Analysing the contributions of genes and parent–child interaction to childhood behavioural and emotional problems: a model for the children of twins

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ABSTRACT

Background. Despite the demonstrable influence of both genes and the family environment on children's behavioural and emotional development, the mechanisms by which these factors are transmitted from parents to their children are not known. Numerous aspects of the family have long been associated with behavioural and emotional problems in children; it is not clear, however, whether these family variables represent genuine environmental risks or secondary consequences of the underlying genetic liability shared between parents and their children.

Method. In this study we present a model for analysing the non-genetic contributions of family background to risk for childhood and adolescent depression and conduct disturbance using simulated data on adult MZ and DZ twins, their spouses and children.

Results. The twin offspring design provides substantial power to detect remarkably small non-genetic effects on parent–offspring resemblance against the background of genetic transmission. As presented, the model is able to resolve the direction of transmission from both parent to child (passive genotype–environment correlation) and child to parent (evocative genotype–environment correlation).

Conclusions. Unlike many other genetic studies, a study of twins and their children can sort out which putative family environmental risk factors do actually have a significant environmental impact on the child and which ones only appear to do so because they are associated with genetic mediation.

INTRODUCTION

Various aspects of the family environment have long been associated with behavioural (Loeber & Dishion, 1983; Rutter & Garmezy, 1983; Loeber & Stouthamer-Loeber, 1986*a*; Kazdin, 1987; Snyder & Patterson, 1987) and emotional problems in children (Weissman & Paykel, 1974; Costello, 1989; Petersen *et al.* 1993). Some of these include harsh and inconsistent parenting, lack of parental involvement and supervision,

low family cohesion, family negativity, discord and conflict, abuse and neglect, and dysfunctional parent–child interactions. However, one of the strongest risk factors for childhood problems is a history psychopathology in the biological parents. Parental criminality has been consistently linked with delinquency in offspring (Rutter *et al.* 1998) and a family history of depression remains one of the strongest non-demographic risk factors for affective disorders in childhood (Merikangas & Angst, 1995).

Associations between parental psychopathology and juvenile behavioural outcomes are ubiquitous but ambiguous. Despite cogent evidence for parent to offspring association, the

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mechanisms by which parents affect their children's psychological functioning have not yet been elucidated. These are likely to include: (1) the direct genetic transmission of risk; (2) the direct environmental impact of the parental disorder; (3) indirect effects of parental psychopathology manifested in disturbed family functioning and impaired parenting; (4) effects of correlates of parental psychopathology including personality disorders and family adversity (Rutter, 1966; Rutter & Quinton, 1984); and (5) the putative impact of the child's behaviour on the parental environment (Bell & Harper, 1977). Resolving these multiple effects may not be possible within the current framework of theory and data available to epidemiologists of behavioural development. Here we provide a model for the roles of genes and parent–offspring interaction in creating associations between putative indices of the home environment and childhood outcomes. Currently, no study provides suitable illustrative data. We use simulated data to show how unselected and selected population-based samples of the children of adult twins may help resolve some of the ambiguities remaining in other kinds of family studies.

Parental risk factors in child psychopathology

It is a commonly held view that psychopathology in parents creates environmental adversity for their children. Numerous studies have shown the adverse effects of parental depression on children by way of impaired parenting (Weissman & Paykel, 1974; Davenport *et al.* 1984; Downey & Coyne, 1990; Radke-Yarrow, 1998). Depressed mothers have been described as more insensitive, inattentive and less psychologically available to their children (Cox *et al.* 1987; Goodman & Brumley, 1990). A parenting style characterized by hostility, irritability and enmeshment (Parker *et al.* 1979) has been shown to be an important risk factor for childhood depression (Weissman & Paykel, 1974; Hammen *et al.* 1987; Radke-Yarrow, 1998), and low parental warmth and over-protectiveness are predicted by a history of parental psychopathology (Kendler & Sham, 1997). However, parental depression is also associated with other interpersonal difficulties including marital discord (Grych & Fincham, 1990), divorce (Briscoe & Smith, 1973; Downey & Coyne, 1990) and

