Chronobiological And Neuropsychological Bases Of Gender Versus Sex Differences In Response To Stress And Pain

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الملخّــص:

معظم دراسات الأسس النفسية والفيزيولوجية للاستجابات للضغوط لا تميز عادة بين ردود الأفعال المرتبطة بالجنس "الثقافي "(أو" النوع") (gender) وردود الأفعال المرتبطة بالجنس البيولوجي. هناك بعض الدراسات الحديثة والنادرة تعترف بوجود التمييز، أما الدراسات التي تأسس هذا التمييز على قواعد عصبية– نفسية فهي أكثر ندرة.

هدف هذا المقال إلقاء بعض الضوء على الأسس النيوروسيكولوجية للفروق"الجنسية" للاستجابات للضغوط والألم، كمتغيرات متداخلة مع عوامل إيقاعية بيولوجية متنوعة ومعقدة، وكاستجابات متميزة أساسا عن استجابات الجنس البيولوجي للضغوط والألم؛ وهذا نظرا لما تم اكتشافه حديثا فيما يخص بعض الأدلة التجريبية لوجود ثنائية شكل جنسي (dimorphism sexual) للمراكز العصبية العليا المسئولة عن الضغط والألم (أساسا المراكز و/أو الدوائر العصبية اللمبية بالمقابل مع المراكز و/أو الدوائر الهيبوثلاموسية).

Abstract:

Most studies of the psychological &/or physiological bases of stress responses do not often distinguish between gender-dependent reactions to stressors and sex-dependent reactions to these stressors; only very few recent studies make the distinction, and even fewer base this distinction on neuropsychological and/or chronobiological grounds .

The aim of this paper is to shed some light on the neuropsychological bases of gender differences in response to stress and pain, as intermingled with various and complex chronobiological factors, and as fundamentally distinct from sex differences in response to stress and pain; this, as far as there is mounting experimental evidence of a sexual dimorphism in the anatomy and physiology of the main higher brain circuits responsible for stress and pain (mainly limbic circuits as opposed to hypothalamic and other lower brain circuits).

Introduction:

That men and women respond, in a different way and manner, to the same acute stress, or daily stressful event, is well known; what has not yet been clearly established, is, to what extent and when do men and women differ in their responses to chronic or persistent stresses and long-lasting or monthly renewed crises and failures. It is suspected, here, that gender differences in response to stress do not necessarily overlap biological sex differences in response stress, as the first kind of response seem to rely more on the activation of the limbic system, whereas the the second kind remain dependent on the activation of autonomous nervous system (mainly the sympathetic nervous system and hypothamo-pituitary-adrenal axis).

It remains also possible to plot behavioural variations of gender-dependent responses to stress (as compared to sex-dependent responses to stress) along the introversion-extroversion and stability-emotionality continuums, as introverts and women appear to respond to stress with more emotional reactivity and less general reactivity, while extroverts and men seem to deal with stressful events with less emotional reactivity and more general reactivity.

Moreover, in a series of pioneering studies and exhaustive research on the psychophysiological basis of introversion-extoversion, Gray(1972) showed that, women in general, and introverts in particular, have a more sensitive septo-hippocampal system (or "fear-frustration" system), are more sensitive to punishment, frustrative non-reward, and partial reinforcement, and are readily conditionable, whereas men in general, and extroverts in particular, have a more

sensitive caudate and ventral tegmental behavioural activation system (or "hope-relief "system), are more sensitive to reward and continuous reinforcement, and are not readily conditio-nable.

In addition to this, it is also known that the septo-hippocampal system exerts a modulating inhibitory control on the HPA axis that hippocampal Theta waves inhibit the Ascending Reticular Activation System (ARAS), and that estrogenous phase often coincides with hippocampal Theta and increased neuronal plasticity in area CA1 of the hippocampus. Given these facts, we can say that gender (and not biological sex) can and must orient behavioural responses to stress through an appropriate regulatory control of both the ARAS and the HPA axis. Therefore, a certain dose of wise introversion and intelligent self-control, associated to discernment and a fair degree of insight and emotionality*1, depend on a healthy septo-hippocampal system, and are always necessary (regardless of sex*2), for selective attention and discrimination learning, cognitive mood readjustment, flexible and adaptive gender-dependent coping with stress, and emotional intelligence.

