 1988; Karalis et al., 1996; Majzoub et al., 1999). Thus, when placental compromise elevated CRH, it had the potential to increase fetal adrenal activity and hence, fetal exposure to glucocorticoids and vascular compromise.

There is recent evidence that vascular compromise and cardiac dysregulation are sex-dependent. For example, human studies of the impact of low birth weight on young adult ANS and baroreceptor control of cardiac function demonstrated that females compared with males showed greater cardiac dysregulation and reduced baroreflex sensitivity in response to stress (Jones et al., 2007). Sex differences in ANS function were reported in several studies (Evans et al., 2001; Snieder et al., 2007), with an emphasis on women's reliance on parasympathetic ANS control and the impact of the menstrual cycle on RRV (Dart et al., 2002; McKinley et al., 2009). These studies, although few in number, provide initial evidence of the importance of designing studies to test the sex-dependency of the fetal programming of vascular and cardiac outcomes, which is rarely considered at the human or preclinical level.

A number of preclinical studies using model animals have underscored this point. Administration of dexamethasone to pregnant ewes resulted in elevated blood pressure later in life (Dodic et al., 1999) (Dodic et al., 2006) In the rat model, such administration resulted in modified hepatic receptor expression and glucose intolerance in the adult offspring (Nyrienda et al., 1998). Similarly, prenatal exposure to dexamethasone in rat models demonstrated reductions in growth and alterations in hepatic triglyceride levels (Drake et al., 2010). When this model was explicitly investigated by sex, these alterations were more severe in females, accompanied by increased hepatic steatosis when placed on a high fat diet (Carbone et al., 2012a). Sex-dependent outcomes (i.e., more in females) were characterized by deficits in growth hormone releasing hormone mRNA within the arcuate nucleus and circulating insulin-like growth factor-1(IGF-1) (Carbone et al., 2012a). Further, in a different study, sex-dependent effects were found in rodents exposed to prenatal dexamethasone, which resulted in *lower* resting state blood pressure in adulthood. However, they were more susceptible to a *hypertensive* phenotype even after a very mild stressors (O'Regan et al., 2008), a susceptibility that was more prevalent in females (O'Regan et al., 2004).

Independent of the rise of fetal programming models of CVD in the mid-1980's, psychiatry since Freud has had a much longer history of an etiologic focus on early developmental factors (including fetal brain development) that impact adult psychiatric outcomes. Population-level studies have demonstrated fetal risk factors for adult onset MDD (van Os et al., 1997; Watson et al., 1999; Brown et al., 2000), for which a final common pathway involving maternal-fetal HPA circuitry activation was proposed (Nemeroff et al., 1984; Holsboer et al., 1987; Arborelius et al., 1999; Heim et al., 2002; Parker et al., 2003; Raison and Miller, 2003; Barden, 2004; Owen et al., 2005). Further, at the human population level, there was a sex-dependent (females higher) risk of the comorbidity of MDD and CVD when exposed to preeclampsia or conditions producing fetal growth restriction (Goldstein et al., 2011).

Preclinical studies have demonstrated sex-dependent effects of prenatal stress on behavioral development for a long time, e.g., (Joffe, 1965). The influence of sex steroids in the process came to the forefront with experiments that more selectively addressed sex behavior (Ward, 1972) and then progressed to other behaviors (Meisel et al., 1979). A selective tie to sex steroids was connected to direct changes in the androgen-metabolizing enzyme, aromatase, in the brains of prenatally stressed rats (Weisz et al., 1982). Between the early studies where stress was administered only late in pregnancy and more recent studies where stress has been examined as a function of different trimesters of pregnancy (Goel and Bale, 2009), it is increasingly clear that the effects of sex steroids, and mechanistic pathways to understand these effects differ across prenatal stages.