overall family disturbance (Hammen, 1991). Moreover, families with a depressed parent are also more likely to experience the adversities associated with low social advantage (Birtchnell *et al.* 1988), and depression is often co-morbid with other psychiatric conditions including alcoholism, substance abuse and disorders of personality (Rutter & Quinton, 1984). Given the pervasive difficulties experienced by both depressed parents and their children, it is not clear whether the problems exhibited in the children are a unique consequence of the parent's depression or of the myriad risk factors that are associated with it.

The case for antisocial behaviour is even more compelling. Many of the variables that are associated with child conduct problems, e.g. a lack of parental supervision and monitoring (Loeber & Dishion, 1983; Loeber & Stouthamer-Loeber, 1986*a*), harsh and inconsistent discipline (Patterson, 1982, 1988; Patterson & Stouthamer-Loeber, 1984; Steinberg, 1987; Patterson *et al.* 1989), a coercive, hostile and punitive parenting style (Patterson, 1982; Loeber & Stouthamer-Loeber, 1986*b*; McCord, 1991; Sampson & Laub, 1997), lack of family cohesion and parental warmth (Macoby & Martin, 1983; Barber & Buehler, 1996; Cashwell & Vaac, 1996; Resnick *et al.* 1997), abuse and neglect (Henry *et al.* 1993), repeated family changes and separations (Henry *et al.* 1993), discord and conflict (Fergusson *et al.* 1992), single and teenage parenthood (Maughan & Lindelow, 1997; Nagin *et al.* 1997), large family size (Rutter & Giller, 1983) and general social disadvantage (Widom, 1989), are often characteristic of parents with a history of antisocial behaviour. The tendency of antisocial individuals to choose partners who are also antisocial further exacerbates the risks to the child (Farrington *et al.* 1996; Krueger *et al.* 2001). Attempts to disentangle the relative importance of these indicators suggests that disruptions in parenting and in the parent–child relationship convey the greatest risk. Antisocial parents show significant impairments in many aspects of parenting, including a failure to monitor and supervise their children, an inability to communicate demands clearly and effectively, and an unresponsiveness to the child's needs (Patterson, 1982; Larzelere & Patterson, 1990). Moreover, those parents with a history of antisocial

behaviour are particularly susceptible to parenting difficulties in response to those social stressors (e.g. frequent family changes and separations, lack of social support, single motherhood) that have been associated with children's conduct problems (Rutter *et al.* 1998).

Genotype–environment (g–e) correlation

Passive g–e correlation

Because many of the salient family variables that influence children's conduct and emotional disturbance are also strongly associated with parental diagnoses, these associations may reflect, at least in part, genetic mediation. In a passive g–e correlation (Eaves, 1976; Rao *et al.* 1976; Cloninger *et al.* 1979; Scarr & McCartney, 1983), genetically determined parental characteristics (e.g. antisocial personality and/or depression) create environmental adversity for their offspring; the children therefore receive both genetic liability from their parents and correlated environmental risk. It is clear that depressed and antisocial parents do provide high risk environments to their children, and the risks to the child likely arise from both the parental disorder and the associated family stress.

Various aspects of parenting behaviour are associated with children's adjustment. One important possibility is that so-called familial risk factors such as parental rejection (Rowe, 1981, 1983), negativity and hostility (Plomin *et al.* 1994; Ge *et al.* 1996; Pike *et al.* 1996), negative control (O'Connor *et al.* 1998), harsh and inconsistent discipline (Ge *et al.* 1996) and lack of parental warmth (Perusse *et al.* 1994; Plomin *et al.* 1994; Ge *et al.* 1996; Kendler, 1996), are not really environmental causes of antisocial behaviour and depression but simply indices of genetic risk or secondary consequences of genetically influenced behaviour.

