Of depression and immunity: does sex matter?

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Abstract
It is firmly established that women experience major depression (MD) at roughly twice the rate of men. Contemporary research has indicated that sex hormones comprise crucial orchestrators of the differences in susceptibility associated to sex in MD, as well as in certain infectious and autoimmune diseases. Interestingly, it has been suggested that altered functioning of the immune system may be implicated in the medical morbidity of this affective disorder. To make matters more complicated, data accumulated largely during the last two decades advocate the innate inflammatory immune response as a mechanism that may contribute to the pathophysiology of MD, mainly through alterations in the ability of immune cells to secrete pro-inflammatory cytokines. Although the literature is limited, the bi-directional influences between the brain and the immune system appear to present sex-related motifs whose elucidation is far from being completely achieved but comprises a matter of intensive research. Herein, we provide a first critical glimpse into if and how sex differences in immunity may be implicated in the pathophysiology of MD. The review’s major aim is to sensitize clinical scientists of different disciplines to the putative impact of immune sexual dimorphism on MD and to stimulate basic research in a need to delineate the neuroimmunological substrate in the appearance, course and outcome of this stress-related disorder.

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Overview
Major depression (MD) affects both men and women, but more women than men are likely to be diagnosed with depression in any given year (Holden, 2005; Kessler, 2003; Kessler et al. 2003, 1995; Kornstein, 1997; Nemeroff et al. 2006; Somers et al. 2006; Stein et al. 2002; Steiner et al. 2005). This sex-dependent differentiation has been largely attributed to the pronounced sex differences that predominate in both the anatomy and function of the human brain, as well as to the sexually dimorphic hormonal milieu (Cosgrove et al. 2007; Kessler, 2003).

According to the World Health Organization (WHO), by 2020 MD is expected to rise to become the number two contributor to the global burden of disease (WHO, 2005). Despite the fact that our knowledge regarding the pathophysiology and the neurobiological substrate of depression has grown exponentially over the last decades, there is still a significant percentage of patients who do not tolerate or respond poorly to current antidepressant medications (Rush, 2007). The latter probably reflects the fact that the term ‘depression’ encompasses a group of disorders, each being characterized by a unique endophenotype that needs to be treated accordingly (Antonijevic, 2006; Hasler et al. 2004).

Intriguingly, a constellation of preclinical and clinical evidence supports the notion that depression and immunity are engaged in a bi-directional relationship, which is characterized by both immunosuppression and activation of the innate immune machinery (McNally et al. 2008; Miller et al. 2009). Depressed patients often show alterations in responses of both the innate and the cell-mediated arms of immunity that are associated with infectious-disease susceptibility (Zorrilla et al. 2001). On the other hand, data accumulated largely during the last two decades advocate the inflammatory immune response as a mechanism that may contribute to the pathophysiology of this affective disorder (Dantzer et al. 2008).
Contemporary research has indicated that sex hormones comprise crucial orchestrators of the differences in susceptibility to MD (Kessler, 2003), as well as during autoimmunity and in the pathogenesis of infectious diseases (Nalbandian & Kovats, 2005). To make matters more complicated, the immune system presents a sexual dimorphism of its own (Ahmed & Talal, 1990; De Leon-Nava et al. 2009; Grossman, 1984; Pilipovic et al. 2008; Stefanski & Gruner, 2006).

Paradoxically, the impact of ‘sex’ is rarely controlled for in studies screening for immune alterations in stress-related disorders (Darnall & Suarez, 2009). Thus, the present review aims to provide a glimpse into immunomodulation in MD, arguing about the fact that being male or female may comprise a critical moderator implicated in the differential sensitivity/susceptibility that the two sexes exhibit upon induction of depressive symptomatology.