*1: not emotionality equated with instability and neuroticism as in Eysenck's purely reticulo-cortical theory of introversion-extroversion.

*2: as a reminder, the three main sex hormones estrogen, progesterone and testosterone exist and are functionally active in both males and females.

1. Gender Differences versus Sex Differences:

Specifically, "sex" denotes biologically based differences and "gender" indicates culturally and socially shaped variations between men and women. Unfortunately, in most published medical literature, authors have replaced "sex" with "gender" using the term "gender differences" to describe any observed differences between men and women; from purely biological differences in sexual anatomy and physiology, and sex-specific diseases, to psychosocial, socio-cultural and ethnological differences.

Although the term "gender" has been used in social sciences for decades, its more recent introduction in the medical lexicon led to its mistaken use as an updated version of the term sex, according to Fishman and his colleagues (Fishman, J et al.1996).

To dissipate this unfortunate confusion between the two terms, used interchan- -geably in the medical literature, we give below an internationally accepted definition for both the term "sex" and "gender":

- Sex: Sex refers to biological characteristics such as anatomy and physiology that distinguish males and females. Sex differences relate to the genetic, cellular or organic and hormonal levels, and result from complex interactions between biological levels and environmental factors. These interactions begin in the genetic and intrauterine environment and continue throughout the lifespan of the individual. Thus, sex differences begin with the fact that every animal-derived cell has a sex. « Within the context of a continuum of

variation, males and females present disparate genetic profiles beyond those responsible for gonadal formation.*1.

It has been noted that as most phenotypic females possess two X-chromosomes, they may potentially express twice the gene product as males although doubles are generally suppressed through the process of X-chromosome inactivation also known as lyonization. Importantly, these gene products may be responsible for cellular function, metabolism and growth.

Genes on X and Y-chromosomes can code for slightly different variants that may contribute to sex differences in physiological response and function*2 ». (CIHR, 2007).

- **Gender:** Gender refers to the array of socio-culturally constructed roles and relationships, personality traits, behaviours, attitudes, values and relative power that society attributes to the two sexes based on a differential basis. Thus gender is relational- gender roles (Health Canada, 2000).

All societies are divided (at minimum) between two categories of sex and gender that are often assigned unequal statuses. «Gender roles, constructs and identities exist not as stable entities, but as expressions that are located along a continuum. Ethnicity, socioeconomic status, sexual orientation, geography and other social identifiers situate women and men differently in the social landscape necessa-rily complicating the relationship between gender, sex and health disparities defined by unequal access to health determinants*3 »(CIHR, 2007). Moreover, gender roles and constructs can have a direct impact on health. For example, care work is generally

associated with the female gender role and may contribute to significant health problems attributable to child care burden, while in many societies, men may be socially conditioned to value risk-taking behaviour and inhibit care-giving behaviours, both of which may be detrimental to men's health, although not all men embrace the risk-taking gender role throughout their lifetimes, and not all women embrace the care-giving gender role throughout their lifetimes.

*1, *2 & *3: underlined by us (M. Belloum).

2. Chronobiological and Neuroendocrine bases of sex-dependent responses to acute stress:

Many studies have reported acute influences of gonadal steroids on cognitive tasks during the woman's menstrual cycle, and emphasized sex differences in response to stress, especially during the proestrus phase of this cycle. Moreover, considerable attention has been given, by Gray (1971) and Gray & Buffery (1971), to sex differences in emotional reactivity in mammals, including man. These authors have explored sex differences in rats and man, and have looked at their neuroendo-crine basis as well as evolutionary adaptive significance. Their results, to be confirmed, thirty years later, by other researchers, showed that:

- the sex difference in fearfulness of mammals appears to be modulated by estrogen, which antagonizes this characteristic.

- female rats are less fearful than normal (as indicated by open field defecation and ambulation scores) when endogenous estrogen levels are high during the estrus cycle.

- estrogen injections lead to decreased open field fearfulness in both males and females .

- in conflict situations male rats exhibit greater proneness to the development of gastrointestinal ulcers than females (with this relationship being reversed during enforced immobilization). Men also, are more prone to psychogenic ulcers than women, suggesting that it is the suppressed aggression in men, rather than anxiety that leads to the ulcerative gastrointestinal changes.

- premenstrual depression in women is suggested to be a reflection of increased fear-fulness due to depleted circulating estrogen.