Evocative g–e correlation

Genotype–environment correlation within individuals or active or evocative g–e correlation (Cattell, 1965; Scarr & McCartney, 1983) arises when children elicit, create, or select correlated environments. In this case, genetically mediated characteristics of the child evoke negative reactions from others that maintain the child's disturbed behaviour. The demonstration of active g–e correlation as a significant mechanism in children's conduct problems has been supported by a number of studies (Pike *et al.* 1996; Neiderheiser *et al.* 1999). Conduct disordered boys evoke negative reactions from strangers as well as their parents (Anderson *et al.* 1986). Morever, antisocial behaviour in children at genetic risk (i.e. antisocial/drug use in their biological parents) was found to correlate with increased negative parenting by the adopting parents (Ge *et al.* 1996; O'Connor *et al.* 1998). Thus, the parenting difficulties that characterize the families of children with conduct problems may not necessarily be a cause but also a consequence of having a difficult child.

Evidence from twin studies

In spite of overwhelming evidence for an association between putative aspects of the home environment and behavioural and emotional problems in children, the evidence for the contribution of the family environment to behavioural variation in twin studies is relatively ambiguous. Numerous twin studies show that twin resemblance in antisocial behaviour is equally divided between genetic and shared environmental factors (Rowe, 1986; Edelbrock *et al.* 1995; Simonoff *et al.* 1995; Eley *et al.* 1999). The results of other studies, however, suggest that the major source of family resemblance is genetic (Graham & Stevenson, 1985; Silberg *et al.* 1996; Gjone & Stevenson, 1997; Slutske *et al.* 1997; Eaves *et al.* 2001; Rowe, 2001). The findings for depression are even more puzzling. Three different samples of twins reared together demonstrate an important role of hereditary factors (Thapar & McGuffin, 1994; Eaves *et al.* 1997; Eley & Plomin, 1997; Silberg *et al.* 1999), whereas studies of adopted away children report a notable absence of genetic effect (Van den Oord *et al.* 1994; Eley *et al.* 1998). Recent analyses show a significant effect of the shared environment, particularly for depression expressed before age 14 (Silberg *et al.* 2001). Thus, although conventional family association studies identify a wide range of putative environmental indices, the evidence for an overall component of variance due to the family environment in twin studies is far from universal. Models and studies are needed that can unify these seemingly inconsistent views of the

role of the family in the development of child behaviour and its disorders.

Despite their many strengths, conventional twin studies are unable to identify or disentangle the role of genetic and family environmental factors in the transmission of risk from parents to children. Even when aspects of the shared family environment are identified, the conventional twin study cannot show whether they are truly environmental in their effect. Furthermore, in conventional studies of twins reared together, active and evocative g–e correlation is always confounded with estimates of genetic variance and passive g–e correlation is confounded with estimates of the shared environmental effect. Furthermore, estimates of the shared environment and passive g–e correlation are inflated by any genetic consequences of assortative mating. As a result, there is always ambiguity surrounding the resolution of genetic and environmental effect.

Adoption studies have been used to infer environmental risk since the parent who provides the rearing environment is different from the parent who transmits the genes to the child (Plomin & Bergeman, 1991). However, adoption studies suffer from a number of serious methodological limitations for assessing environmental risk (Rutter *et al.* 2001). These include difficulty in obtaining a sufficiently representative sample of families, placement in generally low risk environments, the assumption that adoptive parents respond to their children as they would to their biological children and the assumption that there is no environmental risk inherent in the adoption process (Sullivan *et al.* 1995). A population-based sample of the children of twins circumvents many important limitations associated with other family designs.

Although there is a prima-facie case for transmission in both directions, their resolution from one another, and from any underlying genetic association between parent and child is also beyond the capacity of both conventional models for family resemblance and familiar studies of twins, adoptions and nuclear families.