**Sex differences in depression: why should we bother?**

The aetiology behind sex differences in depression is not entirely known but is thought to involve genetic, hormonal, biochemical and social factors. Sex differences in neurotransmitter systems (e.g. serotonergic) and neuroendocrine circuits (i.e. corticotrophin-releasing hormone; CRH) in conjunction with the sexually dimorphic hormonal milieu have been implicated in the differentiated precipitation of depressive symptomatology between men and women (Cosgrove et al. 2007; Kessler, 2003). On the other hand, from the sociocultural perspective it has been suggested that modern women struggle with role overload, while in the context of a ‘sandwich generation’ lifestyle they have to provide care to both their progeny and elders (Grigoriadis & Robinson, 2007; Stewart et al. 2006; Vigod & Stewart, 2009). Moreover, it has been postulated that genetic predisposition to the development of depressive disorders is more pronounced in women than in men since major life stressors appear to exert sex-specific detrimental effects on the female sex (Vigod & Stewart, 2009). According to some reports, MD presents a significantly higher heritability in women compared to men (42% vs. 29% respectively; Jansson et al. 2004; Kendler et al. 2006).

Notably, the expression of depressive symptomatology has been reported to present sex-related patterns. According to some studies, women seem to report increased appetite and weight gain, hypochondriasis and somatic concerns (Kornstein, 1997; Marcus et al. 2005; Young et al. 1990). On the other hand, depressed men tend to report more weight loss and are more likely to struggle with alcohol dependence and substance abuse (Breslau et al. 1995; Marcus et al. 2008).

Apart from exerting devastating influences on men and women as individuals, maternal depression has been reported to affect the child’s development and is associated with children’s disorders (Weissman et al. 2006). Women appear to be at higher risk for depression at specific points in their life, when sex hormones fluctuate, e.g. in puberty, when oestrogens are first rising; in the premenstrual phase; and in pregnancy or the postpartum period (McCoy et al. 2008; Wise et al. 2008). Along with hormonal fluctuations, the dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis that occurs during these periods has also been implicated in stress response and incidence of depression (Nestler et al. 2002). Indeed, the cyclic release of sex hormones has been associated with profound neural influences in both women and female rodents. A recent functional magnetic resonance imaging (fMRI) study supported the view that the sex differences observed in brain activity in stress response circuitry were dependent on women’s menstrual cycle phase (Goldstein et al. 2010). Moreover, hippocampal and cortical spine synapse densities vary across the oestrous cycle in rats (Chen et al. 2009; Cooke & Woolley, 2005; Prange-Kiel et al. 2009).

Preclinical research suggests that females and males respond in a different manner regarding the induction of depressive symptomatology (Dalla et al. 2005, 2008a, b, 2009; Drossopoulou et al. 2004; Kamper et al. 2009; Palanza, 2001; Pitychoutis et al. 2009a). Studies from our laboratory, as well as from other authors, underline the crucial role of sex in the manifestation of sexually dimorphic neurochemical, neurobiological, physiological, behavioural and immune responses to both the induction of depressive-like behaviour, as well as to concomitant antidepressant treatment in animal models of depression (for review see Dalla et al. 2010). Ultimately, the investigation of sex differences in the neurobiology of depression aims to improve diagnosis and hopefully will provide gender-based antidepressant pharmacotherapies (Kornstein et al. 2000).

**Immunity in depression: a double-edged sword?**

**Immunosuppression and medical morbidity in MD**

Depressed patients often show an excess in mortality rates, that according to some reports is as high as
double those found in non-depressed persons (Cuypers & Smit, 2002; Rudisch & Nemeroff, 2003). Medical morbidity of MD has been largely attributed to functional impairments in both the innate and the cell-mediated arms of immunity that may lead to the more pronounced susceptibility that depressed patients present upon infection (Leserman, 2003, 2008; Miller et al. 2009). Notably, large meta-analyses have reached the conclusion that immune function is hampered in depressed patients, while according to some reports this immune impairment is more pronounced in patients who suffer severe depression (Herbert & Cohen, 1993; Irwin, 1999; Zorrilla et al. 2001). Experimentally, immune suppression typically reflects the inhibition of several in-vitro functional immune parameters, such as the proliferative response of lymphocytes to mitogens, the cytolytic activity of natural-killer (NK) cells (CD3\(^-\) CD56\(^+\) and/or CD16\(^+\) cytotoxic lymphocytes that mediate first-line defence against various types of target cells), as well as relevant alterations in white blood cell populations (Zorrilla et al. 2001).

