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Commentary: Nature–nurture interplay in emotional disorders

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The empirical findings on emotional disorders over the age period spanning childhood to adult life provide several important challenges that demand explanation with respect to the key mediating and moderating causal mechanisms. Thus, epidemiological data have shown a substantial rise in the rate of major depressive disorders during adolescence, together with a shift from a roughly equal sex ratio to a marked female preponderance (Bebbington, 1998; Bebbington et al., 1998; Hankin et al., 1998; Kessler, McGonagle, Swartz, Blazer, & Nelson, 1993). It is striking that, with but few exceptions, the disorders showing a female preponderance tend to involve some form of emotional disturbance and usually have an onset during the teenage years or early twenties (Rutter, Caspi, & Moffitt, in press). By contrast, those exhibiting a male preponderance are mainly neurodevelopmental disorders first manifest in early childhood. The implication is that it may be useful to consider mechanisms that apply within age periods, but across disorders, rather than focus on possibly different explanations for the sex ratio found for each psychiatric condition.

It has also become apparent, with respect to findings in both childhood and adult life, that the categorical split between psychopathology and normality is rather artificial and somewhat misleading (Pickles & Angold, in press; Pickles et al., 2001; Rutter, in press; Taylor & Rutter, 2002). Thus, subclinical levels of symptoms have correlates and consequences that are broadly comparable with those that apply to clinically significant disorders. Also, as in the field of internal medicine more generally, it has become clear that many risk and protective factors operate dimensionally with effects within the 'normal' range (statistically speaking), as well as with overt psychopathology or disorder.

Of course, these findings do not necessarily mean that there are no valid categorical distinctions. Both continuities and discontinuities between normality and disorder must be tested for, rather than assumed (Rutter, 1986). Thus, IQ functions dimensionally with respect to associations with scholastic attainment and even social functioning in adult life, but the genetic influences on severe mental retardation are very different from those operating within the normal range (Rutter, Simonoff, & Plomin, 1996). Might the same apply in the domain of affective and anxiety disorders? Possibly. Perhaps, bipolar or psychotic depression might prove to be meaningfully distinct from the more common varieties of unipolar depression (Maher et al., 2002; Rutter, Silberg, O'Connor, & Simonoff, 1999b). The occurrence of episodes of mania seems to index a more severe disorder that probably has a stronger underlying genetic liability, and that does not show any marked female preponderance. However, whether the bipolarity reflects a qualitative, rather than quantitative, distinction remains uncertain (Kelsoe, 2003). Part of the problem in making that distinction stems from the fact that, over the course of a lifetime, many apparently unipolar depressions involve an episode of hypomania or, less often, mania (Angst et al., 2003). Accordingly, cross-sectional comparisons of unipolar and bipolar disorders are likely to be misleading because the former group will, in reality, include cases of the latter group – at least if it is defined broadly. The lesson from the research findings is that the possibility of a categorical distinction needs to be assessed using longitudinal data that refer to *patterns* of symptoms and not just the number or severity of symptoms.

In that connection, it will need to be borne in mind that there may be intra-organismic changes that are brought about by the occurrence of an episode of disorder – so-called 'kindling' effects (Post, 1992; Kendler, Thornton, & Gardner, 2000, 2001). Insofar as this happens, it may mean that the causal mechanisms for the first episode of disorder may not be identical to those underlying recurrences.

Another aspect of possible heterogeneity that is particularly important with respect to childhood and adolescence concerns the age of onset of the first episode. It has generally been assumed that an earlier onset indexes a greater genetic liability (Todd, Neuman, Geller, Fox, & Hickok, 1993). Although that may often be the case, it is not a necessary feature and it will not apply if a childhood onset marks a somewhat different disorder (Harrington et al., 1997). Depressive disorders arising in childhood do not show the female preponderance that is evident during and after adolescence, and, on the whole, they tend not to respond to tricyclic medication (Hazell, Heathcote, Robertson, & Henry, 1995; Geller, Reising, Leonard, Riddle, & Walsh, 1999). Probably, too, they may be more likely to show a comorbidity with conduct disorders (Harrington, Fudge, Rutter, Pickles, & Hill, 1991), and to experience more risk factors in early life, both psychosocial and neurodevelopmental (Jaffee et al., 2002). At one time it seemed that

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the comorbidity with conduct disorder provided the key feature marking heterogeneity, but this may not be the case if strict diagnostic criteria are employed (Fombonne, Wostear, Cooper, Harrington, & Rutter, 2001a, b). Rather, it appears that age of onset constitutes the key feature that requires attention in biological, including genetic, studies. Nevertheless, comorbidity is striking.