Study designs need to combine multiple degrees of genetic and social relationship between generations to resolve genetic and social effects on parent–offspring transmission, with different degrees of genetic resemblance among juvenile relatives to yield leverage on the social impact of children on their parents. Studies of the children of MZ and DZ twins (Nance & Corey, 1976; Heath *et al.* 1985; Eaves *et al.* 1999) may offer a next step. The design has a long history, but the past theoretical framework has tended to focus on specific facets of the design (Nance *et al.* 1978; Rose *et al.* 1980; Haley *et al.* 1981; Heath & Eaves, 1985; Eaves *et al.* 1999). The model we explore here builds on many of these earlier foundations but does so in a way that reflects more specifically the kinds of questions more relevant to the study of the multiple possibilities in which aspects of family background may correlate with juvenile behaviour.

METHOD

Basic model for effects of genes and environment in twins and children

The backbone of the study is the joint analysis of data on twins, spouses and children. Fig. 1 shows a (linear) model for the association between childhood outcomes (C(hild)) and an aspect of the home environment (E) in families comprising pairs of female twins, their spouses and children. The home environment (E) is any relevant aspect of parental psychopathology, parent–offspring interaction, or other index of E. The same model may be used for dyadic measures (such as parental conflict) or measures that are assumed to be functions of the individual parent (e.g. maternal depression) – the general model can capture, e.g. the effects of paternal alcoholism on maternal depression. Thus, E may be influenced by maternal and paternal genetic effects (Gm and Gf) maternal and paternal shared environmental experiences (Cm and Cf) and residual ('unique') environmental experiences (Er). Non-biological spouses can be incorporated in the model by assuming that the parental genes do impact the child's environment, but not the child's genotype. In this case, the path from Gf to Gc is set to zero.

Genetic and environmental influences on the home environment

The paths from maternal genes and shared environment to E are hm and cm respectively. The corresponding paternal paths are hf and cf. If, for example, the putative environment is an aspect of maternal psychopathology not affected directly by their spouses behaviour, the
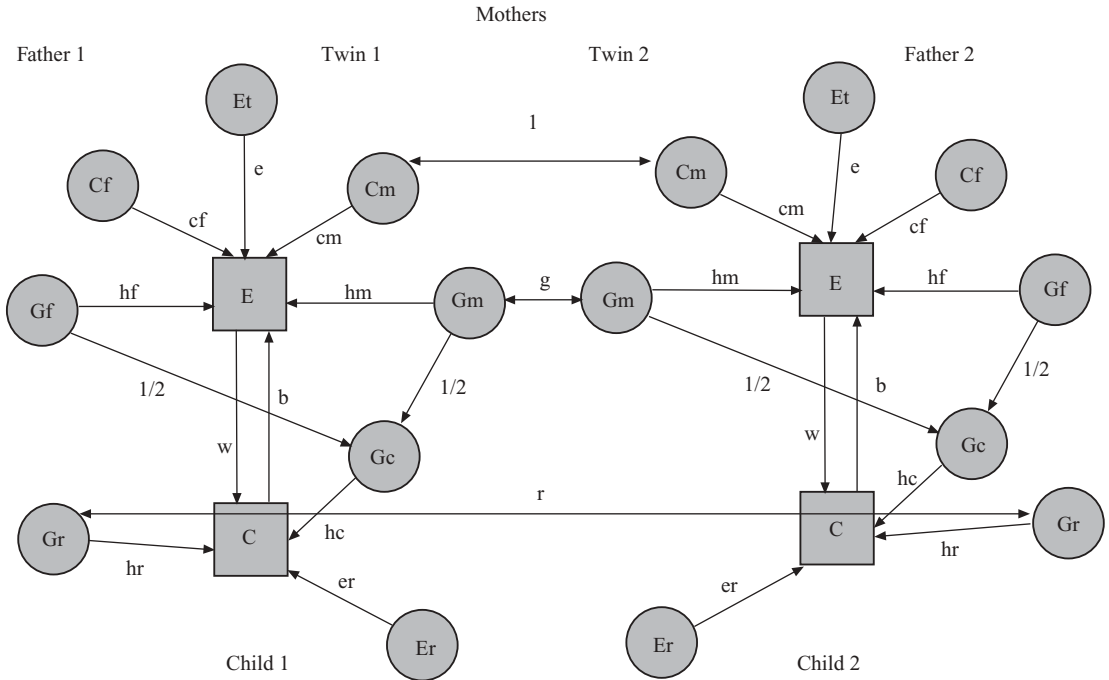
Fig. 1.   Model for correlation of home environment, E, with child phenotype, C, in children of twins.

