Something borrowed, something blue

Spearman Medal winner **THALIA ELEY** *on combining old and new approaches to the development of anxiety and depression.*

ANXIETY and depression are now recognised as major areas of public health concern, associated not only with distress to sufferers but also with serious social consequences in areas of life such as friendships, relationships, education and work. As many as one in five women are likely to be seriously depressed at some point in their lifetime, and roughly half that proportion of men. Both anxiety and depression show considerable continuity over time, with many individuals tracing the start of the problem to childhood (especially the subtype of anxiety, social phobia: Morris, 2001) or adolescence (especially depression: Fombonne *et al*., 2001).

While we know that there is significant genetic influence on both anxiety and depression, little is known about the mechanisms of this genetic risk. Similarly, it has been repeatedly demonstrated that environmental influences such as life events and parenting style are important in the development of these symptoms. Surprisingly, given the 'bit of both' conclusion psychologists have become accustomed to, virtually no research in this area takes into account the possibility that genes may mediate these environment–mental health associations by having an impact on personality or cognitive style. For example, people may influence their own environments by their own personality-led actions (low sociability may reduce number of interactions, thus increasing level of isolation and peer-group difficulties). Furthermore, individuals may alter their perceived environments as a result of their cognitive style – biased attention to threat, interpretation of threat, and recall of threat can all impact on the level of perceived threat in the environment (Vasey & MacLeod, 2001).

These behaviours and aspects of cognitive style are likely to be inherited to some extent, so the associations between environmental stress and emotional symptoms need to be considered from several different levels of risk. I believe that the time has come to combine differing methodologies in order to take a more comprehensive approach the development of anxiety and depression, and other complex phenotypes. In this article I propose that behavioural genetic methods (see box) can be used in combination with other approaches to shed light on developmental models of anxiety and depression.

BEHAVIOURAL GENETIC ANALYSIS OF TWIN DATA

Identical or monozygotic (MZ) twins are created when a single fertilised egg splits into two. As a result, identical twins share all of their genes. Non-identical or dizygotic (DZ) twins are created when two separate eggs are fertilised at the same time – these twins share half their genetic resemblance, as with any other pair of full siblings. Within the twin method, it is assumed that both types of twin are equally influenced by the shared environment, that which makes family members similar to one another (for a discussion of the assumptions of the twin design see Martin *et al.*, 1997).

Aspects of the environment that are child-specific (non-shared environment) result in differences between the twin pairs, so within-pair similarity for identical twin pairs is due to shared genes and shared environment. In contrast, within-pair similarity for non-identical twin pairs is due to sharing half their genes and their shared environment. Any increased similarity seen between identical twins as compared with non-identical twins is attributed to their having twice as much genetic resemblance. The difference in the correlations for identical and non-identical twins is therefore a rough estimate of half the heritability of the trait.

For the adoption design similar principles hold. For adoptive sibling pairs, similarity is due solely to the shared environment. Model-fitting approaches are used to test more complex hypotheses and to provide heritability, shared environment and non-shared environment estimates, with confidence intervals. However, the root of such analyses remains the differing levels of resemblance on the trait(s) of interest for the two types of twin pair.

It never rains but it pours

One of the most prominent features of anxiety and depression is the high level of covariation of the two types of symptoms. One potential source of such covariation is shared risk factors, so one of the first questions I was interested to explore in my research was the extent to which genetic or environmental influences on anxiety were the same as or different from those on depression. Data from adults had revealed

that the genetic influences on anxiety and depression symptoms were largely shared (Kendler *et al.*, 1992). We set out to see if the same was true in children and adolescents.

We collected self-reported anxiety and depression symptoms from 501 twin pairs aged 8 to 16 years (Eley & Stevenson, 1999). For anxiety, 17 per cent proportion of variance was due to genes, 34 per cent to shared environment and 49 per cent to non-shared environment. For depression the values were 36 per cent genes, 15 per cent shared environment (non-significant), and 49 per cent non-shared environment.

