From Diathesis to Dimorphism: The Biology of Gender Differences in Depression

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[ABSTRACT]

Unipolar depression is more common in women than men. We pursue a unifying explanation for the sex difference in the incidence of depression that emerges at puberty and is unlikely to be fully explained as an artefact or as a result of socialization or contemporary sex roles. As symptomatic anxiety disorders show a similar female preponderance in women, we consider the biology of anxiety disorders and their links to depression. Rather than view gender as directly determining differential unipolar depression rates, we alternately hypothesize a primary post-pubertal effect of gonadal hormones on limbic system hyperactivity, so predisposing women to potentially higher rates of certain anxiety and depressive disorders.

EPIDEMIOLOGICAL STUDIES

Community studies have consistently found unipolar depression to be increased in women (Weissman & Klerman, 1977; Weissman et al., 1996). In the US National Comorbidity Study (NCS), the reported lifetime rates for episodes of major depression and/or dysthymia in women was 1.7 times higher than in men (Kessler et al., 1993).

In a meta-analysis of epidemiological studies, Jorm (1987a) noted age distribution differences. The prevalence in females rose sharply from childhood to adulthood before declining somewhat in old age, whereas the male rates rose a little in early adulthood but were then fairly stable throughout life. Of greater utility are age-specific incidence of depression data. In the United States Epidemiologic Catchment Area (ECA) study, a sex difference in major depression was first identified in the 15-19 year age band (Burke et al., 1990) while, in the NCS study (Kessler *et al.* 1993) a female preponderance emerged earlier in the 10-14 years age band. The NCS finding is consistent with two longitudinal studies in New Zealand (Anderson et al., 1987) and New York (Cohen et al., 1993), and thus suggests an influence of puberty on the incidence of depression. Such an association could be artefactual, or driven by social or biological factors, as now considered.

ARTEFACTUAL INFLUENCES

Higher female lifetime rates could reflect episodes being longer and thus more likely to meet diagnostic criteria incorporating illness duration. However, depression in women appears to be no more chronic (Kessler et al., 1994), recurrent (Simpson et al., 1997), nor associated with slower recovery (McLeod et al., 1992) than in men.

Other ‘artefactual’ influences have been proposed. Cohort studies have established that, over time, women are more likely to remember episodes not previously

nominated and more symptoms, while men are more likely to 'forget' previously reported episodes (Angst and Dobler-Mikola, 1984; Wilhelm and Parker, 1994). Thus, higher rates might merely reflect women being more likely to recall and acknowledge depression in surveys (Young et al., 1990), or the phenomenon of 'mood amplification' (Nolen-Hoeksema, 1987), whereby men are more likely to distract themselves and women to focus in a ruminative way. Amplification of their mood state may contribute to depressed women reporting more symptoms than depressed men.

SOCIAL INFLUENCES

Differential exposure to social or environmental stressors could theoretically contribute to the female preponderance of depression, although few such variables have been studied. Kessler (2000) noted that controlling for rape and other forms of sexual trauma in an analysis of the NCS database led to a halving in the gender difference in a first episode of depression. When the variables were broadened, however, to include traumatic experiences more likely to be experienced by men, the female preponderance was similar to the initial analyses. Kessler concluded that the results did not support differences in exposure to trauma as an explanation for gender differences in depression.

SOCIALIZATION AND SEX ROLE INFLUENCES

Gender differences in depression have been attributed to the different socialization and sex roles of males and females, and considered in a comprehensive monograph edited by Frank (2000). Here, Rosenfield (2000) argued that differences in socializing experiences during adolescence activate concepts of masculinity and femininity, shaping dimensions

of the self that, in turn, contribute to the development of internalizing and externalizing disorders – with the former (such as anxiety and depression) being over-represented in women. Further, Rosenfield held that the positioning of women in contemporary society was depressogenic.