paternal paths, hf and cf, would be zero. Thus, if E measures maternal depression, effects of paternal alcoholism on maternal depression would be reflected in the paths hf and cf.

Gc represents those genetic effects on the child that are shared with the genes that also affect the home environment through the parents. Residual genetic effects on child behaviour that do not affect parental treatment are represented by Gr. The paths from Gm and Gf to Gc reflect the contributions of parental genotypes to child genotypes. If the child outcome is influenced in part by parental genes that affect the home environment, the path from Gc to C, hc, will be non-zero.

Environmental interactions between child behaviour and family environment

Reciprocal social interaction between child phenotype and home environment is reflected in paths w and b. Path w represents the direct effect of the home environment on child behaviour. Path b reflects the reverse effect of childhood behaviour on the home environment. Three of the paths in the model, hc, w and b, are crucial

to the possible correlation between indices of the home environment and child behaviour. The model incorporates the two principal sources of genotype–environment correlation in the childhood outcomes. If there are genetic effects on the home environment (hm and/or hf >0) and these genes also influence child outcome ($|hc| >0$) and if the home environment affects the childhood phenotype ($|w| >0$) then there will be 'passive' genotype–environment correlation. If there are genetic effects on child behaviour (hc and/or hr >0) and the child's phenotype influences the family environment, e.g. parental conflict or maternal depression ($|b| >0$), then there will be evocative genotype–environment correlation. In either case, our new model captures both types of g–e correlation.

The model presents other parameters: the genetic correlation, g, between twins (g $=1$ for MZ and $1/2$ for DZ twins); the genetic correlation, r, between the residual genetic effects on the children of twins ($r =1/4$ for the children of MZ twins and $1/8$ for the first-cousin offspring of DZ twins). The correlation of the shared environment in adult twin parents is fixed at unity.

Table 1. *Parameter estimation in* 10 *selected and unselected samples of twins and their children*

Samples* parameter	True	Unselected sample ($N = 6000$ families)				Selected			
		Mean	(s.d.)	Minimum	Maximum	Mean	(s.d.)	Minimum	Maximum
hm	0·5	0·518	(0·056)	0·432	0·593	0·498	(0·088)	0·377	0·598
hf	0·5	0·528	(0·047)	0·450	0·585	0·489	(0·121)	0·243	0·613
hc	0·5	0·504	(0·182)	0·218	0·790	0·603	(0·084)	0·472	0·726
hr	0·5	0·493	(0·128)	0·288	0·694	0·384	(0·228)	0·000	0·598
cm	0·5	0·492	(0·042)	0·430	0·557	0·517	(0·056)	0·461	0·606
cf	0·5	0·474	(0·037)	0·420	0·520	0·496	(0·096)	0·371	0·666
w	0·25	0·223	(0·086)	0·070	0·332	0·195	(0·028)	0·165	0·235
b	0·25	0·254	(0·031)	0·207	0·314	0·259	(0·029)	0·201	0·294

This example simulated non-zero values for all genetic and environmental parameters in the model.
* The sample comprised approximately 1160 families.