Suri and Vaidya, 2012). Further, it has been shown that prolonged glucocorticoid levels enhance neuronal cell death (Reagan and McEwen, 1997), perhaps through morphological changes in hippocampus (Conrad et al., 2007) that may make those neurons more susceptible to neurotoxic challenges (Landfield et al., 1978; Uno et al., 1989; Conrad et al., 2007). More relevant to the programming of fetal brain, increased apoptotic cell death has also been described in the amygdala and other limbic structures after glucocorticoid treatment in developing rats (Zuloaga et al., 2011; Zuloaga et al., 2012a; Zuloaga et al., 2012c).

In fact, maternal treatment with DEX caused hypomethylation of the BDNF promoter in females only in PVN and hippocampus (Carbone and Handa, 2012). This raises the possibility that epigenetic changes (i.e. functional changes to the genome that are not through changes in nucleotide sequence) may be involved in the actions of steroid hormones. Indeed, epigenetic effects on the developing nervous system that result in sex differences in adult brain function have now been reported (McCarthy et al., 2009; Qureshi and Mehler, 2010). However, the absence of $GABA_B$ signaling resulted in lower BDNF levels in PVN of mice (McClellan et al., 2010).

Although BDNF has been implicated in MDD etiology (as discussed above) (Nibuya et al., 1995; Duman, 2004), less is known about the role of this neurotrophin in non-neuronal cells, such as endothelial cells, and in vessel survival and stabilization following vascular injury (Kermani and Hempstead, 2007). Endothelial cells in heart arteries and capillaries, regulators of vascular homeostasis, express BDNF and trkB during development, are particularly high in adulthood (Kermani et al., 2005), and are increased following vascular injury (Kraemer, 2002). These studies suggest an important BDNF role in vascular repair in addition to its role in neuron maintenance and synaptogenesis (Lafuente et al., 2012).

VEGF is a major angiogenic protein that also acts in development and in response to injury in adulthood. In fact, VEGF is found in high density in PVN (Alonso et al., 2005), one of the most highly vascularized brain regions (Finley, 1937; Menendez and Alvarez-Uria, 1987; Frahm et al., 2012), and in hippocampus (Newton et al., 2003). It has also been found to mediate the effect of BDNF on antidepressant treatment in MDD in the hippocampus (Cao et al., 2004; Warner-Schmidt and Duman, 2007), suggesting a neurogenic role for VEGF in the adult hippocampus in MDD. It will be important to test the hypothesis that disruption of maternal gestational glucocorticoids work in part through dysregulation of growth factors in the heart and brain, particularly in PVN and hippocampus, areas important for HPA axis regulation. In fact, DEX administration into adult PVN suppressed VEGF (Alonso et al., 2005), suggesting that effects of glucocorticoids in PVN suppress growth factors.

There is a great deal of work on the role of IGF-1 in the development of CVD, given its relationship to growth hormone (GH) and insulin. Studies have supported a U-shaped relationship in that lower fetal IGF-1 in mice impaired cardiac tissue development, but excess IGF-1 led to excessive growth (LeRoith, 2010). In clinical studies, IGF-1 was inversely proportional to high sensitivity C-reactive protein, a critical inflammatory CVD risk indicator (Sesmilo et al., 2001; Lawson et al., 2007). These studies further reported that estradiol reduced IGF-1 and promoted GH resistance (Heald et al., 2005; Lawson et al., 2007), suggesting potential sex differences in the regulation of IGF-1. In this regard, Carbone and Handa (Carbone et al., 2012a) also demonstrated that, in rats, fetal exposure to synthetic glucocorticoids reduced circulating IGF-1 levels and arcuate nucleus Growth Hormone Releasing Hormone mRNA levels in adulthood, an effect that was only seen in females.

Animal models of chronic stress in IGF-1 treated mice (Duman et al., 2009) and IGF-1 KO mice had a significant impact on reducing immobility, underscoring its antidepressant-like properties (Hoshaw et al., 2005; Malberg et al., 2007; Duman et al., 2009). In healthy populations, IGF-1 decreased with age (Deuschle et al., 1997; Franz et al., 1999; Unden et al., 2002; Weber-Hamann et al., 2009) and was positively associated with decreased levels of depressive symptoms (Unden et al., 2002). However, in MDD, increased IGF-1 was associated with hypercortisolemia (Weber-Hamann et al., 2009); (Deuschle et al., 1997; Franz et al., 1999) but dependent on the woman's menstrual cycle phase (Franz et al., 1999). Thus the role of IGF-1 in MDD is still unclear and in part inconsistent. This may be due to the fact that most of the animal studies included only male mice, and clinical studies of MDD have been primarily female.