- the HPA axis response to stress in the female is initially more rapid and more +intense, but subsides more quickly than that of the male.

Now concerning other studies linking sex difference in response to stress, to limbic functions, hippocampal plasticity and stages of estrus or menstruation it has been reported that:

- in experiments using the Maudsley strains of rats*1, it was found that males had higher concentrations of serotonine in their limbic system than females.

- males and females have different levels of dendritic spine density(i.e synapse formation) in the hippocampus under unstressed conditions, and their limbic neuro-anatomy can respond in opposite direction to the same stressful event (Shors et al, 2001).

- sex difference in response to stress is best expressed in hippocampal neurons, as sex and stress alter dendritic spine density in

area CA1 of the hippocampus but not in the somatosensory cortex (Shors et al, 2001).

- there is strong evidence of sex differences and opposite effects of stress and gonadal steroids on apical dendritic spine density in the male versus female CA1 area of the hippocampus. Namely, that, in response to acute stress, spine density (that is synaptic density between CA3 neurons and CA1 pyramidal cells) is often inhanced in the male hippocampus, but reduced in the proestrus female hippocam--pus, 24h.after the exposure to the stressful event. Moreover unstressed females in proestrus (estrogenic phase) have a greater density of spines in CA1 area than unstressed males (Shors, J.T.et al.2001; Figueiredo, H.F.et al. 2002).

*1: obtained through a method known as selective breeding by Broadhurst (1960), and designed to study the inheritance of fear & sex difference in response to stress.

- exposure to estrogen and estradiol (rather than to male androgens or female proges-terone), endogenously or exogenously during proestrus, enhances hippocampal dendritic spine density (Shors et al, 2001; Figuieredo et al, 2002).

- female rats in proestrus outperfom males and females in other stages of estrus (Shors et al, 1998).

- women are found to bid significantly higher in price auction than man when their estrogen levels are higher (Chen et al, 2005).

- estrogen and estradiol effects on hippocampal dendritic spine density are reversed by progesterone and its metabolites (Murphy & Segal, 2000).

Taken together, all the above cited reports, suggest that males and females of mammalian species respond differently (and sometimes in opposite direction) to the same stressful event; and while high levels of endogenous estrogen, during proestrus, and a particular type of Theta activity, tend to enable females, and not males, to cope with acute stress and improve their performances in hippocampally dependent learning tasks, other neurohormonal and chronobiological factors may be needed to reverse this tendency and orient the behaviour of both sexes, again differently, in face of chronic stress or skilled learning task exigencies .The reports also suggest that the limbic system of males and females is differently influenced by circulating endogenous hormones and neurotransmitters, and that female limbic system tends to be more cholinergic, while male limbic system tends to be more serotonergic (and perhaps also more GABAergic).

3. Brain sexual dimorphism and biobehavioural and neuropsychological bases of gender-differences in responses to stress and pain:

As far as gender differences in response to stress and/or pain do often differ qualitatively from biological sex differences in response to stress and/or pain, and as far as culturally shaped gender motivates and orients behaviour in a different way and manner than does primal sexual drive, it is expected, that the way in which lower brain structures*1 involved in fear, stress and pain are controlled by higher brain structures*2, as a result of evolutionary &/or ethnological as

well as learning factors, is determined by gender rather than by biological sex.

There are several scientific reports of a neuropsychological basis of gender-dependent responses to stress, with recent experimental results pointing to, either differences in size, between men and women, of some important higher brain structures involved in emotional processing and stress, such as the hippocampus and orbito-frontal cortex, or differences in neuromodulation of primary neural circuits involved in stress and/or pain, such as the periaqueductal gray and the HPA axis.

On the other hand, and despite the fact that the biobehavioural "fight-or-flight" theory has dominated stress research for the past five decades, and has concentrated more on studies of males, recent emerging evidence speak of a gender biased patter of response to stress in women, termed "tend-and-befriend" rather than "fight-or-flight".

This "tend-and-befriend" pattern suggest that female stress responses may have selectively evolved to maximize the survival of self and offspring, through caregiving

*1: such as the hypothalamus, the periaqueductal gray and HPA axis.

*2: such as the limbic system and the prefrontal cortex.

processes that depend, in part, and more on estrogenic and oxytocic rather than purely corticotrophic mechanisms for the regulation of sympathetic and HPA axis responses to stress (NIMH, 2003).