T-cell dysfunction in depression has been associated with a worse prognosis in a battery of both infectious and non-infectious medical conditions. Strikingly, a study reported that cancer patients with comorbid depressive symptomatology were 2.6 times more likely to die from cancer within 19 months following diagnosis (Stommel et al. 2002). In women with metastatic breast cancer, suppression of T-cell-mediated immunity was positively correlated with the severity of depressive symptomatology (Sephton et al. 2009). Moreover, according to a recent study, depressed patients infected with human immuno-deficiency virus (HIV) were more likely to develop acquired immuno-deficiency syndrome (AIDS), as well as an increased likelihood of AIDS-associated death (Leserman, 2008). In a study conducted solely in women, it was shown that in HIV infection comorbid MD was associated with reduced NK-cell cytotoxicity, but increased numbers of activated cytotoxic (CD8\(^+\)) T-cells and viral load (Evans et al. 2002). In addition, MD has also been associated with a decline in memory T-cells that respond to varicella-zoster virus antigens (Irwin et al. 1998), with this immune alteration being indicative of a greater herpes zoster risk (Oxman et al. 2005). Interestingly, oxidative-related acceleration of blood leukocyte apoptosis in MD has also been proposed to affect patients’ susceptibility to a panel of different infections (Szuster-Ciesielska et al. 2008).

The inflammatory nature of MD

The notion that immune system activation is implicated in the pathophysiology of MD is supported by in clinical observations in inflammatory disorders, such as rheumatoid arthritis, multiple sclerosis, diabetes and coronary artery disease, that have been associated with increased prevalence of depression (Elenkov, 2008). Being beyond the scope of this paper to review in detail the mechanistic insights pertaining to the interactions between the brain and the immune system in depression, the interested reader is referred to several recent outstanding papers on the topic (Dantzer et al. 2008; Khairova et al. 2009; Maes, 1994; McNally et al. 2008; Miller et al. 2009; Miller, 2010).

At least a subpopulation of patients suffering from MD has been shown to exhibit inflammatory activation manifested by elevated secretion of monocyte-derived pro-inflammatory cytokines, namely interleukin-1 (IL-1), IL-6 and tumour necrosis factor-\(\alpha\) (TNF-\(\alpha\)), products of T-cell activation (e.g. soluble IL-2 receptors) in both the periphery and the cerebrospinal fluid, as well as acute phase proteins and adhesion molecules in the blood (Miller et al. 2009). Notably, meta-analytical approaches have exposed the peripheral blood elevations of IL-6 and C-reactive protein as the most consistent findings regarding the induction of an inflammatory state in MD (Howren et al. 2009; Mossner et al. 2007; Zorrilla et al. 2001). Moreover, it has been hypothesized that in depression the CD4\(^+\) T-helper 1/T-helper 2 (T\(_{H1}/T_{H2}\)) cytokine balance is impaired due to excess secretion of pro-inflammatory cytokines (i.e. IFN-\(\gamma\)), with this ratio being normalized upon antidepressant treatment (Myint et al. 2005). Most importantly, according to some reports depressed patients that do not respond to antidepressant pharmacotherapy are even more likely to present significant increases in blood concentrations of these inflammatory markers (Lanquillon et al. 2000).

It should be noted that the induction of an inflammatory state may not directly oppose the suppression of cellular immunity, since inflammation has been experimentally shown to both activate and suppress several immune functions through direct and compensatory mechanisms (Laroux, 2004; Naor et al. 2009; Woiciechowsky et al. 1999). For instance, in terms of immunosuppression, it has been speculated that lipopolysaccharide (LPS)-induced inflammatory activation of \(\beta\)-adrenergic receptors or prostanoids may exert a suppressive effect on NK-cell activity and thus increase susceptibility to experimental metastases (Harmey et al. 2002; Naor et al. 2009).
The induction of an inflammatory state by administration of cytokine inducers, such as LPS or vaccines, produces a mild state of nosothymia [from the Greek words νόσος (nosoς) ‘disease’ and θυμικό (thymiko) ‘affective and sentimental state of an individual’], termed as ‘sickness behaviour’. Several key-features of sickness behaviour overlap with the clinical symptoms of depression, most prominent being the general suppression of motor activity, anhedonia (inability to experience pleasure), activation of the HPA axis and alterations in monoamine utilization (Dantzer, 2001; Dantzer et al. 2008; MohanKumar et al. 1999; Pitychoutis et al. 2009b; Yirmiya, 1996; Zampeli et al. 2009).

