

Women's mental health: what don't we know?

Saúde mental da mulher: o que não sabemos?

A recent issue of the journal *Science*, marking its 125th anniversary, has been devoted to 125 questions: "What don't we know?". One of the questions addressed the relevance of genetic variation to personal health, acknowledging that genetic dissection of diseases such as cancer, asthma and heart disease is galloping ahead, whereas progress in other disorders such as depression is much slower.

Evaluating physical, social and mental impacts of disease, depression was the fourth leading cause on the Global Burden of Illness list in 1990 and is predicted to be the number ONE leading cause in the year 2020. The morbidity associated with depression in women is even greater. Not only do twice as many women suffer from the disorder when compared to men, but they also have a higher rate of comorbid conditions, both physical and mental.

From the age of menarche until well after menopause women also suffer from specific mood disorders including premenstrual dysphoria, perinatal and perimenopausal depression, as well as mood and anxiety disorders associated with infertility and pregnancy loss. Women endure more eating disorders, generalized anxiety disorder (GAD), posttraumatic stress disorder (PTSD), and autoimmune diseases. Women are also less tolerant to alcohol use and have a higher prevalence of pain disorders. They are influenced to a greater degree by seasonality, suffer more from jet lag and from shift-work, and last but not least metabolize drugs differently than men.

Most of this very valuable information has only been gathered in the last 30 years but much more still needs to be learned.

Some of the bigger questions to be answered are obvious: why is it that women are more vulnerable, more at risk to develop these disorders? What causes the sex/gender discrepancy? How can we better identify those who are at risk? What preventative measures can be put in place? And last but not least: how can we "tailor" better female specific treatments/interventions?

In addition, the still much-debated question of nature versus nurture seems even more relevant to the higher prevalence of mood and anxiety disorders in women. The evolutionary perspective suggests that possible male-female asymmetries in preference for certain types of relationships, a differential investment in reproduction and childrearing, as well as social options (or the lack of), all contribute to the fact that women are more vulnerable to mood (major depression and dysthymia) as well as anxiety disorders (especially GAD and PTSD).

Women are exposed to uncontrollable stressors, both psychological and physical, including violence, abuse and rape, from an early age on, much more often than men.

Although such stressful life events may influence the onset and course of depression, GAD and/or PTSD, not all women who encounter stressful situations develop these disorders. It is suggested that an individual's response to environmental insults is moderated by her genetic makeup.¹ Thus, complex psychiatric disorders are probably not caused by genes alone. The hypothesis of a gene-by-environment interaction is very promising. It "accommodates" genetic polymorphism/vulnerability, environmental pathogens as well as stressful life

events. It may also address the, at times, much more interesting question of resilience. Nevertheless, the fact that many of the female specific mood and anxiety disorders have an adult or late onset seem to indicate that genetic factors play only a small or partial role in their pathogenesis.

To complicate matters even further, women, from the age of menarche and on, are exposed to the effects of fluctuations in gonadal steroids throughout their menstrual cycles, during pregnancy, postpartum, perimenopause, menopause and beyond. These, at times, abrupt changes along the hypothalamic-pituitary-gonadal axis interact with the stress-induced activation of the hypothalamic-pituitary-adrenal axis in a manner that is yet not fully understood.

Again, hormonal fluctuations alone do not cause premenstrual, perinatal or perimenopausal mood/anxiety disorders. The effects of reproductive steroids on the brain are highly context dependent, but these female specific mood disorders provide an opportunity like no other to study endocrine related mood and anxiety disorders.²

Moreover, it is now evident that the brains of women and men are anatomically, chemically and functionally different and that some of these variations occur in brain regions involved in emotion, cognition, memory and behaviour. Further discoveries in this field could point the way to sex-specific therapies for both women and men with mental disorders.³

It is hoped that within the next decade we will be able to identify specific genetic markers which might help us better understand how the balance between female reproductive neuroendocrine events, neurotransmitter function, sensitivities to psychosocial, environmental and physiological factors relate to women's mental health.⁴⁻⁵

Whether psychiatric genetics will find these pathways to discovery remains to be seen.

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References

1. Caspi A, Sugden K, Moffitt TE, Taylor A, Craig IW, Harrington H, et al. Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. *Science*. 2003;301(5631):386-9.
2. Rubinow DR. Reproductive steroids in context. *Arch Women's Ment Health*. 2005;8(1):1-5.
3. Cahill L. His brain, her brain. *Sci Am*. 2005;292(5):40-7.
4. Steiner M, Dunn E, Born L. Hormones and mood: from menarche to menopause and beyond. *J Affect Disord*. 2003;74(1):67-83.
5. Soares CN, Joffe, H, Steiner M. Menopause and mood. *Clin Obst Gynecol*. 2004;47(3):576-91.