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INVITED REVIEW

The aetiology of depression

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ABSTRACT

This review will start by considering studies of the genetic contribution to the liability to depression, and go on to consider some of the ways in which environmental factors can modify gene expression. This will lead on to the pathways by which the genetic factors also appear to control stressful life events in adolescence and adult life, and then to a consideration of causes that are entirely environmental. We will conclude by considering the causes of the gender differences in the prevalence of depression during adult life.

Genetic studies

Early studies of the genetics of depression concluded that genetic factors account for approximately 40% of the variance in both males and females, with most of the remainder being attributed to an individual's unique environment (Thapar & McGuffin, 1996; Kendler & Prescott, 1999). More recently, Kendler *et al.* (2001) have included male–female dizygotic twins as well as the usual same-sex MZ and DZ twins, and found that if broad definitions of illness are used, then the heritability of depression is greater in women than in men. They conclude that the genes are correlated, but not necessarily the same, and that the impact of some loci on risk for major depression may not be the same for men and women. Kendler *et al.*'s (2006*a*) study of a large Swedish twin series confirms these findings, by showing the hereditability for depression is 29% in males, but 42% in females.

Interactions between genes and the environment

It seems likely that there are a number of distinct genetic pathways to depressive illness, and at least two of these are known. The 5-HT transporter gene (5-HTT) on chromosome 17 (17q11.2) is one of these, and it has been argued that there is an interaction with stressful life events that appears to determine the liability to depressive illness. Those people with the long homozygote are relatively resistant to life stress; while those with the short homozygote are highly sensitive to it, with rates for depression rising from around 9% in those who have not experienced stressful life events, to around 40% in those who have experienced four or more stressful events (Caspi *et al.* 2003).

These findings have now been confirmed by others (Eley *et al.* 2004; Kendler *et al.* 2005*b*; Zalsman *et al.* in press; Wilhelm *et al.* in press), and partially confirmed by others using different environmental measures. Grabe *et al.* (2005) used unemployment and the presence of chronic disease; Kaufman *et al.* (2004) maltreatment and the absence of social support in childhood, and Fox *et al.* (in press) maltreatment and low maternal support in childhood. Eley *et al.* (2004) also identify the tryptophan hydroxylase site as also being a significant predictor of depression. There have been two failures to replicate this interaction between genes and environment: Gillespie *et al.* (2005) used a list of threatening life experiences, while Willis-Owen *et al.* (2005) used a scale of 'health and life experiences': both these studies included older subjects, and it is possible that the effects described by others are stronger during the first two decades of life.

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These papers illustrate two important principles: the linear relationship between number of events and likelihood of depression in those with homozygous short chromosomes illustrates that some genes manifest only in certain social environments, while the unresponsivity of the homozygous long 5-HTT genotypes illustrates that some people are resilient to stress for genetic reasons, and this will be quite independent of specific illness-related genes. This last observation fits well with Rijsdijk *et al.*'s (2003) observation that the tendency to have a low score on the General Health Questionnaire has a genetic component.

How genes might control stressful life events

Brown & Harris (1978) were the first to demonstrate that episodes of depression were likely to be antedated by stressful life events. For some time it has been known that stressful life events are partly hereditable (Plomin *et al.* 1990; Kendler *et al.* 1993; Thapar & McGuffin, 1996) but it has not been clear how this can be possible, and what the intervening mechanisms might be.

The determination of personality has a substantial genetic component (Torgerson *et al.* 2000) and this in turn determines the type and frequency of stressful life events that will be experienced during adult life. Early studies (Fergusson & Horwood, 1987; Headey & Wearing, 1989; Poulton & Andrews, 1992) used Eysenck's neuroticism ('n') as an indicator of vulnerability to depression later in life, but Farmer *et al.* (2002) have argued that in this study 'n' is influenced by mood, and in her particular study does not reflect a vulnerability trait.

Saudino *et al.* (1997) showed that although 'n' is involved in undesirable life events, a major portion (82%) of genetic variance on such events could be accounted for independently by 'Openness to Experience', and concluded that genetic influences on life events appear to be entirely mediated by personality. It seems unlikely that openness to experience is related to current levels of symptomatology, so that in the genetic control of personality we have an independent genetic pathway influencing vulnerability to depression, in addition to 'n' and similar measures.

Van Os & Jones (1999) using a large birth cohort showed that the effect of aggregated life events on mental health was greater in women than in men, in individuals with higher childhood 'n' and poorer childhood mental health. Higher maternal 'n' was also associated with greater sensitivity to life events, independent of the subject's 'n', suggesting possible familial transmission of vulnerability. In addition, higher childhood 'n' predicted, independent of later mental health, greater likelihood of reported exposure to life events. In general, individuals with higher childhood abuse also reported more life events.

Farmer *et al.* (2003) using a sib-pair design and Cloninger's temperament and character scales showed that their depressed probands were much more harm avoidant, less novelty seeking and less reward dependent than either their non-depressed sibs, or controls.