Indeed, data indicate that approximately 30–50% of patients undergoing IFN-α or IL-2 immunotherapy for the treatment of several viral diseases (i.e. chronic hepatitis C or HIV infection) or certain types of cancer (e.g. malignant melanoma and renal-cell carcinoma) develop MD (Capuron et al. 2002; Capuron & Miller, 2004; Musselman et al. 2001). Of note, in the context of cytokine administration in medically ill patients, the term MD refers to a substance-induced mood disorder according to DSM-IV-TR criteria (APA, 2000; Capuron et al. 2006).

Intriguingly, in patients suffering from inflammatory/autoimmune disorders pharmacological interventions that aim at reducing excess inflammation have been reported to act synergistically with antidepressant drugs to the alleviation of comorbid depressive symptoms, such as skin clearance of psoriasis, treatment with etanercept ameliorated depressive symptomatology, irrespective of improvement in psoriatic symptoms, such as skin clearance and joint pain (Tyring et al. 2006). Moreover, in a recent study acetylsalicylic acid co-administration resulted in significant remission in depressed patients previously non-responsive to fluoxetine monotherapy (Mendlewicz et al. 2006).

Sex differences in immunity

Sexual dimorphism in immune function is observed in vertebrates and also in a number of invertebrate species, covering an evolutionary spectrum from snakes to humans (Darnall & Suarez, 2009; De Leon-Nava et al. 2009; Saad & Shoukrey, 1988). The longer lifespan of women in many societies has been partly attributed to their enhanced resistance against certain infections and some non-infectious diseases (WHO, 2009; Nunn et al. 2009).

Interestingly, animal data suggest that female rodents have higher serum immunoglobulin (Ig) levels (especially IgM), greater and more prolonged antibody responses and shorter skin allograft rejection time (Grossman et al. 1991). Moreover, females present higher levels of IgA in lung lavage fluids, while this seems to be the case for the ocular system in males (Sullivan & Hann, 1989). The structure and cellularity of the thymus (i.e. the central T-cell pool) presents sex-associated differences. The relative thymus weight in female rats exceeds that of males, but the thymic catecholamine content is greater in males (Leposavic et al. 2008; Pilipovic et al. 2008; Pitychoutis et al. 2009a).

Despite the fact that the total lymphocyte count is similar between the two sexes (Bouman et al. 2004; Giltay et al. 2000), the relative number of T-cells within the whole lymphocyte population has been reported to be lower in males (Bouman et al. 2004).

Females generally achieve higher titres of auto-reactive antibodies (Ansar Ahmed et al. 1985). Interestingly, numerous diseases of autoimmune origin are much more likely to occur in women, possibly due to the enhanced immune reactivity. Indeed, autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, Graves’ disease, and Hashimoto’s thyroiditis, show a clear female preponderance (McCombe et al. 2009). In addition, male rodents generally exhibit depressed immune responses and increased susceptibility to sepsis following trauma haemorrhage, whereas immunoreactivity in pro-oestrous females is maintained or even enhanced in view of high oestrogen concentrations (Angele et al. 2000).

Immune sexual dimorphism has been hypothesized to reflect an evolutionary preserved trait, in the context of the interesting ‘immunocompetence handicap hypothesis’ (Folstad & Karter, 1992). According to this debatable hypothesis, only highly immunocompetent males that can handle the elevated testosterone concentrations required in order to express their ornaments, are finally selected as ‘good-gene carriers’ by females (Nunn et al. 2009).