From the Isle of Wight survey (Rutter, Tizard, & Whitmore, 1970) onwards, it has been obvious that it is common for people (both adults and children) to show several supposedly distinct psychiatric disorders (Angold, Costello, & Erkanli, 1999a). This includes both the concurrent co-occurrence of different disorders and also sequential patterns (Kim-Cohen et al., in press). The question, however, is what this comorbidity means (Caron & Rutter, 1991; Rutter, 1997). Clearly, some examples of supposed comorbidity (for example, probably, that among some of the different varieties of anxiety disorder) reflect invalid distinctions in the prevailing classification systems. Some, too, will derive from shared risk factors, genetically or environmentally influenced. Others, however, may derive from the risks from one disorder that are created for another disorder. The need is for systematic research that can pit alternative hypotheses against each other with respect to specific patterns of comorbidity.

Such research will need to question the diagnostic boundaries that are laid down in the currently used classification systems such as DSM-IV (American Psychiatric Association, 1994) and ICD-10 (World Health Organization, 1992). Thus, in the field of adult disorders, findings indicate that there is considerable overlap in the genetic liability for anxiety and depressive disorders (Kendler, 1996). On the other hand, although many different anxiety disorders share the same general liability, there is also some specificity (Kendler et al., 1995a). Family studies, too, point to some differences between depressive and anxiety disorders (Klein, Lewinsohn, Seeley, & Rohde, 2001; Harrington, Fudge, Rutter, Pickles, & Hill, 1990; Harrington et al., 1994) even though earlier anxiety often leads on to later depression (Kovacs, Gatsonis, Paulauskas, & Richards, 1989; Merikangas et al., 1996) and despite considerable comorbidity between anxiety and depression (Angold et al., 1999a). As noted years ago, anxiety is the most pervasive, but least perspicuous, of psychiatric symptoms. Like depression, it is a normal human emotion, it is a non-specific indicator of malaise, and it is an indicator of specific syndromes. Ways need to be found to make these distinctions and to study their meaning.

Nature–nurture interplay

Early quantitative genetic studies in psychiatry tended to assume that there could be a neat partitioning of the population variance into genetic and environmental effects, with the two summating to 100 per cent. It is now clear that this is a seriously misleading way of conceptualising the situation (Rutter & Silberg, 2002; Rutter, Pickles, Murray, & Eaves, 2001). Behaviour geneticists used to claim that gene–environment interactions (G × E) were rare (Plomin, DeFries, & Fulker, 1988) but it is now evident that, to the contrary, they are common. In the field of psychopathology, this has been shown with a range of twin and adoptee designs (Kendler et al., 1995b; Jaffee et al., in press; Cadoret, Cain, & Crowe, 1983; Cadoret, Troughton, & O'Gorman, 1987; Cadoret et al., 1996; Cadoret, Yates, Troughton, Woodworth, & Stewart, 1995; Silberg, Rutter, Neale, & Eaves, 2001a) and it has also been found, even more convincingly, with molecular genetic strategies (Caspi et al., 2002, in press a) that allow genetic effects to be measured directly rather than inferred in a 'black box' fashion. Genetic effects on amygdala function, too, have been found to apply only under stress conditions (Hariri et al., 2002). Animal studies, similarly, have shown important gene–environment interactions (see, e.g., Bennett et al., 2002; McClearn, 2002; Murphy et al., 2001; Vieira et al., 2000). It is odd that (with some notable exceptions) behaviour genetics has been so slow to appreciate the key role of G× E. After all, it has been known for a long time that there is huge individual variation in response to all manner of environmental stresses and hazards and it would be decidedly curious if genetic factors were not involved in such individual differences. There are two consequences of this neglect of G × E. First, in quantitative behaviour genetic studies that do not separately identify G × E (that is, most studies), the heritability estimate will be misleadingly high because the genetic term incorporates G × E. What is supposedly all-genetic actually reflects the co-action of G and E. Second, molecular genetic studies that do not measure environmental risks are in danger of missing genetic effects that mainly operate through influences on susceptibility to environmental adversities (see Caspi et al., 2002, in press a).