This analysis also revealed a genetic correlation of 1.00 between depression and anxiety, indicating that the genetic influences on anxiety are entirely shared with those on depression. The shared environment correlation was just .25, and that for the non-shared environment was zero, indicating that environmental influences are largely specific to the type of emotion.

In the meantime another paper had been published on parent-reported anxiety and depression symptom scores from a sample of children and adolescents that presented similar results (Thapar & McGuffin, 1997). These results suggest a diathesis-stress model in which there is a shared genetic predisposition to emotional symptoms, with the type of environmental stress resulting in the specific symptom type.

Specifying environment risks

There is considerable evidence that environmental stresses increase emotional problems during childhood, including poor parenting (Maccoby, 1991), marital discord (Cummings & Davies, 1994), parental divorce (Dong *et al.*, 2002) and economic hardship (Spence *et al.*, 2002). However, this work tends to examine either depression *or* anxiety, or to consider combined groups rather than exploring the role of specific associations between stressor-type and symptom-type. In contrast, work in adults has suggested a specific association between loss events (such as death of a parent) and depression, and between threat events (such as terminal illness) and anxiety (Finlay-Jones & Brown, 1981).

We decided to examine the specificity of stressor type to anxiety and depression in our sample. We visited 90 families, of which 61 were twin pairs in which at least one child scored high (more than one standard deviation above the mean) for anxiety or depression, and 29 were control pairs (both members low on both measures). We interviewed the twins and their mothers using the Psychosocial Assessment of Childhood Experiences (Glen *et al.*, 1993). Life events and ongoing stressors were rated using a 'best-estimate' procedure incorporating information from both the child and mother interview. Life events deemed to be independent of the child's behaviour were classified for loss and threat, and chronic stressors were classified by type, of which three were common enough to warrant analysis: friendship problems, family relationship problems and schoolwork problems.

A comparison of children scoring high on depression with the remainder of the sample revealed a significantly increased rate of loss events, and all three types of chronic stressor. Threat events were also more common, but not significantly so. Children high on anxiety experienced significantly more threat events than the remainder of the sample, but differences for all other experiences were non-significant. These findings are compatible with the evidence cited above for specificity of environmental influences to symptom type. Unfortunately, owing to the small sample we were not able to take advantage of the sample consisting of twin pairs, but in a larger sample of twins it would be possible to use such data to examine the role of genetic and environment factors on the association between specific types of both stressor and symptom.

Why no shared environment?

One of the most surprising aspects of the results from the behavioural genetic literature concerns the role identified for environmental influences. It appears to be non-shared or child-specific environment that plays the greatest part, with shared environment contributing little. An exception to this rule is anxiety, for which shared environment has been repeatedly found to be important, particularly for fears and separation anxiety (Eley, 2001). This may reflect a learning effect, with children associating danger with objects or situations to which the parent shows a fear reaction. However, for variation in depression, there is a notable lack of shared environment with genetic effects accounting for around 30–40 per cent of the variance, and shared environment estimated at just 10–15 per cent, with the remainder due to non-shared environment.

This is something of a conundrum, given the well-replicated findings that familial factors such as poverty, parental conflict, divorce and loss of important attachment figures, notably parents (Brown & Harris, 1978), all play a role in the development of depression. I propose two possible solutions to this puzzle. First, shared environment may be more important for *extreme* levels than for variation in the normal range of depression during childhood and adolescence. Second, shared environmental influences may play their part by interacting with other risk factors, which then mask the effects of the shared environment. I consider these explanations now.