Kessler (2000), though, argued that such a sex role argument was based on false assumptions from 1970's research, which showed that higher levels of non-specific psychological distress in women were confined to those who were married. Kessler concluded that such a difference was not due to a protective effect of marriage on men, because the female preponderance emerges earlier than "adult gender-role differentiation and greatly predates marriage" (p 68). If social factors determined a female preponderance of depression we would expect their influence on illness course, but the data suggest a key influence only on incidence.

Sex roles, and particularly the changes that occur in adolescence, may alternately reflect inherent biological processes that are influenced secondarily – rather than determined - by socialization experiences.

CONCEPTUAL MODELS

Kessler (2000) observed we need to explain why "women are more likely than men to have a first onset of depression beginning in adolescence and continuing through the end of midlife" (p 79). Two broad models are worthy of consideration.

The first allows that certain changes at puberty directly determine the female preponderance of depression. If valid, the preponderance should be ubiquitous throughout the female population, but gender differences are usually absent in college

and university students (Hammen and Padesky, 1977) and in socially homogeneous adult samples (Jenkins, 1985, Loewenthal et al., 1995; Wilhelm and Parker, 1994). Such variable expression argues against a model invoking puberty as a necessary and sufficient determining cause.

The second model invokes the concept of a vulnerability diathesis factor coming into operation at puberty, but with the diathesis often activated by social factors to generate the gender difference in depression rates. If valid, the vulnerability factor should be increased universally – even if depression is not - in women after puberty.

We now consider the case for anxiety or emotional responsiveness emerging as such a vulnerability factor in puberty and acting at either the Axis I 'symptom' level or at an Axis II 'temperament' or trait level.

SYMPTOMATIC ANXIETY DISORDERS

Epidemiological studies show that anxiety disorders are also more common in females. Lifetime NCS rates of 'any anxiety disorder' were 30.5% for females and 19.2% for males, compared to 21.3% versus 12.7% for major depression (Kessler et al., 1994). Females were, therefore, 59% more likely than men to experience an anxiety disorder and 68% more likely to experience depression, quite comparable preponderance rates.

If a gender difference in anxiety determines the gender difference in depression, then its effect should be eliminated by controlling for anxiety disorders preceding depression onset. Two studies have pursued this hypothesis. Breslau et al. (1995) analyzed 1000 young adult members of a United States health maintenance organization - reporting that a prior history of anxiety greatly increased the risk of major depression in

women and men, and that gender differences in prior anxiety disorders accounted for much of the female preponderance of depression. However, there was no interaction between gender and prior anxiety - that is, prior anxiety was as great a risk factor for depression in males as in females. Parker and Hadzi-Pavlovic (2001) undertook a similar analysis of the NCS database, quantifying female sex and preceding anxiety as both contributing to major depression and dysthymia, but with female sex having a stronger influence. They, too, failed to find any interaction effect. These studies support a model viewing the gender difference in depression as secondary to a gender difference in anxiety, but neither design allows rejection of an alternate possibility of a gender difference in a higher-order factor predisposing both to anxiety and depression, a model we will pursue in considering the role of temperament.

Whether or not this first model is valid, it is likely that differing expressions of anxiety would have differing associations with depression. Generalized Anxiety Disorder (or GAD) is the anxiety disorder probably most closely associated with depression, while also having been defined as a marker of an anxious 'temperament' style (Akiskal, 1998). According to a review by Brawman-Mintzer and Lydiard (1997), GAD is a condition (or a heterogeneous set of conditions) that involves prolonged, maladaptive stress responses - observable in the locus ceruleus-norepinephrine-sympathetic nervous system, the HPA axis and the cholecystokinin system, while abnormalities in other CNS modulators such as 5-HT and GABA have also been observed.

Many authors have suggested that a common genetic mechanism underlies both GAD and major depression. In one study, Kendler et al. (1992) also proposed that differential clinical manifestations of the two disorders reflected environmental shaping

factors rather than genetic differences. Roy-Byrne and Katon (1997) suggested that perturbations in the GABA-benzodiazepine neuronal system that were thought to underlie anxiety could also lead to perturbations in monoamine neurotransmitter systems underlying depression, suggesting that GAD is a trait-like platform conferring vulnerability for the development of major depression and other anxiety conditions.