Neuroimmune sex differences in depression and stress: evidence from the clinic and from animal models

In the original expression of the ‘macrophage theory of depression’, R. S. Smith hypothesized that the higher prevalence of MD in women is associated with
the activating property of oestrogens on the macrophage lineage (Smith, 1991), thus considering the possibility that sex may play a causal role in the immune alterations displayed. Most importantly, this notion was expressed prior to 1993, at a time during which women were seriously under-represented in clinical trials (Uhl et al. 2007). To the best of our knowledge, relatively few studies in the literature have attempted a direct comparison between males and females regarding their immunocompetency both in humans and in experimental paradigms of depression.

In their interesting meta-analysis of numerous studies Zorrilla et al. (2001) noted that the sex ratio implemented, as well as the sex-matching of controls, or even the severity of depression, comprise factors that may affect the statistical outcome and should be ‘dissected’ in future studies. Nowadays, scant but intriguing evidence from both the clinic and animal models of depression support the notion that the bi-directional influences between the brain and the immune system in stress and depression present sex-related motifs whose elucidation is far from being completely understood but provides a fertile ground for intensive experimentation.

According to some reports, depressed men often show higher mortality rates compared to women (Penninx et al. 1999; Zheng et al. 1997), whereas others do not reach this conclusion (Cuijpers & Smit, 2002; Roberts et al. 1990). Sex appears to have a striking influence on depression-related reduction of NK activity. Despite the fact that meta-analytical approaches question whether the differences observed in the number of circulating immune cells are consistent, a decline in NK cell numbers and NK cytolytic capacity was found in men but not in women suffering from depression, compared with sex-matched healthy individuals (Evans et al. 1992).

Chronic mild stress (CMS) is considered by many researchers as one of the most valid animal models of MD and has long been associated with alterations regarding immunoreactivity (Bekris et al. 2005; Kioukia-Fougia et al. 2002; Willner, 2005). Until recently, immune alterations in the CMS model of depression were determined on either male (Azpiroz et al. 1999; Kubera et al. 1998, 2001) or female rodents (Edgar et al. 2002, 2003; Silverman et al. 2002). In a recent study from our laboratory, we screened for sex differences in cellular immunoreactivity in the CMS model. According to our results, and in contrast to those of Evans et al. (1992) in humans, CMS-treated female rats presented a relatively immunosuppressive phenotype compared to males, as evidenced by the impaired NK and lymphokine-activated killing (LAK) responses (Pitychoutis et al. 2009a). Moreover, following both CMS and chronic antidepressant treatment, thymic monoamines presented sex-related alterations, as well as intriguing associations with peripheral T-cell responses (Pitychoutis et al. 2009a).

Although cytokine-induced depression has been observed in both men and women undergoing cytokine immunotherapy for the treatment of various diseases, there is still no consensus on whether sex comprises a major differentiating factor regarding the development of MD (Raison et al. 2005). This is not unrelated to the fact that the majority of experimental studies investigating immune-related alterations both in depressed individuals and in animal models of depression have focused on either males or females and not on inter-sex differences (Dalla et al. 2010; Darnall & Suarez, 2009; Edgar et al. 2003; Eisenberger et al. 2009; Kubera et al. 1998; Wright et al. 2005). Studies with IFN-α administration in humans are dichotomized between those that do (Fontana et al. 2002; Gohier et al. 2003; Koskinas et al. 2002) and those that do not (Bonaccurso et al. 2002; Kraus et al. 2003) find the female sex to be more likely to develop depressive symptomatology. Despite the controversial findings, sex differences in ex-vivo cytokine production have also been reported in MD patients (Kim et al. 2007).

Most importantly, recent studies suggest that the mechanisms implicated in sickness behaviour may succumb to sexually dimorphic influences, with both pro- and anti-inflammatory cytokines being associated with sex-specific phenotypes. For instance, in a recent study, Eisenberger et al. (2009) reported that IL-6 elevations following LPS administration were significantly associated with depressed mood in women but not in men. In another study, female mice in which the gene for the anti-inflammatory cytokine IL-10 was ablated (IL-10 knock-out) displayed increased depressive-like behaviour in the forced swim test of behavioural despair, compared to both male IL-10 knock-out mice, as well as to their wild-type counterparts; this phenotype was reversed upon exogenous IL-10 administration (Mesquita et al. 2008). These results indicate that a sexually dimorphic regulation of the cytokine network may be associated with the manifestation of sex-specific depressive-like behavioural responses.