Moreover, the existence of a sexual dimorphism in the anatomy of higher brain structures, involved in emotional behaviour associated with stress, has been confirmed by many recent experimental studies, which reported that:

- the hippocampus is larger in women than in men with respect to total brain size (Goldstein, J.M. et al, 2001).

- chronic stress causes damage to the hippocampus in male rats and monkeys compared to little, if no damage at all, in females of these same animal species (McEwan, B.S, 2000).

- the amygdala is significantly larger in men than in women with respect to total brain size (Goldstein, J.M. et al, 2001).

- the human amygdala functions in a sex-related hemispheric way to emotional facial expression, with the left amygdala being significantly more active in response to happy faces in females than in males, whereas the opposite pattern occurring for the right amygdala (Killgore and Yurgelun-Todd, 2001).

- orbito-frontal cortex volume, with respect amygdala volume, is larger in women compared with men, suggesting that women have greater tissue volume available for modulating amygdale input (Gur, R.E. et al, 2002).

- the prefrontal cortex is rich in sex hormone receptors, has among the highest concentration of estrogen receptors in the human brain (Bixo, M. et al, 1995), and is also associated with sex differences in response to stress (Shansky, R.M. 2004).

There is also growing evidence, from past and recent scientific literature of a neurochemical sexual dimorphism, as studies reporting

"sex differences" in monoamine content in the human brain found that:

- levels of monoamine oxydase (MAO) were significantly higher in several brain regions in women than in men (Robinson, D.S. et al, 1977).

- the mean rate of serotonin synthesis, assessed by positron emission tomography (PET), was found to be 52% higher in males than in females (Nishizawa et al,1997).

- significantly different levels of opioid receptor binding in several brain regions in men versus women, including the amygdala and thalamus, were revealed by PET scan (Zubieta, J.K. et al, 1999).

In the same context of "sexually dimorphic" neurochemical modulation of brain structures involved in emotional responses associated with stress, pronounced gender-related differences have been observed in the regulation of the limbic-hypothalamic-pituitary-adrenal (LHPA) activity under basal and stress related conditions.

These gender-related differences have unequivocally been demonstrated to depend on the organizational effects of gonadal steroids during early brain development, and throughout adulthood (Patchev, V.K & Almeida, O.F.X., 1998). Thus, although it is often thought that that glucocorticoids are the most important factor in regulating HPA axis, the importance of the modulatory effects of gonadal steroids on LHPA may be reflected, for example, in gender differences in the incidence of psychopathologies that are often associated with LHPA dysregulation, that in turn can be treated through neuroprotective hormone replacement strategies.

To sum up, we can say that gender differences in response to stress are best expessed through sexually dimorphic limbic and prefrontal cortex neuronal activities, which in turn are regulated by female hormones having anti-stress effects.

That estrogen and other female hormones like oxytocin and prolactin have anti-stress and anxiolytic effects is a well documented fact (Uvnäs-Moberg, K. 1998; Mantella, R.C, 2004; Torner, L et al, 2001; Gray & Buffery, 1971; Shors et al, 1998; Shors et al, 2001), as not only do such female hormones specifically bind to a great number of receptors in hippocampus, amygdala and prefrontal cortex, therefore priming these structure for better dealing with stressors, but also determine, through their neuromodulatory effects on LHPA, gender differences in coping with these stressors.

Now concerning gender differences in anxiety disorders, as indicators of gender differences in emotional responses associated with stress, it has been found that women often outnumber men in panic disorder, post-traumatic stress disorder (PTSD), generalized anxiety disorder (GAD) and social phobia, with men and women

being equal at developing obsessive compulsive disorder (OCD) (Yonkers, K.A et al, 1998; Breslau, N. et al, 1997).

Moreover, in a study using samples of male-male, male-female and female-female twin pairs, it was found that, while there are sex differences in exposure or sensitivity to stressful life events, there is no overall gender difference in sensitivity to depressogenic effects of these stress life events, despite the existence of gender differences in

this sensitivity as far as only three out of eighteen stressful events are concerned (Kendler, K.S. et al, 2001).

Another scientific fact of paramount importance, in the study of sex-related or gender-dependent response to stressors, is the very recently discovered fact of sex differences in stress-induced analgesia (SIA) and sexual dimorphism in the anatomi-cal and functional organization of the main brain circuit for pain.