4.5 Impact of Developmental Rates on Sex Differences in Comorbidity

Several brain characteristics develop at different rates in males and females (Tobet and Hanna, 1997), and these rates of development can depend on the perinatal gonadal steroid milieu. There are a number of molecules that have shown sex-dependent differences in the developing hypothalamus, including ERα and ERβ and GABA$_B$ receptor R1 subunit (Wolfe et al., 2005), islet-1 (Davis et al., 2004), calbindin and nNOS (Edelmann et al., 2007), all of which may appear sex-dependent only transiently during development. Studies are needed to assess the rate at which the PVN and other key stress circuitry brain regions, such as the hippocampus and amygdala, develop in males versus females, the role of gonadal steroid hormones and their receptors, and sex-dependent genetic factors. These studies will determine whether changing the developmental rate may be a critical factor for determining the developmental susceptibility of the PVN and/or other HPA regions to stress-induced alterations leading to selective sex-dependent vulnerability for MDD and/or CVD in adulthood.

5. Conclusions

The comorbidity of major depressive disorder (MDD) and cardiovascular disease (CVD) will be the number one cause of disability worldwide in 2020 and thus a major public health problem that will necessitate new therapeutic initiatives. Unfortunately, there are few scientists in either psychiatry or cardiology that focus their investigations on understanding the higher rate (almost twice the risk) in women than men. The fetal programming of MDD and CVD has been proposed independently of each other, and both fields have proposed prenatal stress models. This review argues that the comorbidity of MDD and CVD, and in particular the significant sex differences, arises in part from hormone-dependent pathogenic processes initiated during fetal development that result in greater risk in women than men. Specifically, the fetal origins of MDD and CVD result from alterations in the prenatal *maternal* environment that result in her producing excess glucocorticoids, which then drive sex-dependent developmental alterations of the *fetal* HPA axis circuitry with implications for mood and stress regulation, ANS function, and the vasculature into adulthood. These alterations include disruptions of pathways associated with GABA in neuronal and vascular development and growth factors (such as BDNF, VEGF, and IGF-1) that have critical roles in development and adult response to injury in the heart and the brain. Further, developmental timing of these disruptions is key, given that the impact of some of these molecules on neuronal and vascular development only occur in sex-dependent ways at particular periods in fetal development. Thus, further investigations of the sex-dependent development of these key brain regions, such as the PVN, the role of gonadal steroid hormones and their receptors, and sex-dependent genetic effects will be critical for an understanding of the origins of sex differences in the comorbidity of depression and cardiovascular disease and the potential development of novel sex-dependent therapeutics.

Acknowledgments

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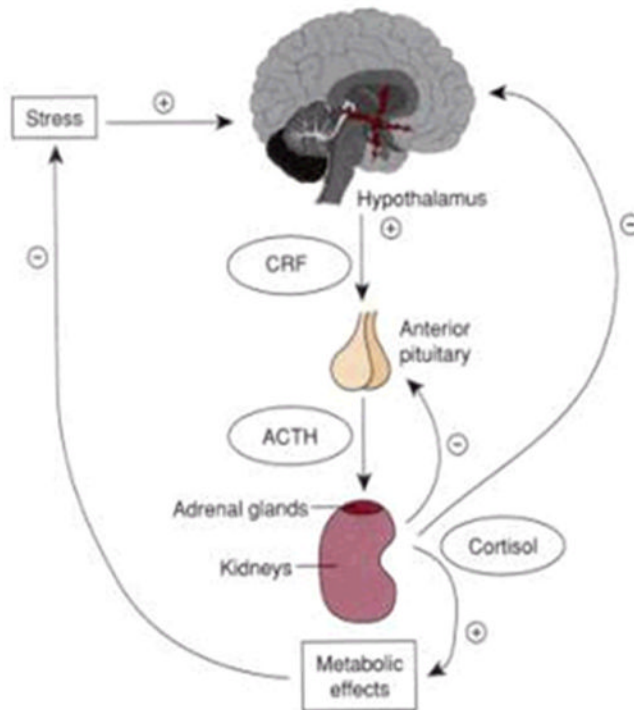
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Highlights