Behavioural responses in LPS/cytokine-induced sickness have been scarcely referenced to be differentially expressed between males and females. While female rats exhibit greater sensitivity than males to LPS and/or cytokines in several aspects of behaviour,
including sexual activity and reward to mild sucrose (or saccharin) solutions (Avitsur et al. 1995, 1997; Avitsur & Yirmiya, 1999; Merali et al. 2003), ex-vivo experiments have shown that LPS-challenged macrophages derived from male mice produce higher levels of inflammatory cytokines than similarly treated female-derived cells (Marriott et al. 2006), suggesting that males may be more susceptible to bacterial sepsis than females. Furthermore, female rats develop tolerance to repeated LPS administration more quickly than male rats (Engeland et al. 2003), with this phenomenon being oestrous cycle-dependent (Engeland et al. 2006).

A recent study screened for sex differences in neurochemical patterns and behavioural manifestations in LPS-induced ‘sickness behaviour’ (Pitychoutis et al. 2009b). According to these findings, male and female rats experienced sickness in a different context, underlined by sex-differentiated sickness-associated behaviours (i.e. pain sensitivity, anorexia) and serotonergic responses in limbic brain regions implicated in the pathophysiology of MD. As commented in this study and confirmed by others, female vulnerability to LPS administration is reflected in the elevated corticosterone responses and is probably mediated by sex steroids (Frederic et al. 1993; Spinedi et al. 2002, 1994; Tonelli et al. 2008). Moreover, another study documented that repeated intranasal LPS challenge induced a sexually dimorphic increase in hippocampal TNF-α mRNA levels only in female rats, a finding that lends support to the notion that neural cytokine secretion patterns present sex-related modulation upon immune stimulation (Tonelli et al. 2008).

The type of stressor appears to be of prime importance regarding the induction of an immune response (Darnall et al. 2008; Suarez, 2008; Suarez & Krishnan, 2006). Notably, it has been shown that the pro-inflammatory cytokine secretion pattern in response to a psychosocial stressor (the Trier social stress test), presented sexual dimorphism; being boosted in women but decreased in men, alterations in cytokine levels were associated with decreased glucocorticoid sensitivity in female subjects (Rohleder et al. 2001).

Recent evidence also supports the notion that the kinetics of cytokine and antibody production varies significantly between the two sexes upon presentation of various stressors (immune, psychological, etc.; Darnall et al. 2008; Edwards et al. 2006; Pitychoutis et al. 2009b). These results point to an important time factor that dissociates inflammatory responses between the two sexes and would benefit from further clarification.

Crosstalk between the brain and the immune system: putative sex-related influences

It is widely accepted that the HPA axis interacts with the gonads to regulate sex hormone production. On the other hand, sex hormones also influence HPA axis activity. It is of special interest that the HPA axis and sex hormones play a crucial role in both the development of the immune system and the mounting of effective immune responses (Morale et al. 2001). Moreover, it has become apparent that gonadal and stress hormones may play a major role in predisposing females towards depressive disorders (Solomon & Herman, 2009). Indeed, sex-dependent HPA axis regulation following exposure to both chronic and acute stress paradigms is well-characterized (Drossopoulou et al. 2004; Iwasaki-Sekino et al. 2009; Pitychoutis et al. 2009b; Tsigos & Chrousos, 2002) and sex differences regarding immune reactivity have been largely attributed to this sexual dimorphism (Gaillard & Spinedi, 1998; Morale et al. 2001; Spinedi et al. 2002).

Sex-specific influences of housing conditions have been described in relation to HPA axis regulation and immune function (Brown & Grunberg, 1995; Grewal et al. 1997). Social instability affects females more than males (Haller et al. 1999) and crowding is stressful for males but actually calms females; basal corticosterone levels were found to be higher in isolated than in socially housed female rats, while the opposite association seems to hold true for males (Brown & Grunberg, 1995). Given the immunotrophic nature of glucocorticoids, animal studies exploring neuroimmunological phenomena should take into account putative sexually dimorphic social interactions.