Indeed, the finding, reported in 2006, in the April issue of the Journal of Comparative Neurology, by a research team led by Dr Anne Murphy of the Georgia State Department of Biology & the Center for Behavioural Neuroscience in Atlanta (USA), is the first proof of anatomical and functional sex differences in response to nociceptive stimuli in rodents. The American team discovered, for the first time, that male and female rats are anatomically different in the periaqueductal gray (PAG) area of the brain, and that persistent pain activates the PAG-RVM circuit*1 differently in males and females.

It was also, concurrently shown, that inflammatory pain activated the PAG-RVM circuit to a greater degree in males than in females, and that morphine reduced the response of this circuit to pain in males but not in females (Loyd and Murphy, 2006).

As for studies on human gender-dependent responses to pain, it was found that men and women had different central nervous system (CNS) responses to aversive visceral stimuli [caused for example by irritable bowel syndrome(IBS)], and that men tend to respond to these stimuli with more activation than deactivation of the classic pain area*2 and related emotional motor system*3, while women tend to

respond with equivalent or greater deactivation, as compared to activation, of these same structures.

*1: the PAG-RVM circuit (or Periaqueductal gray-rostral ventromedial medullary circuit) is the main brain circuit for pain and the essential neural circuit for opioid based analgesia.

*2: dorsal anterior cingulated, insula and thalamus.

*3: ventral anterior cingulated, amygdala, ventral striatum, and periaqueductal gray (PAG).

It was also shown, that activation seemed more restricted to areas like the insula, the thalamus and PAG in men, wherea it seemed more restricted to the amygdala and anterior cingulate in women (Berman, 2004).

In further studies, reported by Sniezek(2005), on human gender-dependent nociception and antinociception, it was also shown that:

- women are more prone to feeling pain than men, but are able to regulate their pain with hormones.

- women with high levels of estrogen dealt with pain much better than women with low levels of estrogen.

- high levels of estrogen seemed to activate recently discovered mu-opioid receptors in the brain for the release of endorphins, the natural pain-killers.

Conclusion:

To sum up, we can say that gender-dependent responses to acute stress &/or acute pain in particular, or to persistent, episodic or chronic stress &/or chronic pain in general, remain very complex, and involve not only cyclic gonadal hormone activity and opioid and non-

opioid analgesia, but also a number of other factors like GABA and other neuroactive agents*1, nerve growth factor (NGF), sympathetic nervous system function, and also psychosocial factors. Nevertheless gender-dependent response to stress or pain are better expressed in the hippocampus and some specific related limbic structures in all mammalian species. And, while the hormone estrogen appear to be the most salient and most powerful factor responsible for gender versus sex differences in coping with acute stress or acute pain, other non-estrogen-induced neuromodulations are at play in the septo-hippocampal system, and may involve mainly oxytocic receptors, GABAergic receptors (progesterone influenced), noradrenergic receptors (glucocorticoid influenced?), serotonergic receptors and to a lesser extent dopaminergic receptors; and may probably be activated in face of persistent &/or chronic stress situations.

Menstrual cyclicity could also put women at more risk than men for developing a wide range of pains without well-defined peripheral pathology. The result, in the end, would be a greater variability in female responses to stress and pain than males. This greater variability could be due to the likely more limbic, more emotional and more "deactivating"(i.e homeostatic) processing of pain in women, as compared to the likely more thalamo-cortical, "more cognitive" and more"activating" processing of pain in men. The important message, from all this, is that chronobiological factors in general; that is all types of cyclic temporal factors, in addition to neurohormonal factors, are likely to be much more important for stress&/or pain perception in both sexes than has been realized up to now.

However, it remains to be said that further research on the biobehavioural and neuropsychological bases of gender biased responses to stressors, along the lines of recent theories on evolutionary and acquired brain sexual dimorphism, is needed to understand the regulatory functions of human emotions, the psychoneuroendocri-nology of emotionally intelligent behaviour, and the nature importance of estrogen and oxytocin as anti-stress hormones. Nevertheless, this kind of research must be *1: such as serotonine, dopamine, thyrotrophin-releasing hormone, calcium-dependent nitric oxide, and various peptides conducted bearing in mind the importance of the different phases of the menstrual cycle in women, age, brain hemispheric dominance in men and women, and cultural and ethnological factors shaping behaviour during infancy, to unequivocally distinguish gender-dependent reactions from purely gonadal responses in stress situations.

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