Similar issues arise with respect to gene–environment correlations (rGE). There is abundant evidence that, through their behaviour, individuals shape and select their environments and, moreover, that this is so for environments that involve substantial risks for psychopathology (Rutter et al., 1997). There are several consequences of this neglect of rGE. First, as with G × E, unless specifically identified, it will be incorporated in the genetic effects term, so misleadingly inflating heritability (because the effect involves both G and E). Second, because the rGE involves environments carrying psychopathological risks (see Caspi et al., in press b for an example with the unusual strength of showing this in terms of longitudinal data across informants), there will be violation of the Equal Environments Assumption (EEA),

which is fundamental to the twin design (see Rutter, Silberg, O'Connor, & Simonoff, 1999a; Rutter et al., 2001). The violation arises because part of the difference between MZ and DZ pairs will stem from environmental effects, as shown by effects on the phenotype within MZ pairs (see Caspi et al., 2003b; Kendler & Gardner, 2001; Carbonneau, Eaves, Silberg, Simonoff, & Rutter, 2002; Pike, McGuire, Hetherington, Reiss, & Plomin, 1996a; Pike, Reiss, Hetherington, & Plomin, 1996b). The violation is of little consequence with respect to estimates of the overall genetic effect because there are no theoretical or practical consequences if, for example, the 'true' heritability is 40% rather than 50%. On the other hand, the consequences will be greater for the study of the effects of *specific* environments (rather than the overall environmental effect).

Anxiety disorders

With these considerations in mind, the concepts, strategies and findings of the important papers in this special section can be discussed. Eley et al. (2003) are innovative in their focus on anxiety-related behaviours in preschool children, an age group that has been very little studied so far. It is of interest that, for the most part, the findings closely parallel those in older age groups. That is to say, anxiety features show a moderate heritability, with considerable genetic overlap among different features, but also appreciable specificity. The main specificity applied to obsessive-compulsive behaviours that were regarded as anxiety features in the past but are no longer so today. There is continuing uncertainty about the connections between the obsessive features that are relatively common in early childhood and obsessive-compulsive disorder as seen in middle childhood and later. However, the latter (at least in some cases) seems to be associated more with multiple tics than with anxiety disorder (Rapoport & Swedo, 2002).

The findings are also interesting in showing substantial shared environmental influences, especially on separation anxiety, and on the associations among separation anxiety, fears and obsessive-compulsive behaviours. Much has been made in the past of the supposedly small effects of the shared environment (Plomin & Daniels, 1987), and this has been misinterpreted by some as meaning that family influences are unimportant except at the extremes (Rowe, 1994; Harris, 1998). The effects of the shared environment are actually greater than claimed once both measurement error and continuities over time are taken into account (Rutter et al., 1999a, 2001). However, the distinction between shared and nonshared environmental effects does not concern family and extra-family influences as observed; it is solely concerned with whether such influences tend to make siblings more or less alike. Family-wide influences that impinge differentially on siblings will bring about nonshared effects despite being family wide. The distinction does not even concern child-specific influences as observed. Thus, although *not* highlighted in their paper (see Rutter, 2000), Pike et al. (1996a) found that child-specific measures of family negativity had greater shared than nonshared environmental effects.

Nevertheless, the findings from Eley et al.'s (2003) study are important in indicating the role of shared environmental effects on anxiety features (but not obsessional ones) in the preschool years. They note, in a thoughtful, empirically based, fashion that this could be because anxiety in very young children is, to a considerable extent, a phenomenon of dyadic interactions. Also, they note that, at age 4 years, the predominant environment is within the family and that young children have less opportunity to shape and select their environments than is the case when they are older. The need now is to assess these (and other) alternative modes of environmental influence within a genetically sensitive design able to differentiate between genetic and environmental mediation.