Peripheral and central influences of sex hormones appear to be the major candidates regarding the sex differences observed in both cytokine-induced sickness and immune alterations in depression (Fig. 1). These hormones exert significant immunotrophic influences by acting both directly or via compensatory routes and ultimately producing sex-related effects on immune function. Oestrogens have been reported to enhance both humoral and cell-mediated in vivo and in vitro immune functions, vs. androgens and progestins that are primarily immunosuppressive (Olsen & Kovacs, 1996). Although the modulation of peripheral immune responses by sex steroids is complex and far from being elucidated, these hormones are able to regulate a number of processes regarding immunoreactivity, including maturation and selection of thymocytes and T- and B-cell effectors’ functions, the differentiation and function of antigen-presenting cells,
Fig. 1. An overview of putative neuroimmune interactions in major depression: sex hormones influence this crosstalk on all its levels. (a) In major depression, the bi-directional communication between affected neurotransmitter systems and the hypothalamus–pituitary–adrenal (HPA) axis results in enhanced secretion of glucocorticoids (GCs) by the adrenal cortex; the sympathetic nervous system (SNS) also modulates immune function directly (i.e. catecholamine secretion in the microenvironment of immune cells), as well as indirectly (i.e. thymus innervation). (b) In immune cells, GCs interact with nuclear receptors and exert major immunosuppressive influences that have been associated with the increased susceptibility of depressed patients to both infectious and non-infectious diseases. (c) On the other hand, chronic inflammatory conditions, several stressors and pathogen-associated molecular patterns (PAMPs) result in enhanced peripheral pro-inflammatory cytokine secretion; during an inflammatory episode a ‘replica’ of the peripheral immune response is created within the CNS by cytokines and inflammatory mediators that signal the brain via different routes and consequently stimulate the in-situ production of prostaglandins and cytokines. (d) Induction of pro-inflammatory mediators by glial cells affects neurotransmitter metabolism (e.g. serotonin and glutamate) and HPA axis reactivity, as well as neuronal integrity and synaptic plasticity, by hampering brain-derived neurotrophic factor (BDNF) signalling in stress-sensitive regions such as the hippocampus. (e) Neural inflammatory activation by causing a wide spectrum of neuroimmune, neurochemical and neuroendocrine effects, ultimately leads to the induction of depressive symptomatology (e.g. anhedonia, and fatigue). BDNF, Brain-derived neurotrophic factor; CAs, catecholamines; CRP, c-reactive protein; DA, dopamine; GABA, gamma-aminobutyric acid; GCs, glucocorticoids; Glu, glutamate; HPA, hypothalamus–pituitary–adrenal; NA, noradrenaline; NK, natural killer cells; PAMPs, pathogen-associated molecular patterns; SNS, sympathetic nervous system; 5-HT, serotonin.
as well as cytokine production by immune cells (Olsen & Kovacs, 1996). As far as mature T-cells are concerned, oestrogens may induce a biphasic effect on \(T_{H1}\) and \(T_{H2}\) functions; low doses promote \(T_{H1}\), while high doses promote \(T_{H2}\) responses (Pernis, 2007). Moreover, these hormones have been reported to regulate the expression of several chemokine receptors and thus to influence T-cell trafficking, possibly in a sex-related manner (Lengi et al. 2007; Pernis, 2007).

Notably, the cyclic release of oestrogens has been shown to exert signifcant effects on immunity. For instance, it has been shown that the ability of murine lymphocytes to proliferate in response to mitogens (e.g. concanavalin A or LPS) is oestrous cycle-dependent (Krzych et al. 1981), while as noted by Cannon (1998), circulating and tissue concentrations of pro-inflammatory cytokines (i.e. IL-1/\(\beta\)), vary temporally through the menstrual cycle and pregnancy in women.