Such a model would be assisted by epidemiological and biological studies determining those anxiety disorders most closely associated with – and disposing to – depression, and showing sex ratio covariation with unipolar depression. In an independent publication (Parker and Hadzi-Pavlovic, 2003), analyses of the NCS study indicated that GAD and panic disorder were the two anxiety disorders most closely meeting those criteria.

TEMPERAMENT

A temperament model allows any link between certain anxiety disorders and depression to more reflect the influence of a higher-order common temperament determinant. If it is a relevant diathesis factor, we are first required to demonstrate a female preponderance in expression.

'Neuroticism', albeit variably defined, is a candidate temperament trait. A meta-analysis of studies reporting sex and age-specific norms for neuroticism inventories found females had higher scores across all age groups, although gender differences were greater in young and middle-aged adults than in children and the very elderly (Jorm, 1987b). The curvilinear pattern for neuroticism data was very similar to data reported by

that author for depression (Jorm, 1987a), except that the gender difference in depression completely disappeared in the very young and very old.

If explanatory, we need evidence that neuroticism is indeed a risk factor to depression, and that its influence is modifiable by social factors (thus explaining the absence of a gender difference in depression in certain socially homogeneous groups). Numerous studies have demonstrated that neuroticism is a 'true' predictor of first episodes of depression (e.g., Hirschfeld et al., 1989), while Katon et al. (1994) identified 'neuroticism' as the best predictor of persistence of depression in primary care. In a population-based Australian study (O'Shea, 2002), female adolescents had significantly higher neuroticism scores than males, but elevated scores in both females and males were strong independent predictors of first-onset major depression. The gender differential in the onset of depression was significantly reduced after adjusting for neuroticism scores, so that the greater chance of girls developing depression essentially reflected their higher neuroticism levels.

'Neuroticism' has been variably defined over time, with definitions using constructs ranging from autonomic lability to a 'neurotic' character style. The former 'biological' focus appears more relevant to our topic. McCleery and Goodwin (2001) argued that 'high-neuroticism' subjects may have a down-regulated HPA axis designed to prevent harmful overactivation, with such subjects showing a diminished cortisol response to dexamethasone-corticotropin-releasing hormone tests. In a neuroimaging study, Canli et al. (2001) tested whether individual differences in brain reactivity to emotional stimuli were correlated with personality style. Neuroticism scores were

correlated with the level of brain activation to negative stimuli (stressful pictures) in localized brain regions (left temporal and frontal lobes).

A possibly related construct is ‘stress responsiveness’. Boyce (2001) reviewed studies assessing reactivity within the autonomic nervous system as a measure of stress susceptibility. In their study of 6-7 year-old children, boys were more likely to be assigned to ‘externalizing’ and girls to ‘internalizing’ behavioral categories, with ‘internalizers’ showing high reactivity relative to low-symptom children, principally in the parasympathetic branch, while ‘externalizers’ showed low reactivity in both autonomic branches. The authors reviewed literature suggesting that resting heart rate in children is positively associated with anxiety disorders and heart rate variability is inversely associated with affective and anxiety disorders, whereas parasympathetic dysregulation is predictive of chronic behavioral (or more externalizing) problems in children.

Another related construct is Cloninger’s (1986) concept of ‘harm avoidance’, hypothesized to be “a tendency to respond intensely to aversive stimuli signals, to inhibit behavior and avoid punishment, leading to cautious, inhibited and apprehensive behaviors”.

These findings support ‘neuroticism’ (or ‘emotional responsiveness’) as a candidate higher-order diathesis temperament factor for the gender differences in depression. There is then a need then to consider the nature of the link between such variables and the emergence of a female preponderance in depression in adolescence.

GENDER DIFFERENCE CHANGES AT PUBERTY

The emergence at puberty of a female preponderance in depression could theoretically reflect age, age-related events or pubertal changes. Angold et al. (1999) considered previous longitudinal and retrospective studies and showed that widening in the gap between female and male rates of depression can be localized to Tanner stage III (that is, transition to mid-puberty) regardless of the timing of puberty.