Kendler *et al.* (2003) conclude that 'n' predicts the occurrence of most stressful life events, and found that in MZ twins the level of 'n' in one twin predicted both the occurrence of life events in the other as well as the quality of interpersonal relationships in the other. In a later paper Kendler *et al.* (2004) show that early sexual abuse increases the sensitivity of the individual to later stressful life events, and that the occurrence of depression can be predicted by a combination of 'n' assessed in childhood, childhood abuse and stressful life events.

Environmental influences

The level of reactivity of the hypothalamopituitary axis (HPA) axis at birth will be set genetically, and experiences after birth will serve either to decrease or increase the sensitivity of the axis. Measures of 'neuroticism' and 'harm avoidance' in adult life will serve as an indirect measure of the sensitivity at any particular time, while hormonal assays are a direct measure.

Immediately after birth, good maternal attachment is an important environmental influence that decreases the sensitivity of the axis. Studies on rats have demonstrated decreased HPA responsiveness in adult life when a young rat receives care from a 'licking and grooming' mother, and cross fostering shows this to be independent of genetic influences (Meaney, 2001). These changes have been shown to be mediated

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by altered methylation of DNA, and transcription factor (NGFI-A) binding to glucocorticoid receptors (Weaver *et al.* 2004). In contrast, maternal separation causes increases in HPA responsiveness.

In humans, the most important early environmental contribution to later depressive and anxious symptoms is the quality of maternal attachment. A securely attached child displays social competence, feels sympathy for others, and exerts controls on responses to interpersonal conflict. This is the first experience in life which can alter the level of HPA responsiveness that was set at birth. The two environmental influences that are known to increase HPA responsiveness after birth are emotional deprivation (Gunnar *et al.* 2001) and childhood maltreatment (Gunnar & Donzella, 2002). Numerous environmental factors are associated with disrupted attachment, including severe early deprivation such as being reared in an orphanage (Rutter *et al.* 2001), maternal deprivation, and maternal depression (Cox *et al.* 1987).

Heim and colleagues argue that children exposed to traumatic life experiences develop an increased sensitization of those parts of the nervous system related to stress and emotion, and in consequence develop an increased vulnerability to later stress due to hyper-reactivity of corticotrophin-releasing factor, as well as other neurotransmitter systems (Heim *et al.* 2000; Heim & Nemeroff, 2001).

The earliest changes that reflect depressive phenomena have been described in 5-year-old children of depressed mothers. Murray *et al.* (2001) have shown that when these children are placed in a play situation involving interpersonal challenge with another child that may involve personal failure, that they – compared with controls – show a marked tendency to make negative statements about themselves. They displayed hopelessness, pessimism and low self-worth – but they only displayed these when in the affectively charged environment. Neither they nor their mothers reported such feelings at other times.

In their study of 61 female monozygotic twins discordant for depression, Kendler & Gardner (2001) identified three patterns of abnormality that identified the affected twin. In the first, the affected twin had a sickly, overprotected childhood with phobic symptoms, but fewer relationship problems as an adult. The second pattern described low maternal warmth and much higher levels of anxiety and rebelliousness in childhood, left school early, married as a teenager and had high rates of alcoholism, divorce and stressful life events. The third pattern had a cold father, an authoritarian mother with higher anxiety in childhood, many relationship problems with partners and a high divorce rate, higher rates of alcohol dependence and low social support from relatives with overall highest adult rates for stressful life events. These last two patterns are reminiscent of Brown & Harris's (1993) working-class depressives.

Children who have been subjected to neglect, and physical or sexual abuse not only have far higher rates of depression and anxiety in adolescence, but also display self-harm behaviours, eating disorders and have problems establishing satisfactory sexual relationships (Mullen *et al.* 1994; Swanston *et al.* 1997), as well as higher rates of depression in adult life (Bifulco *et al.* 1991). Low maternal care can also produce high rates of adult depression in the absence of childhood sexual abuse (Hill *et al.* 2001).

Explanations for the gender differences

There are three possible explanations for the female excess in depression: genetic, hormonal and social. The studies cited above indicate that genetic factors are partly responsible for the gender differences. Staley *et al.* (2006) argue that the decrease in 5-HTT availability in the diencephalon is much more marked in depressed women than depressed men, and is especially marked among younger women. However, it is not necessarily true that different genes are responsible in men and women – it is possible that some factors in females enhance gene expression.

One such candidate is the hormone oestrogen, since Seeman (1997) argues that

> the off-and-on binding to intra-nuclear estrogen receptors in the brain somehow renders women vulnerable to stress, perhaps through glucocorticoid-induced neuronal toxicity. The cyclic nature of estrogen secretion from puberty to menopause and, subsequently, its almost total withdrawal may account for the special vulnerability of women to mood and anxiety disorders. Recurrent estrogen

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withdrawal, starting in the early teens, may interfere with one of the natural functions of estrogen, the ability to neutralize the effects of glucocorticoids released during stress.

Another hormonal explanation combines social explanations with the observed differences in friendship patterns between boys and girls, with higher needs that girls have for affiliative ties with their own sex, and a greater tendency to attribute environmental difficulties to their own shortcomings. Sex hormones – especially oxytocin – differentially heighten affiliative need, and when this accompanies normal adolescent difficulties with transitions within peer groups or dyadic friendships, in the presence of disappointing events this leads to depression (Cyranowski *et al.* 2000). This fits well with the timing of the increased rate, but remains a speculation rather than a demonstrated fact – as the heightened affiliative need due to oxytocin has been demonstrated in cattle, but not in humans.