RESULTS

Model performance and power

The performance of the full model was evaluated with simulated families comprising pairs of twins, spouses and one child per twin. After some preliminary exploration of power, 1000 families were simulated for each of MZM, MZF, DZM and DZF kinships. A total of 2000 DZMF pairs were generated. A wide range of sets of parameter values was simulated, covering the simplest to the most complex form of the general model. The most demanding case assigned non-zero population values to all parameters. Each scenario was replicated ten times, and within each replicate the data were analysed in two ways: (1) parameters were estimated from the full dataset comprising all 6000 randomly sampled response vectors; (2) analyses were repeated by setting to missing all parental observations in families where neither child fell within the upper or lower 5% of the distribution of the outcome variable. ML model-fitting of the full set of complete and incomplete data vectors after selection yields unbiased estimates of the parameters (Little & Rubin, 1987) is shown in Table 1. More detailed analysis shows that estimates have smaller standard errors when the twin correlations are smaller in either or both sexes.

Table 1 shows that the parameters can be recovered with reasonable precision from both the unselected and selected sample for the full model. The most important parameters are the genetic communality between the home environment and child phenotype (hc), the paths (w) between home environment and child behaviour and the path (b) from child phenotype

Table 2. *Power (%) of tests for non-genetic parent–offspring association in children of twins*

Variance from non-genetic effects %	Selecting top 10% through child		Selecting top 5% through child	
	Bidirectional %	Parent→child %	Bidirectional %	Parent→child %
1	85	23	75	18
2	96	34	87	25
5	100	62	98	42
10	100	87	100	66
15	100	96	100	81
20	100	99	100	90
25	100	100	100	95

Power is tabulated for families out of 6000 kinships selected on top 10% ($N = $ c. 1120) and top 5% of screened trait ($N = $ c. 570). Data are generated under only parent–child transmission against background of genetic effects, but power of tabulated for test of bidirectional environmental transmission ($w = b = 0$, df = 2) and parent→child transmission ($w = 0$, df = 1).

to family environment. In the selected samples the standard deviations of these three parameters are 0·08, 0·03 and 0·03 respectively.

Simulations of different selection strategies showed that the best compromise between power, cost and availability involved preliminary assessment of 6000 twin–offspring kinships with follow-up of the parents and both cousins in any kinship in which either or both of the cousins fell with the top 5% of the distribution of the selected trait. Typically, this strategy involved the follow-up of 580 kinships. The most demanding environmental hypothesis tests for directional non-genetic effects (w) of parental treatment on child behaviour. An unbiased test of w requires that b and hc are estimated as free parameters. Table 2 summarizes the power for two tests of non-genetic effects against the

background of genetic association between parent and child. The 'bidirectional' test of the reciprocal effects of parent–offspring and off-spring–parent transmission $(b = w = 0)$ yields a chi-square for 2 df. The 'directional' test of parent–offspring transmission $(w =)$ yields a chi-square for 1 df. These tests are more conservative than would be realized by the *a priori* assumption that b is zero, but reflect 'honest doubt' about the direction of causation.

The twin-offspring design gives us substantial power ($> 85\%$, selecting families with a child in the top 10%) to detect remarkably small non-genetic effects on parent–offspring resemblance against the background of genetic transmission. Indeed, it will be possible to detect effects as small as 1% of the variance in this design when the direction of transmission is not specified. The more demanding test of specific parent–offspring transmission has a power approaching 90% when the impact of the parental environment explains 10% of the variance in childhood outcome. Such effects are much smaller than the squared correlations typically reported between major environmental indices and adolescent outcomes.

DISCUSSION

Although the above model captures the three main sources of parent–offspring association that are theoretically important: (1) genetic effects on the child that are shared with the genes that affect the home environment; (2) direct effect of the home environment on the child; and (3) the effect of childhood behaviour on the home environment, a number of critical simplifying assumptions have nevertheless been made: (1) homogeneity of juvenile genetic and environmental effects across age and sex; (2) the same genes and environments affect variation in adult male and female twins; (3) independence of genetic and shared environmental effects in adult twins (no 'passive' genotype environment correlation); (4) additive gene action; (5) random mating. We comment briefly on the implications of each.

The model assumes that genetic and environmental effects in children are homogeneous across sexes and ages. The paths hc, hr, w and b may be allowed to vary by sex (categorical values) and/or age (continuous values).