1. Fetal origins of depression-CVD comorbidity are sex-dependent and produce higher risk in women.

2. Prenatal stress models explain shared sex-dependent effects on adult mood, stress, ANS, and vasculature.

3. Disruptions of developmental pathways associated with glucocorticoids, GABA, growth factors, gonadal steroids and genes are key.

4. The sex-dependent development of the hypothalamic paraventricular nucleus is critical.

5. Developmental timing is essential for understanding sex-dependent effects.

Figure 1. Shared Brain Circuitry between Stress Response, Mood and HPA Regulation
Stress response circuitry in the brain is shared with HPA and HPG regulation and a number of these regions are found to be abnormal in MDD, structurally (operationalized as MRI brain volumes) and functionally (operationalized in studies of fMRI or Positron Emission Tomography or PET).
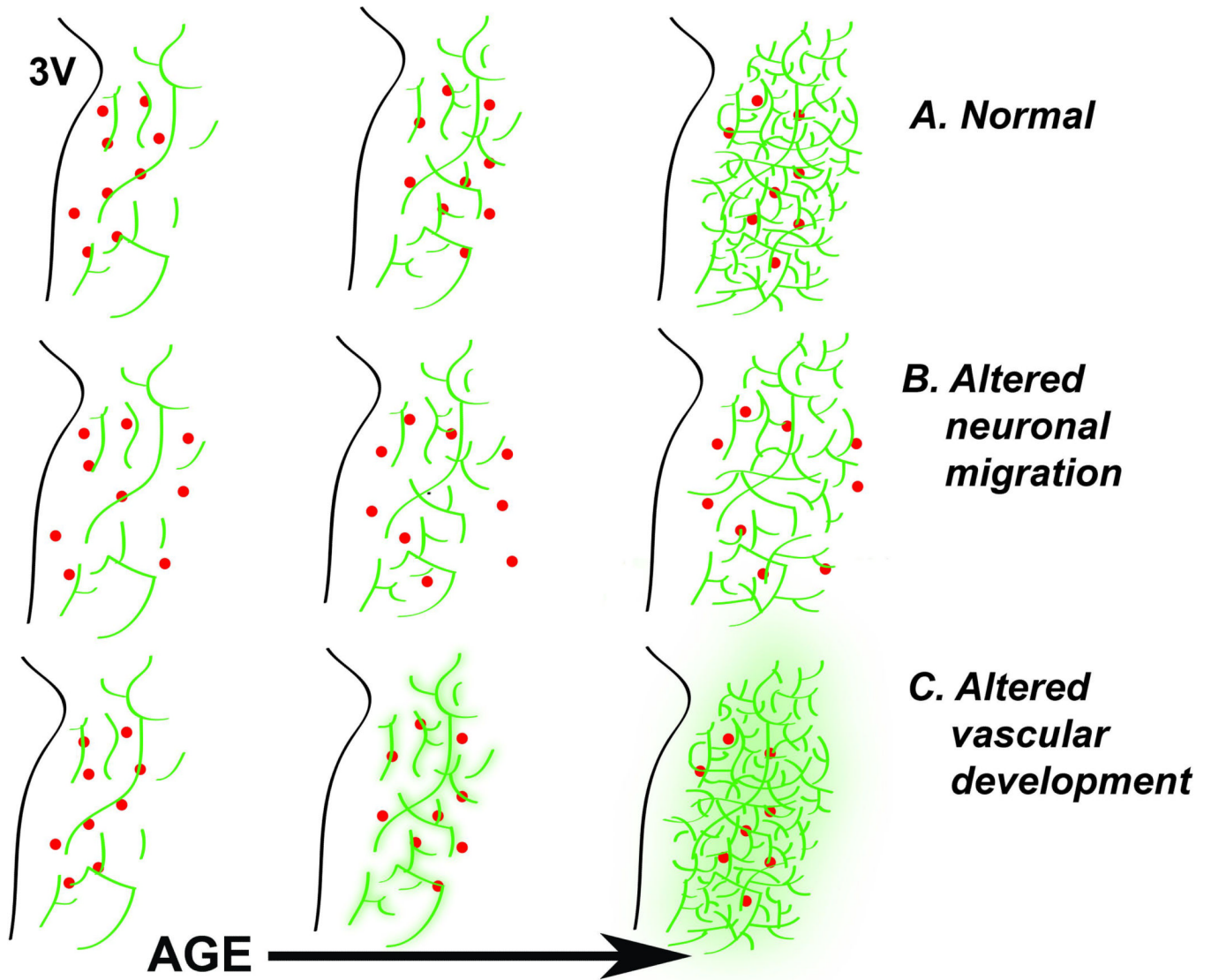
Figure 2. Potential interactions of PVN neuronal and vascular development
Schematic diagram of coronal section illustrates the development of PVN neurons (red dots) along the proliferative zone of the third ventricle (3V) and their migration laterally with age (A). At later ages there is a major expansion of PVN vasculature (Green lines). The neuronal relationship to vascular elements (e.g., proximity) could be altered to create disease susceptibility (B), or the blood brain barrier function could be compromised leading to disease susceptibility (C).