Oestrogens have also been shown to act on all glial cell types, including microglia and astrocytes (Arevalo et al. 2009; Sierra et al. 2008). In MD, the aforementioned cellular types present functional dys-regulations including alterations in cytokine secretion patterns (McNally et al. 2008). It is of interest that the depletion of oestrogens has been found to increase the levels of pro-inflammatory cytokines (Bismar et al. 1995), while in studies implementing murine microglial cells, these hormones were found to increase IL-10 levels in vitro (Dimayuga et al. 2005). Oestrogens have been associated with neuroprotection mainly through their ability to induce growth factors by all glial cell types that promote neuronal survival (Arevalo et al. 2009). In accordance, recent studies have indicated that oestrogens not only elicit antidepressant-like actions (Halbreich & Kahn, 2001) but also improve the therapeutic outcome when co-administered with antidepressants that target the serotonergic system (Estrada-Camarena et al. 2006a,b; Soares et al. 2001).

Sex differences in neural inflammatory signalling cascades generated upon transduction of the peripheral cytokine signal within the brain have also received attention. NF-\(\kappa B\), a crucial transcription factor positively implicated in multiple aspects of the inflammatory machinery, has been proposed as a possible orchestrator of these neuroimmune sex differences (Eisenberger et al. 2009). In support of this, mononuclear NF-\(\kappa B\) activation was markedly enhanced in women but not in men following a night of sleep loss, which is considered an acute stressor known to increase pro-inflammatory cytokines (Irwin et al. 2008).

Obesity can be considered a subclinical inflammatory condition that has been associated with depression (Luppino et al. 2010). Notably, it has been suggested that men and women differ substantially in adiposity (Heyward & Stolarczyk, 1996) and that distortion of the HPA axis function in depression may favour fat accumulation (Adam & Epel, 2007). Given that the adipose tissue comprises an endocrine organ that provides about 30% of total IL-6 (Bastard et al. 2006; Mohamed-Ali et al. 1998), its interaction with sex hormones and the HPA axis could provide a playground for a sexually dimorphic neuroimmune milieu in the periphery.

Elegant genomic research highlights the fact that numerous immune-related genes located on the X chromosome encodes receptors, chaperones, transcription factors and other molecules that may be implicated in immune sexual dimorphism (Fish, 2008; Migeon, 2007). Given that certain polymorphisms in pro-inflammatory cytokine genes have been associated with mood disorders (Clerici et al. 2009), it could be speculated that the sexually dimorphic responsiveness of the immune system in MD may be related to polymorphisms in immune-related genes that ‘behave’ in a different manner between the two sexes; however, to the best of our knowledge evidence regarding this matter has yet to come forward. In this context, and despite the elusive functional significance, it has been shown that the IFN-\(\gamma\) promoter contains putative oestrogen response elements (EREs) and that a genetic variation within this promoter creates an ERE-like element that is capable of binding oestrogen receptor-\(\alpha\) (ER-\(\alpha\); Fox et al. 1991; Gonsky et al. 2006; Pernis, 2007). Besides genetic predisposition, other risk factors related to health-associated behaviours that have been reported to present sex-related motifs in depressed patients, such as appetite, exercise, smoking habits and alcohol dependence, may also be implicated in the sex differences observed in immunity (Grant et al. 2004; Husky et al. 2008; Marcus et al. 2005, 2008).

**Epimyth and future challenges**

Only scant research investigating neuroimmunological phenomena has directly assessed the role of sex in depression. Most of the available data refer to research conducted on either male or female subjects or in mixed samples of both sexes, in which the ratio of males to females suffered significant variations. Future research is imperative to clarify the complex associations between the immune system and the brain in depression. Therefore, the puzzling question posed...
herein: ‘whether sex matters in view of immune alterations in MD’, still cannot be answered since the impact of sex in neuropsychiatric disorders is only poorly understood.

Despite the unequivocal need to determine whether/which of the reported immune alterations are of clinical importance, one cannot overlook the absolute necessity to explore human and animal biology, in both health and disease. It is possible that oestrogens’ actions on the immune system and the brain from ‘womb to tomb’ may have a significant impact on the pathophysiology, as well as in the course and outcome of MD. Hopefully, ‘sex-oriented’ neuroimmune preclinical experimentation, in parallel with clinical research, may expose sex-related biological, mechanistic or even pharmacotherapeutic insights into affective disorders.

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Statement of Interest

None.

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