Depression rates for boys decline between the ages of 10 and 16 years (Angold et al., 1999), possibly related to the processes of adrenarche which progress from mid-childhood. Observation suggests that a number of anxious worrying and shy pre-pubescent boys become more assertive, engage in risk behaviors and assume adolescent male 'immortality' – a change that must be suspected as increasing their resilience to depression. In support, Cohen et al. (1993) showed that the gender rates of overanxious disorder (equating to the concept of 'neuroticism') in adolescence could be explained more by a pubertal drop in male rates rather than by a distinct increase in female rates. Further, Rosenfield (2000) reported that, in a sample where there were no gender differences at age 12, the distinct gender difference at 15 years had occurred "only because boys had decreased in their levels of depressive symptoms" (p 33) in conjunction with the boys' increase in independence, self-confidence, superiority, self-esteem and "decline in extreme levels of other-salience for males" (p 33). Such findings indicate that pubertal changes have the potential to decrease, as well as increase, the incidence of depression. We need then to overview key hormonal changes, both ones increasing risk in females and, an issue rarely considered, possibly decreasing risk in males.

HORMONE CHANGES AT PUBERTY: A BRIEF OVERVIEW

As described by Frohman et al. (1999), gonadotropin-releasing hormone (GnRH) neurons of the medial basal hypothalamic region provide the central neural drive of reproduction for both sexes. Their axons release bursts of GnRH, which travel to the anterior pituitary and bind to specific membrane receptors producing luteinizing hormone (LH) and follicle-stimulating hormone (FSH) - the gonadotropins - which are released into the systemic circulation to direct gamete and gonadal hormonal production.

In males, LH stimulates testosterone production stimulates spermatogenesis, supports the male secondary sexual organs, and influences other tissues, leading to increased muscle mass, increased facial and body hair, and enlargement of the epiglottis, deepening the voice. Testosterone has been implicated in “the great increase in aggression” in males during adolescence (Skodol, 2000), while studies of the male climacteric have shown increased depression, mood swings, anxiety and irritability in association with declining testosterone levels (Sternbach, 1998).

In females, FSH stimulates ovarian follicle development at the beginning of each ovarian cycle. FSH and LH together stimulate ovulation mid-cycle as well as production of the ovarian steroid hormones (estrogen and progesterone) that, in turn, support secondary sexual organs. Estrogen causes breast development and increases subcutaneous deposition of fat, while its psychological effects will be considered shortly.

A pulsatile GnRH pattern is critical for gonadotropin stimulation. Pulse frequency is modulated by feedback of circulating gonadal steroid hormones as they change during the ovarian cycle, with estrogen having a positive feedback loop to the hypothalamic-pituitary axis. Pubertal awakening and adult functioning of the GnRH system are

modulated by many factors acting centrally, including adequate nutrition, length of day and seasonal cues. Many types of stress can also modulate the GnRH system, mediated by factors including beta-endorphin and CRH-containing neuronal systems.

LINKS BETWEEN HORMONAL AND PSYCHOSOCIAL CHANGES

In a theoretical model, Cyranowski et al. (2000) argued that both social and hormonal mechanisms stimulate 'affiliative needs' for females at puberty, and that such increased needs can interact with adolescent transition difficulties to create a depressogenic diathesis for at-risk females at puberty. They also reviewed studies implicating oxytocin in mammalian affilliative behaviors, with oxytocin neurotransmission regulated by fluctuating levels of the estrogen and progesterone.

ESTROGEN

Seeman (1997) extensively reviewed the organizing role of estrogens in the developing brain and their maintenance role in the aging brain. Neuroprotective neurotrophins up-regulate the density of estrogen binding sites and estradiol up-regulates the level of the neurotrophins to prevent cell death, promote cell growth and enhance neural communication. Gonadal hormonal receptors are present in brain regions mediating both cognition and affect, where they act as genetic transcription factors and respond to hormonal stimulus.