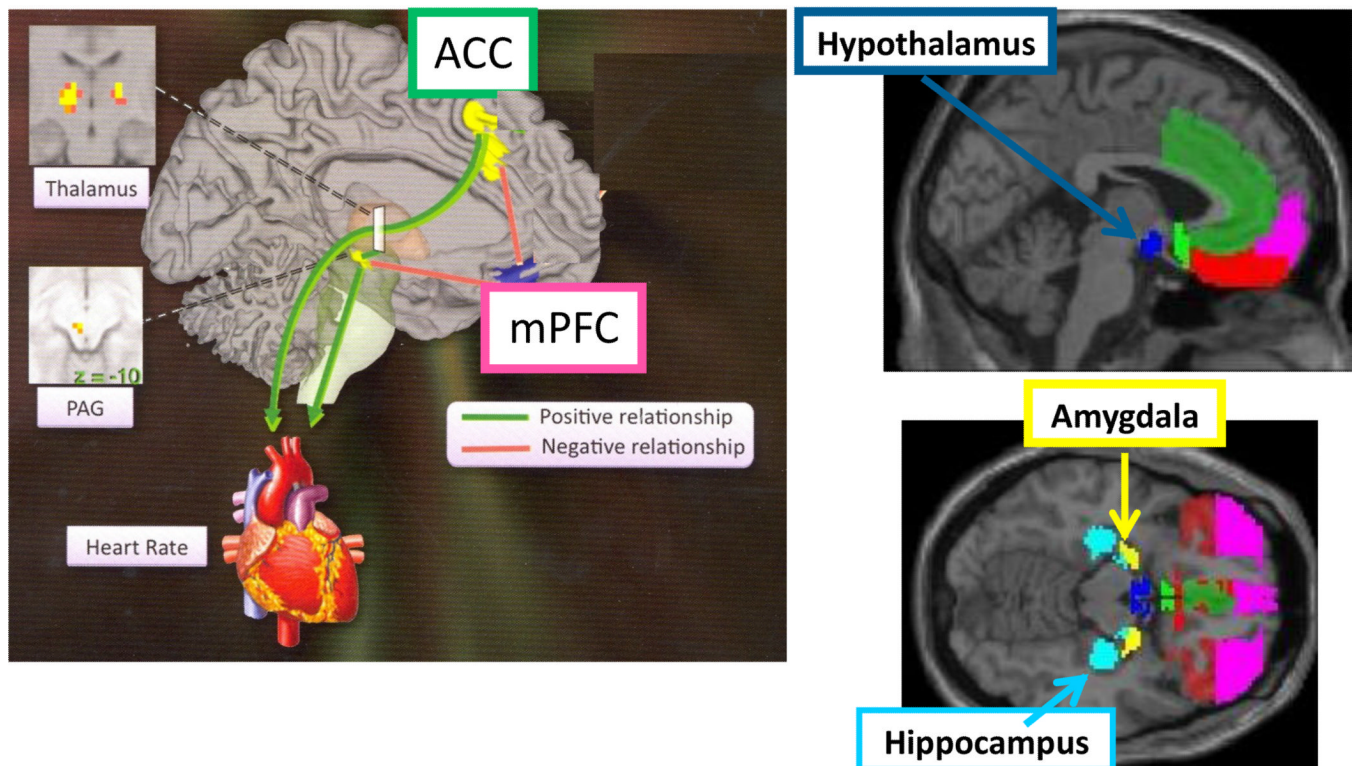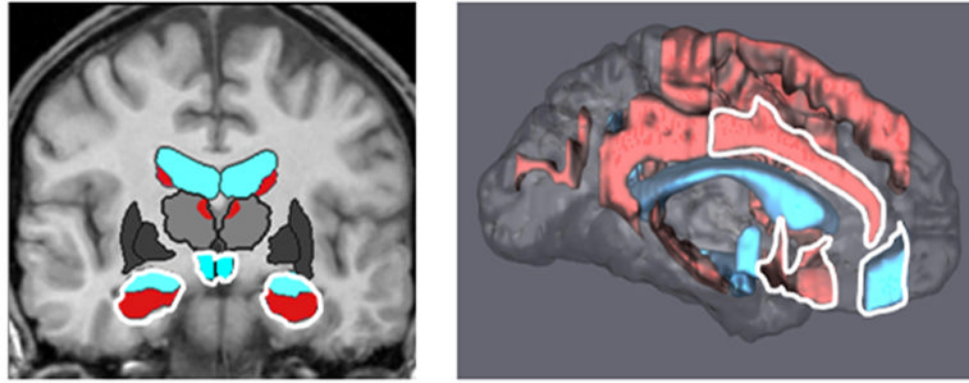
Figure 3. Brain Regions Shared between Mood, Stress, and ANS
Brain regions implicated in CNS regulation of stress, mood and anxiety disorders are also involved in the CNS control of the heart (through ANS). Left image and upper right is parasagittal and lower right is horizontal. Shared sex-dependent development of this neural circuitry provides a rationale for the fetal programming of sex differences in the comorbidity of MDD and CVD. (Image adapted from Lane and Wager, NeuroImage 2009, volume 47, issue 3)