Exposure to androgens from the foetal testes during pregnancy masculinizes the developing brain, rendering it incapable of supporting cyclical hormonal activity in later life, and producing a more lateralized brain. Without such stimulation, a female brain develops. Experiments a few hours after birth have shown consistent differences between male and female neonates, with males more likely to fixate on a mobile containing a weird mixture of facial features, but females spending more time looking at a mobile of a girl's face (Connellan *et al.* 2001). These differences are in turn related to the female's greater tendency to empathize, and the male to systematize (Baron-Cohen, 2002). Empathizers are better at imagining what others are feeling, and have a greater preference for intense social relationships, while systematizers are interested in how things work, have superior spatial skills and may derive pleasure from solitary activities. During infancy there are consistent differences observable in the patterns of pre-school play displayed by each sex – with females preferring collaborative play often involving dolls, while males are territorial and use relatively unsubtle techniques to ascend dominance hierarchies

Experiencing sexual abuse, another risk factor for depression, is more common in girls than boys, and we have already seen how important sexual abuse is in sensitizing an individual to later stressful life events. The experience of being a victim of bullying is of course highly unpleasant for either sex, but only in girls is there a strong relationship to later depression (Bond *et al.* 2001).

As childhood progresses, friendship patterns assume much greater salience for girls. Although having no friends is important for both, boys are relatively immune because they derive satisfaction from lonely activities typical of systematizers – computers, model building, bird watching, stamp collecting and so on. Female friendship networks in childhood are dominated by verbal communications with emotional language, males by performance language. Females show high turnover of close one-to-one friendships within a relatively stable network; in contrast males show a relatively low turnover of close friends but also within a relatively stable network. Thus, compared to males females throughout childhood and adolescence are more exposed to intercurrent disappointing experiences than are boys within their friendship framework. This suggests that females are more exposed overall to one of the risks for emotional disorders, namely acute disappointments in confiding relationships. Such acute disappointments are, however, potent risks for depression for both sexes in first episode depressions in adolescents (Goodyer *et al.* 2000). Empathizing, being a female trait, may increase the liability for emotional symptoms in the presence of acute disappointments. This would be a child as well as adolescent difference but the emergence of depression is a post-pubertal event. Thus, compared to males more females may become depressed in adolescence as a result of an interaction between acute close friendship disappointments, high empathizing and hormone changes post puberty. Given that the increased liability for affective disorders in girls is best indexed by sex hormones and not observable physical change it is likely that the additional risk reflects these post-pubertal psycho-relatively endocrine changes rather than then external changes of physical development.

In middle childhood, the development of friendships is the most important non-family activity related to later depression, with those who have not formed friendships being at

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greater risk, as they have greater difficulties handling negative events. If a child fails at key tasks, and receives no encouragement from parents or teachers, feelings of shame, helplessness and hopelessness now make their appearance. Early cognitive changes relevant to depression now occur, and these seem especially likely if there is a tendency to ruminate.

Given the greater tendency for girls to ruminate and have negative automatic thoughts, the stage is set for higher levels of dysphoria and an increased rate of depression. Kendler *et al.* (2005*b*) show that women report higher levels of social support than their twin brothers, and are more sensitive to low levels of support than their brothers. These findings are of course wholly consistent with the greater importance that friendship patterns have for females.

Nazroo *et al.* (1997) showed that wives are at greater risk of depression following a stressful life event than their husbands. This greater risk is due to their respective gender roles – wives found events involving children, housing or reproductive problems more salient, while husbands found events involving work and financial provision more salient. The wives were more likely to become depressed following their events, and more likely than their husbands to report self-blame. These findings are similar to those of Kendler *et al.* (2001), who showed that while the rates at which the two sexes experienced life events was similar, that females were more likely to experience housing problems, loss of confidants, crises and interpersonal difficulties, while men were more likely to experience problems at work, job loss, robbery and legal problems. Maciejewsky *et al.* (2001) showed that women are three times more likely than men to develop depression after a stressful life event, but this appeared to be because a wider range of life events are pathogenic for them; some, like death of a partner or divorce, are equally likely to be followed by depression in each sex. In a study of male twins, Kendler *et al.* (2006*b*) show that while there are broad similarities between the sexes, that childhood parental loss and low self-esteem were more potent variables in the model in men than in women.

Given the complexity of the genetic pathways that are involved in the aetiology of depression, the high probability that there are important interactions between genes and with life events during childhood, and the importance of interactions between genetic factors and hormones, disentangling the respective importance of genetic and environmental factors seems like yesterday's problem. In addition to these highly important genetic factors, the quality of maternal attachment can be shown to be environmental in cross-fostering experiments, and the presence of childhood abuse must be at least partly environmental. It is likely that future research will uncover still further genetic pathways to depression, but perhaps our present knowledge allows us to grasp at least the outlines of the final picture.

Declaration of Interest

None.

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