Eley et al. (2003), quite properly, draw attention to the high attrition (nearly 50%) in the sample studied, and to the fact that the attrition was significantly biased, with a greater loss of children from socially disadvantaged backgrounds. They do not present findings on the greater loss of children born to teenage parents, but this has been evident in other reports on the same sample (Dale et al., 1998) and it is important because it is such a good index of psychosocial risk (Jaffee, Caspi, Moffitt, Belsky, & Silva, 2001; Moffitt & the E-Risk Study Team, 2002), albeit not necessarily for anxiety disorders. It is probable that this biased attrition does not affect many aspects of the patterns found by Eley et al. (2003), but it is likely that it may have led to an underestimate of environmental effects. As universally appreciated in behavioural genetics, the quantitative partitioning of the variance applies specifically to the population studied. If the population is biased with respect to the distribution of either genetic or environmental risks, this will necessarily influence findings (see Stoolmiller, 1999 for a discussion of the issue with particular reference to adoptee samples).

Young, Smolen, Stallings, Corley, and Hewitt (2003) report a lack of an association between allelic variations in the serotonin transporter gene (5 HTTLPR) and internalising problems in children aged 4 to 12 years in a longitudinal sample of 711. A positive association has been found in adults (Lesch et al., 1996) with a mixture of subsequent replications and nonreplications (Lesch, 2003). Young et al. (2003) do not report findings on the level of, or possible bias in, attrition but it is noted that 30% of the sample had missing data for a third of the assessments between 4 and 12 years. The age-to-age correlations were low from age 4 (.33 between 4 and

12) and only moderate in later childhood (.56 between 11 and 12). It is surprising, therefore, that structural equation modelling (or other statistical techniques) were not used to derive a latent trait that reflected persistence over time. Young et al. (2003) also note that the measure they used (Parent Child Behavior Check List) lacks diagnostic specificity and relies on just one informant. However, if the genetic effect is on a temperamental feature such as neuroticism or on general emotional disturbance (rather than a specific psychiatric disorder) then that may not matter. What is probably more important is that the gene was studied without reference to environmental risk. Caspi et al. (2003a) found that the genetic effect associated with allelic variation in the serotonin transporter gene largely operated through its influence on susceptibility to psychosocial risk environments. Molecular genetic research, like quantitative genetic research, is going to have to take rGE and G × E seriously if the genes underlying liability to multifactorial psychopathological disorders are to be identified in a replicable fashion.

Depression

The five papers on the genetics of depressive disorders provide some interesting and important messages. Scourfield et al. (2003) focus on the possible changes in the meaning of depressive disorders over the age period spanning childhood and adolescence. Their cross-sectional data, based on parent reports for a sample of 670 twin pairs aged 5 to 17 years, showed a difference between children under 11 and adolescents over 11, with genetic effects stronger in adolescents and shared environmental effects stronger in children. Heritability was also higher in females than males. Longitudinal data over a 3-year period were available on a subsample of 338 twin pairs; these showed new genetic influences coming into operation as the young people grew older. Curiously, however, genetic influences played no significant role in the continuities in depression over time. Self-report data were available only for adolescents; unlike the parent data these showed no differences between males and females in heritability.

As the authors point out, the findings are necessarily limited by the fact that they largely rely on questionnaires completed by mothers. The longitudinal data are supportive of the cross-sectional genetic evidence from their own (Rice, Harold, & Thapar, 2002) and other studies (Silberg et al., 1999) of an increase in the heritability of depression during adolescence, resulting from the emergence of new genetic effects. The evidence from the published literature overall is by no means entirely consistent, and the lack of genetic effects on continuity in this study seems unlikely to be valid. Nevertheless, evidence is accumulating suggesting that there are differences between childhood depression and adolescent depression, with genetic factors more important in the latter, perhaps especially in females.

Rice, Harold, and Thapar (2003) similarly used a population-based twin register to obtain parent questionnaires on a sample of 1468 twin pairs aged 8 to 17 years. Both depressive symptoms (over a 3-month period) and life events (over a 12-month period) were assessed. The results showed a significantly greater number of behaviour-dependent life events in adolescents than in children, and an increased genetic covariance between life events and depression. The findings are consistent with the suggestion that the greater heritability of depression in adolescence might be due to an increase in gene–environment correlation involving dependent negative life events.