Female hormones are recognised as having a role in mediating sensitivity to stress. Exploring why women are more sensitive to perceived and exposed stress than men, Seeman speculated that estrogen cyclicity may render women more vulnerable to

the neurotoxic processes engendered by stress hormones. Further, she suggested that the cyclicity of changing hormonal levels (between puberty and menopause) may contribute to their greater post-pubertal vulnerability to mood and anxiety disorders. Recurrent estrogen withdrawal may interfere with estrogen's ability to neutralize the effects of glucocorticoids released during stress.

Seeman also noted the anxiolytic effects of ovarian steroids. All modulate the GABA-A benzodiazepine receptor, with progesterone metabolites acting as agonists and estrogens up-regulating the receptor. However, their cyclical withdrawal is thought to 'kindle' neuronal systems to promote anxiety states and perhaps explain women's greater sensitivity to the anxiogenic effects of non-specific stress. Such hormonal influences are likely to be indirect, as estrogens do not directly dampen mood. It is more likely the 'off-and-on' binding to intranuclear estrogen receptors in the brain that renders women more vulnerable to stress, perhaps through glucocorticoid neuronal toxicity. Estrogens also directly stimulate the CRH gene, perhaps explaining the slightly increased incidence of hypercortisolism of females - and the preponderance of depressive, anxiety and eating disorders.

In considering the role of estrogens in the epidemiology and treatment of anxiety disorders, Pigott (1999) detailed estrogen's enhancement of neurotransmission by influencing the synthesis, receptor sensitivity and metabolism of monoamines (norepinephrine, dopamine, serotonin). Halbreich (1997) described how estrogen increases serotonergic (5-HT) post-synaptic responsivity and increases both the number of serotonergic receptors and neurotransmitter uptake, with a cumulative effect as a 5-HT agonist. Estrogen's enhancement of serotonin function through multiple actions,

especially an increase in serotonin transporter sites and decrease in monoamine oxidase activity, may help explain gender difference in anxiety disorders.

Estrogen decreases the responsiveness of the alpha 2-adrenergic receptor and facilitates norepinephrine neurotransmission, effects that may also contribute to gender differences in stress responses. Men have a greater release of norepinephrine than women after pharmacological blockade of the alpha-2 receptor, thought to represent the chronic attenuation of the alpha-2 receptor response in women by estrogen (Schmidt et al., 1997). In addition, any stress response mediated by the locus ceruleus-norepinephrine system appears likely to be attenuated in the presence of estrogen (Lindheim et al., 1992). The loss of the ability of estrogen to suppress the stress response in females might also contribute to the exaggerated stress response in perimenopausal women (Seeman, 1997).

PROGESTERONE

Progesterone is hypothesized to have biological effects opposing the actions of estrogen and may have a direct dampening effect on mood (Seeman, 1997) – with an anxiolytic influence thought to be due to its effect on the GABA-benzodiazepine receptor complex (Majewska, 1992). Unlike estrogen, progesterone enhances monoamine oxidase activity (Chakravorty and Halbreich, (1997), and it assists in dismantling synapses constructed by estrogen at the beginning of the menstrual cycle.

Most of the actions of progesterone result in the antagonism or neutralization of the actions of estrogen (Sherwin, 1996), so that the introduction of progesterone to hormone replacement therapy may neutralize the mood-enhancing and stress-attenuating effects of estrogen. There are many complexities in understanding the roles of

progesterone, particularly when many of its metabolites (e.g., pregnanediol and allopregnenolone) have different biological actions to progesterone itself. Thus, the net biological effects of progesterone are dependent on the prevailing metabolic pathways and the relative availability and associated biological actions of the various metabolites (Majewska, 1992).