Figure 4. Stress Response Circuitry in the Brain is Highly Sexually Dimorphic
Brain regions implicated in the stress response circuitry are some of the most highly
sexually dimorphic brain regions in the brain (e.g., hypothalamic nuclei, central medial
amygdala, hippocampus, mPFC, ACC). Figure 3 highlights the brain regions in MR images
and shows which regions are larger in volume (cm^3) in the female brain (in red), relative to
cerebrum size, and which are larger in the male brain, relative to cerebrum size (in blue).
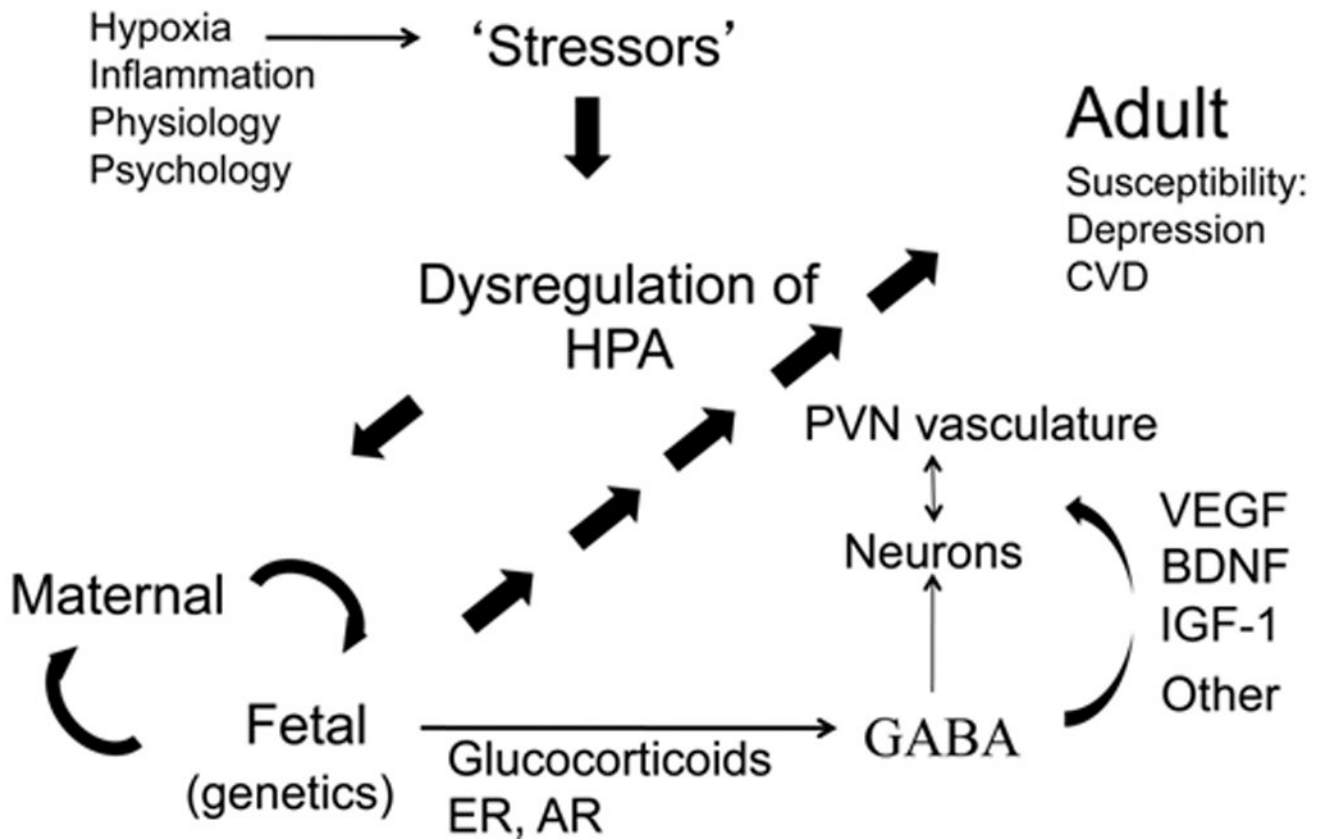(Adapted from Goldstein, et al., 2001, Cerebral Cortex)

Hypoxia → 'Stressors'
Inflammation
Physiology
Psychology

Adult
Susceptibility:
Depression
CVD

Dysregulation of
HPA

PVN vasculature

Neurons

VEGF
BDNF
IGF-1
Other

Maternal

Fetal
(genetics)

Glucocorticoids
ER, AR

GABA

Figure 5. Mechanisms Associated with Sex-Dependent Fetal Stress Circuitry Development Implicating Comorbidity of MDD and CVD in Adulthood
Schematic depiction of the interactions among stressors of the mother leading to dysregulation of her HPA axis that then influences maternal-fetal interactions in a sex-dependent developmental manner. In the fetal compartment, glucocorticoids and sex steroid influences (e.g., estrogen and androgen receptors (ER, AR)) impact GABA and growth factors, which alter neuronal and vascular cellular components.