In both these studies from Cardiff, some uncertainties remain because of the data missing on some two-fifths of the sample, the reliance on parental questionnaires, and the arbitrariness of the age cut-off (necessary because of sample size constraints). Nevertheless, the findings serve to strengthen the postulate that the influences on depression alter over the teenage years and that at least part of the increasing role of genetic effects is explicable on the basis of gene–environment correlation.

The paper by Glowinski, Madden, Bucholz, Lynskey, and Heath (2003) differs both in being based on a much larger twin sample (3416 pairs – almost all in the age range 13 to 19 years) and in using a structured telephone interview with the young people themselves to derive a measure of clinically significant major depressive disorder. The participation rate of 85% was high but the sample was confined to females. The rate of depressive disorder rose markedly from about 2.6% for 12- to 14-year-olds to about 17.4% for 17- to 18-year-olds. Genetic effects accounted for some 40% of the population variance and nonshared environmental effects for the remainder (although this will have included measurement error). Shared environmental effects were not evident for major depressive disorder, although they were for subclinical depression – raising queries about the continuities in causal influences across the dimension of severity. The authors note the relatively low agreement between parent and child reports of depression, as similarly found in other studies. They also note the uncertainties that inevitably derive from the wide confidence intervals even for a study as large as theirs. Thus, for the full ACE model, the interval for genetic effects was 4 to 57, for shared environmental effects 0 to 30, and for nonshared environmental effects 43 to 75. Their thoughtful discussion of some of the key issues in using model fitting in quantitative genetic analyses constitutes a particularly valuable part of the paper, in addition to the substantive importance of the new findings on depressive disorder as distinct from the dimension of depressive symptoms.

Burcusa, Iacono, and McGue (2003) also used a standardised interview assessment to diagnose major depressive disorder (MDD), in their case focusing on 624 17-year-old pairs. The main comparison used was that between the 27 pairs concordant for MDD, the 107 discordant for MDD and the 490 concordant for not having MDD, the focus being on the presence/absence of psychiatric disorders other than MDD in the cotwins with and without MDD. The results showed that there was substantial comorbidity between MDD and most other forms of common psychopathology (reflecting emotional disturbance or disruptive behaviour). This comorbidity was strongest within individuals but extended across twin pairs in which one twin, but not the other, had MDD. Unfortunately, the sample size did not allow the separation of genetic and environmental familial influences and the lack of anxiety measures in males precluded meaningful gender comparisons. The findings show the extent of familial comorbidity but do not elucidate its causes.

In many respects, the paper by Eaves, Silberg, and Erkanli (2003) is the most interesting, and provocative, of those on depression. Earlier reports from the Virginia Twin Study of Adolescent Behavioral Development (VTSABD) had shown: genetic influences on the liability to anxiety and depression (Eaves et al., 1997); that genetic influences on prepubertal anxiety accounted for much of the genetic liability to post-pubertal depression (Silberg, Rutter, & Eaves, 2001b); that genes influencing depression were also implicated in exposure to dependent life events (Silberg et al., 1999); that life events had an environmentally mediated effect on the liability to depression (Silberg et al., 1999); and that genes influenced susceptibility to life events with respect to their role in the liability to depression (Silberg et al., 2001a). In other words, there was evidence of main effects of genes and of environments, but also significant gene–environment correlations and interactions.

The same general story has emerged in twin studies of adults (Kendler et al., 1995b; Kendler, Neale, Kessler, Heath, & Eaves, 1993; Kendler & Karkowski-Shuman, 1997; Kendler, 1996; Kendler, Karkowksi, & Prescott, 1999). Kendler, Gardner, and Prescott (2002) have argued, through the modelling of multiple measures, that the genetic influences on liability to depression operate through several rather different routes that include main effects on depression, effects mediated through more general emotional disturbances (incorporating anxiety disorders and neuroticism), effects involving disruptive behaviour that predisposes the individual to exposure to acute and chronic stresses and adversity, and effects involving susceptibility to such environmental hazards.