LINKS BETWEEN REGULATORY HORMONES AND ANXIETY: A SUMMARY

Three primary neurotransmitter systems mediate anxiety: the locus ceruleus-norepinephrine system, the serotonin system, and the GABA-benzodiazepine receptor complex. The female gonadal hormones are suggested to have a substantial regulatory role in the function of these neurotransmitter systems, affecting the synthesis, release turnover and metabolism of these neurotransmitters, as well as modulating the expression of their own receptor-regulating genes. As detailed by Pigott (1999), (i) MAO activity is decreased by estrogen and increased by progesterone; (ii) neurotransmission is facilitated by estrogen and inhibited by progesterone; (iii) for synapses, estrogen is trophic while progesterone dismantles, and (iv) mood is enhanced by estrogen and progesterone dismantles. Such data argue (Pigott, 1999) for these hormones enhancing women's vulnerability to develop anxiety disorders and the clinical course of pre-existing anxiety.

Since progesterone metabolites act as agonists (anxiolytics) for the GABA-A benzodiazepine receptor (Majewska, 1992) and estrogens up-regulate this receptor (Maggi and Perez, 1986), the cyclical withdrawal of progestins and estrogens has been proposed as 'kindling' neuronal systems and promoting anxiety states. If true, then

cyclical changes in gonadal hormones across the menstrual cycle, during pregnancy and postpartum would be expected to be associated with changes in anxiety and depression. Longitudinal studies suggest that the menstrual cycle can substantially influence the onset and course of anxiety disorders (Shear, 1997), while pregnancy and post-partum influences on anxiety have also been described (e.g., Pigott, 1999).

LIMBIC SYSTEM HYPERACTIVATION

We have noted studies demonstrating that women are more likely to receive a diagnosis of GAD and to score higher on measures of neuroticism. These two constructs provisionally shape the concept of a diathesis factor conferring greater responsivity to negative emotional stimuli, and then to certain expressions of both anxiety and depression. As Eysenck (1981) defined 'neuroticism' in terms of limbic activation - with those scoring high on the temperament style being prone to intense autonomic discharges, a limbic system hyperactivation model appears salient.

Limbic structures such as the amygdala affect autonomic regulation and have been implicated in psychiatric disorders involving processes that regulate emotion (Kagan et al., 1988). More specifically, Shear (1997) suggests that brain sites associated with anxiety (such as the limbic forebrain and brainstem monoamine-containing cells) have binding sites for gonadal steroids. George et al. (1996), in a PET study examining self-induced mood induction, showed that women had significantly increased blood flow in limbic and paralimbic structures during sadness activation compared with men. Earlier we noted the study by Canli et al. (2001) demonstrating that higher neuroticism scores correlated with brain activation in left temporal and frontal regions in response to a

negative stimulus. Thus, we argue that post-pubertal women are more likely to demonstrate limbic system hyperactivation in response to certain negative stressors as a consequence of gonadal hormone influences, with higher 'neuroticism' scores being a marker of that emotional responsiveness propensity, and that such a diathesis generates the established gender differences in anxiety and depression.

From an ethological perspective, the advantages of variations in a genetically-based behavioral pattern of vigilant defense assisting individual survival and survival of those under the individual's care appear straightforward. While such differential sex roles may no longer be so evident in contemporary western communities, contributory differential biological processes remain – providing a diathesis that is presumably capable of being attenuated or increased by social factors.

CONCLUSION

We propose that women's greater capacity to experience limbic system hyperactivation and emotional responsiveness not only once had evolutionary advantages, but also the potential to dispose to a greater likelihood of both anxiety and depression, driving the female preponderance in unipolar depression that is evident in community studies. We have detailed how such a differential is likely to be activated by pubertal changes in gonadal hormones (both in females and in males).

The longstanding finding of a female preponderance in depression encouraged theorists to pursue direct causes, be they biological, social or other determinants of 'depression'. But 'anatomy is not necessarily destiny' in this instance, in that – as noted earlier - there are a number of studies establishing absent or attenuated gender differences

in socially homogeneous groups. Thus, we propose an alternative diathesis-stress model, and have speculated on the nature of the diathesis factor. At the most parsimonious level, we suggest that post-pubertal women are at risk because of hormonal influences activating a diathesis or propensity that, subject to socialization and sex role factors, may generate the female preponderance in both anxiety and depressive disorders observed in community studies. We suggest that such a model has the potential to refine epidemiological as well as biological and social psychiatric research.

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