Chapter 2

ADHD and Genetics: A Consensus Reconsidered

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Attention deficit hyperactivity disorder (ADHD) illustrates psychiatry's transformation of childhood misbehaviour into medical diagnosis, as seen in a 2002 'Consensus Statement on ADHD' by Russell Barkley and more than 80 other ADHD researchers (Barkley *et al.*, 2002. For a response to the Statement, see Timimi *et al.*, 2004). In their Statement, Barkley *et al.* claimed that there is 'no disagreement' among 'scientists who have devoted years, if not entire careers' to the study of ADHD, that it is a 'real medical condition'. Twin studies were said to have provided evidence that ADHD is 'primarily inherited', and that the importance of genetic factors influencing deficits in attention and inhibition are 'nearly approaching the genetic contribution to human height'. Barkley *et al.* went on to claim that one (unnamed) gene 'has recently been reliably demonstrated to be associated with this disorder', and that 'the search for more is underway by more than 12 different scientific teams worldwide at this time'.

By 2008, however, concerted worldwide efforts have failed to discover the genes presumed to cause ADHD and other major psychiatric disorders. It was expected that such genes would have been found in the current 'post-genomic era'. However, they have not been found. This has led to sobering assessments by psychiatric geneticists Kenneth Kendler and Peter Propping, who have based their careers on the argument that important genetic factors underlie psychiatric disorders. In 2005, Kendler concluded, 'The strong, clear, and direct causal relationship implied by the concept of "a gene for..." does not exist for psychiatric disorders. Although we may wish it to be true, we do not have and are not likely to ever discover "genes for" psychiatric illness'

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(Kendler, 2005, p. 1250).[1] And in the same year, Propping wrote, 'Whereas genetically complex traits are being successfully pinned down to the molecular level in other fields of medicine, psychiatric genetics still awaits a major breakthrough' (Propping, 2005, p. 2). Thus, the field of psychiatric genetics may be approaching a period of crisis.

Barkley has written elsewhere that ADHD is a 'developmental failure in the brain circuitry that underlies inhibition and self-control' (Barkley, 1998, p. 67), which he linked to genetic factors. Comings *et al.* (2005, p. 13) also cited genetics in support of brain dysfunction theories of ADHD, writing, 'the finding that ADHD is a genetic disorder suggests the defective genes involved cause a dysfunction of the prefrontal lobes'. Thus, like other areas in psychiatry, questionable genetic theories and brain dysfunction theories of ADHD continue to cross-validate each other.

Reviewers of ADHD research often discuss the perceived importance of genetic factors, which they cite in support of a 'predisposition-stress' (diathesis-stress) model of causation. This model holds that ADHD is caused by an inherited predisposition combined with exposure to environmental triggers. However, Breggin and others have stressed the primacy of environmental factors and have questioned the validity of the ADHD diagnosis itself, seeing it as a label justifying the use of drugs to control children's behaviour (see Breggin, 1998, 2001a, 2001b; see also DeGrandpre, 1999; Leo, 2002).

In this chapter I will argue that genetic theories of ADHD, a diagnosis already of questionable validity, rest on very shaky foundations. In the process, I will show that the research cited in support of these theories is flawed on several critical dimensions rarely discussed in scientific papers, in the media, in textbooks, in scholarly reviews, or in popular works.

ADHD family studies

Research suggests that ADHD-type behaviours, like most human behaviours, tend to cluster in families (Biederman *et al.*, 1986; Biederman *et al.*, 1995; Biederman *et al.*, 1990; Cantwell, 1972; Faraone *et al.*, 1991; Morrison and Stewart, 1971; Nichols and Chen, 1981; Welner *et al.*, 1977). However, although ADHD-type behaviour may be *familial* in the sense that it 'runs' or clusters in families, we cannot determine whether this clustering is caused by the greater *genetic* resemblance of family members, since families also experience

similar environmental factors. As schizophrenia genetic researchers Gottesman and Shields (1982, p. 69) have written, 'that a disease is familial does not necessarily imply that it is genetic. Familial clustering can also be transmitted through culture, infectious sources, or learning.' And more recently, ADHD genetic researchers Faraone and colleagues (2005, p. 1313) observed that 'family studies cannot disentangle genetic from environmental sources of transmission'.[2] I agree with these assessments.