Likelihood ratio tests of parameter heterogeneity can be constructed by comparing the likelihoods obtained when parameters are allowed to vary with context with the likelihood when parameters are constrained to be the same by age and sex (Eaves *et al.* 1997).

In the adult twins, non-scalar sex differences (Neale & Cardon, 1992) reduce the correlation between unlike-sex DZ pairs relative to that for like-sex DZ pairs. They may be included in the 'ACE' model for the adult twins without affecting model identification or biasing estimates of w, b and hc (Eaves *et al.* 1997).

The effects of passive correlation between the genes and environments of parents will contribute to estimates of cm and cf without biasing the critical parameters of parent–offspring interaction (Eaves *et al.* 1997).

In the parents (adult twins) the effects of dominance and/or epistasis can be included in the model for twin resemblance subject to the usual constraints (Neale & Cardon, 1992). These effects do not bias estimates of the critical parameters w, b and hc. Since the offspring of twins are either half-siblings or (single) first cousins, dominance (and epistasis involving heterozygous effects) does not contribute to their covariance and will only increase estimates of the residual environmental variance. Additive × additive epistasis will lead to a slight upward bias in the estimate of the additive residual genetic variance in the children but will not bias significantly the estimates of the crucial parameters of inter-generational transmission.

Other problems that need to be addressed in practice include the impact of age differences between cousins on resemblance in the children of twins design. The effects of age differences on cousin resemblance may be approximated by modelling the decay of correlation as a function of increasing age differences (Eaves *et al.* 1977, 1978, 1986, 1989; Tambs *et al.* 1993). The model assumes intact families in which both biological parents are present and measured. It is difficult to anticipate the implications of variations on this basic family structure. For example, absence of a biological father may effect the means and variances of the family environment depending on whether or not there is a paternal surrogate. The model can be adapted to reflect these variations if the family structure is carefully documented.

Assortative mating probably poses the great-est problem for the children of twins design. However, the fact that the design includes twins and their spouses provides a powerful basis for the analysis of the causes of spousal resem-blance (Eaves, 1979; Eaves & Heath, 1981; Heath *et al.* 1985). In so far as mate selection is based on social or heritable components, the pattern of correlations among twins and their spouses will be different. The fact that our model includes the spouses of MZ and DZ male and female twin parents provides unique op-portunity to resolve these hitherto confounded components of spousal similarity. Preliminary work suggests that if these effects are present, some of their consequences for family trans-mission can be identified (Truett *et al.* 1994; Eaves *et al.* 1999).

The true implications of assortative mating and varying family structures on the twin-offspring model have still to be explored with the analysis of real data. We have recently been funded to study depression and disruptive be-haviour in the children of adult twins, enabling us to examine the effect of these and other po-tentially important influences (e.g. rater effects, shared environment of the twins) on the model.

All potential problems notwithstanding, the study of the children of twins may allow further progress in disentangling the true environmental impact of specific parental variables (parental psychopathology, marital conflict, impaired par-enting) on children's behavioural and emotional problems from the secondary consequences of underlying genetic liability shared by parents and their children. Because the design can sort out which putative family environmental risk factors do actually have a significant environ-mental impact on the child and which ones only appear to do so because they are associated with genetic mediation, intervention efforts can focus on variables that actually do carry an environmentally mediated risk. This is not to imply that interventions aimed at environ-mental factors that in part carry genetically mediated risk are not effective, but that there are likely different implications for prevention and treatment from these different forms of en-vironmental risk mediation (Offord *et al.* 1999). As currently proposed, the design can simul-taneously resolve the direction of transmission from both parent to child and child to parent.

The model can also be extended to consider several environmental indices, for example pa-ternal alcoholism and maternal depression, or parental anti-social personality and parental coldness or marital discord. Furthermore, the model extends to the multivariate case by al-lowing for multiple sources of genetic and en-vironmental influence in the parental generation and vectors of path coefficients corresponding to hm, hf, cm, cf and et.

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