Extremes analyses

Perhaps the lack of evidence for shared environmental influence in child depression

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is due to the fact that behavioural genetic studies with this age group have tended to look at variation in the normal range. However, three studies (including ours) have specifically examined the level of genetic and environmental influences on variation in normal scores on a trait and compared this with results for those individuals with high scores (Eley, 1997; Rende *et al.*, 1993; Rice *et al.*, 2002). The results have been remarkably consistent. Although within each study the differences were not significant, all three found greater shared environmental influence for those with high depression scores, as compared with the contribution of shared environment to individual differences in the normal range. This suggests that aspects of the family environment that lead to similarity within twin pairs only become important for high levels of depressive symptoms.

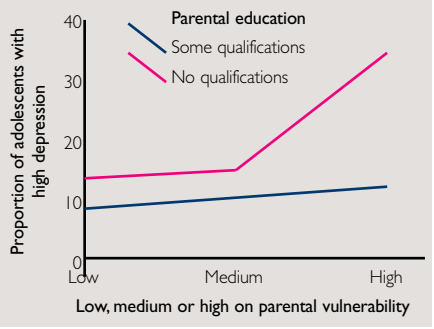
Many studies examining the role of family factors in depression consider those with high depression scores rather than exploring causes of variation in the normal range. This may explain why these two research worlds have appeared to come up with contradictory results. However, this does not fully explain the puzzle, since depressive disorder, which is also arguably the extreme end of the depression continuum, does not appear to be influenced by the shared environment. So we turn to the impact of interactions.

Interaction effects

Risks from the family environment may act by increasing vulnerability, but discrete stressors may be necessary for actual symptoms to result. Such interactions would be masked within the non-shared environment term in a traditional twin model. Similarly, interactions between shared environmental influences and genetic risk factors would be masked within the genetic term. As a result, unlike both the genetic and non-shared environment estimates, which include interaction effects, the shared environment term includes just main effects of shared environment. This makes it particularly important to examine how family risk factors might interact with discrete child-specific stressors and also with genetic risks.

To this end we collected data from 1818 adolescents of 1294 parents. Parents provided information on poverty, housing, family relationships, family life events, and their own employment and education. Parents and their siblings also reported on their own depression, anxiety and neuroticism. This was used to make a familial risk factor for anxiety/depression/neuroticism by maximising the resemblance between parents and their siblings. In other words, analyses were conducted to find factor scores that led to parents and their siblings being as similar as possible on the factors. We found that in addition to sex and age, the familial risk factor and parental educational level (none versus some qualifications) were the strongest predictors of high depression scores in the adolescent offspring. Furthermore, there was a significant interaction between the two risk factors – adolescents whose parents had no qualifications and were in the highest third of scores on the familial risk factor score were three times more likely to be in the high depression group (see Figure 1) (Eley, Liang *et al.*, in press).

FIGURE 1 Parental influence on depression



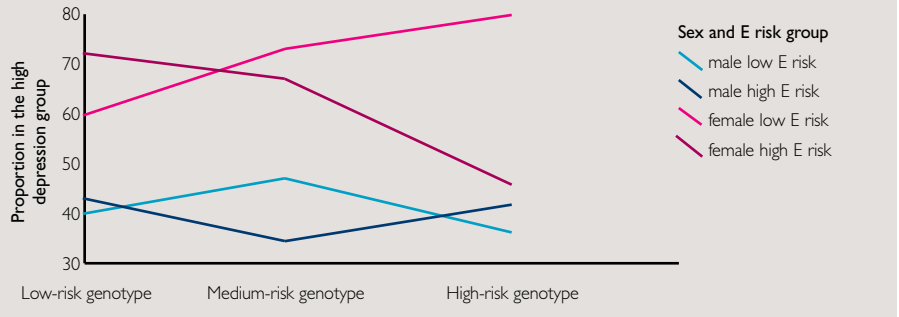
The next step was to search for specific gene–environment interactions. We obtained DNA samples from 377 of the adolescents, selecting those in the top and bottom 15 per cent on depression scores. We were interested in examining the role of genetic markers within the serotonin system, and their possible interaction with environmental risk factors. We chose to explore genes within the serotonin system partly because of the well-known impact of serotonin re-uptake inhibitors as a treatment for depression, and also because of a high-profile finding in this area. This related to a gene called the serotonin transporter, and the relevant variant was in the section of the gene that turns it on and thus has an impact on the functional output of the gene. This gene had been previously associated with a triad of depression-related personality traits, including neroticism (Lesch *et al.*, 1996), and had also been the focus of considerable replication attempts, not all of which have been successful (Ball *et al.*, 1997).