What is innovatively new in this Eaves et al. (2003) paper is the use of a Markov Chain Monte Carlo (MCMC) approach to separate the main effects of genes and environment from the interaction of genes and environment ($G \times E$) and gene–environment correlations (rGE). Expressed simply, the omission of either rGE or $G \times E$ (or both) from the overall model resulted in a significant reduction in fit. The more usual linear modelling of twin data has made it highly problematic to measure $G \times E$ in the presence of rGE, forcing misleading oversimplification in the assumptions used.

Eaves et al. (2003) note that the failure to include $G \times E$ and rGE in the study of genetic influences on depression is liable to lead to an overestimate of nonshared environmental effects. That is a pertinent methodological message but the more important substantive message is that, although there are main genetic effects on depression, part of the genetic effect operates through influences on anxiety that precedes (as well as accompanies) depression, and that genes have substantial indirect influences through routes involving rGE or G× E or both (Rutter & Silberg, 2002). Some geneticists have been sceptical about the reality of $G \times E$ in relation to psychopathology (but have approached $G \times E$ in an unhelpful way – see Rutter & Pickles, 1991; Rutter & Silberg, 2002; Plomin et al., 1988; Plomin & Hershberger, 1991) and have used evidence on rGE to argue (correctly) that some of the effects of risk environments are genetically, rather than environmentally, mediated (Plomin & Bergeman, 1991). What has received less emphasis from behaviour geneticists is that an important part of genetic effects on mental disorder is dependent on an interplay (co-action) between genes and environment (because of rGE and $G \times E$). From a practical, as well as theoretical, point of view, of course, identification of rGE and G× E is of limited value in its own right. What is needed is knowledge on *how* these indirect effects are mediated. Such elucidation will require discriminating measures of the environment, together with designs that can separate genetic from environmental mediation of risk (or protection). Molecular genetic research with both humans (Caspi et al., 2002, 2003a) and other animals (Bennett et al., 2002; Murphy et al., 2001) has already begun to be informative in that connection. There are two important research implications. First, insofar as genetic effects are dependent on $G \times E$, the search for susceptibility genes is likely to be much more difficult if risk environments are not well measured. Second, the prevailing assumption that vast samples will be needed to study nature–nurture interplay (Luan, Wong, Day, & Wareham, 2001; Colhoun, McKeigue, & Davey Smith, 2003) may not be correct if the interplay effects are as strong as they seem to be in some cases. Both the human and animal positive findings have been derived from quite ordinary sample sizes. Almost certainly, however, success will be reliant on focused hypotheses combined with high-quality environmental measures. Better measurement is likely to prove to be as crucial, if not more

so, than bigger samples (Wong, Day, Luan, Chan, & Wareham, 2003).

Despite the high promise of these quantitative and molecular genetic strategies, four important cautions are necessary. First, as ever, replication is essential. Second, although the study of rGE and G× E could be very informative in elucidating the causes of sex differences in the liability to major depressive disorder (Rutter et al., in press), as well as the rise in the incidence of depression during the adolescent age period (Glowinski et al., 2003; Hankin et al., 1998), that remains a task for the future. The Eaves et al. (2003) findings do not, as yet, include psychosocial risks other than life events, do not include males as well as females, and they do not directly consider age effects. It is important to appreciate that all the genetic studies of age effects up to now have dealt with age in a rather crude arbitrary fashion. Because the limited available evidence indicates that the female preponderance for major depression arises around the age of puberty and diminishes about the time of the menopause (Bebbington et al., 1998), sex hormone effects may well be influential (Angold, Costello, Erkanli, & Worthman, 1999b). However, it is not likely that hormones directly predispose to depression. Rather, it may be that they affect gene expression in some way (Petronis, 2001). Third, uncertainties remain on the continuities and discontinuities between ordinary sadness, subclinical depression and overt handicapping major depressive disorder. The extent to which the genetic liability to bipolar disorder involves influences that are separate from those underlying unipolar disorder also remains unclear. Fourth, although genetic advances in the years ahead are likely to have a major impact on clinical practice, we should not underestimate the challenges involved in understanding just how gene–environment interplay is involved in the causation of multifactorial disorders (Bell, 2003).

Neural effects

The final two papers are different in focusing on possible neural effects, rather than on genetics (although, of course, the two are bound to be interconnected). Nelson et al. (2003) used functional brain imaging (fMRI) to test for possible age differences in the pattern of neuronal activation that accompanies the recognition of facial emotion. This is of potential relevance for an understanding of the rise in depressive disorders during adolescence if only because of the association between depression and emotional memory bias, and the possibility that social cognitive processes are implicated in the liability to depression; and in the rise of depression during adolescence (Nelson et al., 2002; Hankin & Abramson, 2001). Seventeen adults (with a mean age of 30 years) were compared with 17 young adolescents (with a mean age of 13 years), both groups being free of psychopathology. The memory task provided the means of comparing recognised and unrecognised faces. The findings are provocative, but puzzling in that there were no age differences in memory performance despite some age differences in the pattern of neuronal activation. The authors draw attention to important methodological limitations, but suggest that the engagement of regions related to emotion, such as the left anterior cingulate gyrus and the temporal pole, may be more important for successful encoding in adolescence than adult life. Whether or not this is at all relevant in the processes responsible for the liability to depression has yet to be determined but the study does show the potential of functional imaging for examining age effects.

O'Connor, Heron, Golding, Glover, and the ALSPAC Study Team (2003) tackled the entirely different question of whether high levels of maternal anxiety in late pregnancy have effects on the fetus that lead to behavioural consequences in childhood. An epidemiological longitudinal sample provided the data, with maternal measures both pre- and post-birth, and child measures of emotional/behavioural disturbance at 47 and 81 months of age. An odds ratio of about 2 was found for disturbance at 81 months, after controlling for obstetric risks, psychosocial disadvantage and postnatal anxiety and depression. They argue, on that basis, that maternal stress/anxiety has a programming effect on the fetus that persists until at least middle childhood, an effect that has parallels in animal data. They note the limitation that all the measures derive from maternal questionnaires, although it seems unlikely that this could account for the timing effects. There was also some bias in the 30% attrition, which just might be relevant.

The findings are persuasive in suggesting some kind of effect of maternal anxiety on the fetus but quite what this involves remains unclear. Thus, although there were significant effects from prenatal maternal anxiety, after controlling for postnatal anxiety, there were also effects from postnatal maternal anxiety and this would have to involve a different causal mechanism. Also, the effects applied to a broad range of problems in children and not just to emotional disturbance so that it is not obvious that effects on neuroendocrine functioning will provide the physiological mediator. That is particularly so given that there were effects of maternal anxiety in early as well as late pregnancy (so that the timing of effects is unclear), no interaction with psychosocial risks in childhood, and effects across the dimension of anxiety and not just in relation to high anxiety. The findings raise important questions, and are valuable in opening up a line of enquiry, but it remains rather uncertain what mechanisms are involved and it remains dubious whether prenatal effects play a role in the genesis of anxiety or depressive disorders.

Conclusions

The first generation of genetic studies was primarily concerned with making the case that there were important genetic influences on psychological traits and on mental disorders. That case is well established and it is obvious that genetic factors have a significant influence on individual differences in virtually all human behaviours.

The second generation sought to cast doubt on the importance of environmental influences, except at the extremes; emphasised that some of the effects of environmental risk circumstances were genetically mediated; and argued that differences between families in psychosocial risk were of little consequence. It is now clear that all these arguments were substantially overstated, although they were not entirely wrong (Rutter et al., 1999a, b, 2001). The current generation of genetic studies, of which the papers in this special section provide a good representation, has moved on to seek to answer more specific and searching questions about some of the key epidemiological features (such as age and gender differences, and the continuities between normality and disorder). Solid answers have yet to be obtained, but substantial progress is being made. The findings amply confirm the pervasive importance of genetic influences but, equally, they emphasise the need to consider multiple indirect routes that involve both risk dimensions that are not diagnosis-specific and a complex interplay between nature and nurture deriving from genetic effects on liability to risk exposure and susceptibility to environmental risks. It is also crucial that the evidence points to psychopathological progressions (such as that between anxiety and depression), age differences in causal processes, and gender differences in effects. The findings call out for a better integration between genetic and psychosocial research, reliance on appropriate molecular genetic epidemiological strategies (Tabor, Risch, & Myers, 2002), and investigations to identify the pathophysiological processes involved in genetic effects.

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