Our measure of environmental risk was a standardised sum of the aspects of environment reported by the parents in the first wave of the study. The sample was split into those above (high) and those below (low) the mean for environmental risk. We found weak evidence for an interaction between genotype, sex and environmental risk – the version of the gene typically associated with depression, anxiety and other related phenotypes did carry a risk for high levels of depression, but only in girls in the high environmental risk group (see Figure 2) (Eley *et al.*, 2003). These results clearly need replicating, but they provide support for the hypothesis that risk factors for depression interact with one another.

Cognitive style and information processing

Behavioural geneticists have become used to borrowing the methods of psychosocial researchers and molecular geneticists in order to identify specific aspects of environmental and genetic risks. Another approach will be to import methods from other areas of psychology. Several aspects of brain functioning could be considered as mediators of genetic and environmental risks, and one that may prove fruitful is information processing. It seems plausible that the general genetic vulnerability to

FIGURE 2 Interacting effects on depression – serotonin genotype, environmental (E) risk and sex



anxiety and depression described above acts by influencing core processes associated with stress reactivity. In other words, individuals with a high level of vulnerability may be more highly tuned to detect and react to threat than those with a lower level of vulnerability.

We have recently begun to examine attentional processes with regard to the development of childhood anxiety, including cognitive biases associated with panic. Two key features of panic disorder (PD) in adults are sudden bodily sensations, such as a pounding heart, and the interpretation of these sensations as dangerous (Clark, 1986). This has led to the development of psychological models of PD that emphasise catastrophic interpretations of bodily sensations. These models suggest that panic attacks are triggered by internal cues, which are then interpreted as threatening and result in anxiety (McNally, 1999). Such theories have led to experimental research exploring individual differences in the perception of bodily cues, specifically good heartbeat perception (Ehlers *et al*., 1988), and fear of anxiety sensations or 'anxiety sensitivity' (Reiss, 1986), as potential risk factors for development of PD.

A variety of designs have been used to explore heartbeat perception in relation to panic, but the most reliably replicable results have been obtained using the mental tracking paradigm (Schandry, 1981). In this task individuals are asked to count silently to themselves the heartbeats they feel during a discrete period of time. Using this technique, PD patients have been found to be better at counting their heartbeats without taking their pulse than a variety of other groups, including normal controls and individuals with infrequent panic attacks, simple phobia or depression (for a review see Ehlers & Breuer, 1996).

We assessed heartbeat perception and anxiety sensitivity in a sample of 79 children aged 8 to 10 years from a local primary school. We found that in children, as in adults, panic/somatic symptoms are associated with both enhanced heartbeat perception and increased anxiety sensitivity. Those with high levels of panic/somatic symptoms were seven times more likely to have good heartbeat perception and had anxiety sensitivity scores one standard deviation higher than the remainder of the sample. Multivariate analyses revealed that these two phenotypes had independent associations with high panic/somatic symptoms (Eley, Stirling *et al*., in press). We are now conducting these and other tasks assessing aspects of cognitive style associated with anxiety, in a sample of twin pairs aged 8 years. We plan to use the data to examine whether cognitive style mediates genetic and environmental risks on the development of anxiety symptoms.

In summary, I hope I have shown that by borrowing methods from other areas of psychology and combining them with behavioural genetic methods, we can begin to understand not just the level of impact of genetic and environmental influences on the development of anxiety and depression, but the processes by which these risks take effect.

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