Twin research

Researchers' understanding that the familial clustering of ADHD can be explained on environmental grounds led them to seek other methods to determine whether genetic factors play a role. According to Faraone and colleagues (2005, p. 1313), 'adoption and twin studies [are needed] to determine whether genes account for the familial transmission of a disorder'.

All ADHD twin studies have used the 'classical twin method' (more commonly known as 'the twin method'). This research technique compares the resemblance of reared-together MZ twins (also known as monozygotic or identical twins; who share 100 per cent genetic similarity), versus the resemblance of reared-together same-sex DZ twins (also known as dizygotic or fraternal twins; who share an average 50 per cent genetic similarity). Based on the assumption that both types of twins experience the same kinds of environments, known as the 'equal environment assumption' or 'EEA', twin researchers argue that a statistically significant higher concordance rate (which means that both twins are affected) or correlation of MZ versus same-sex DZ twins is caused by the greater genetic resemblance of the former. There have been no studies of 'reared-apart' ADHD twins.

Although the twin method depends on additional assumptions,[3] the equal environment assumption has been the main area of contention between twin researchers and their critics. From the development of the twin method in the mid 1920s, until the early 1960s, twin researchers defined the EEA – without qualification – as the assumption that MZ and DZ twins share the same types of behaviour-influencing, physical, and treatment environments. I have called this the 'traditional EEA definition' (Joseph, 2004a). However, as most twin researchers now concede, the evidence clearly shows that MZ twins spend more time together, more often have the same friends, are treated more similarly by parents and others, and so forth (Kendler,

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1983; Joseph, 2004a, 2006). Moreover, MZs share a closer emotional bond than DZs, and more often view themselves as being two halves of the same whole (that is, they experience what some psychologists call 'identity confusion'; see Ainslie, 1985; Jackson, 1960).

In the face of such evidence, twin researchers should have recognized that the twin method – just like a family study – is unable to disentangle the potential influences of genetic and environmental factors. Instead, while belatedly recognizing that MZ twins do indeed experience more similar environments than DZs, some twin researchers attempted to rescue the twin method by *redefining* the equal environment assumption. Behaviour geneticists and others have renamed the EEA as the 'equal trait-relevant environment assumption' (Carey and DiLalla, 1994), referred to here as the 'trait-relevant EEA'. According to Kendler and his colleagues, who define the EEA in the 'trait relevant' sense:

> The traditional twin method, as well as more recent biometrical models for twin analysis, are predicated on the equal-environment assumption (EEA) – that monozygotic (MZ) and dizygotic (DZ) twins are equally correlated for their exposure to environmental influences *that are of etiologic relevance to the trait under study* [emphasis added]. (Kendler *et al.*, 1993, p. 21)

By 'trait relevant', twin researchers mean aspects of the environment that have been shown to contribute to the psychiatric disorder in question. For example, exposure to trauma contributes to post-traumatic stress disorder. Table 2.1 outlines the two current definitions of the EEA.

Table 2.1 The two definitions of the equal environment assumption (EEA) used by contemporary twin researchers

The 'traditional' EEA definition
MZ twins and same-sex DZ twins experience equal environmental influences
The 'trait relevant' EEA definition
MZ twins and same-sex DZ twins experience equal environmental influences that are of etiologic relevance to the trait under study

Proponents of the trait-relevant EEA recognize that MZ twins experience more similar environments than DZs, but argue (e.g. Bouchard, 1993, 1997; Lyons *et al.*, 1991) or imply (e.g. Kendler, 1983) that *critics* of the twin method bear the burden of proof for demonstrating that MZ and DZ twins experience dissimilar trait-relevant environments. However, it has been observed that 'a basic tenet of science is that the burden of proof always falls squarely on the claimant, not the critic . . . Consequently, it is up to the proponents of these techniques to demonstrate that they work, not up to the critics of these techniques to demonstrate the converse' (Lilienfeld *et al.*, 2003, p. 3).

Thus, *twin researchers* bear the burden of proof for demonstrating that the greater environmental similarity of MZ versus same-sex DZ twins does not completely explain the common finding that MZs are more concordant for psychiatric disorders than are same-sex DZs. Several twin researchers (e.g. Hettema *et al.*, 1995; Kendler, 1983) have argued that the twin method is supported by a body of empirical 'EEA test' research. However, it has been shown elsewhere (Joseph, 2006; Pam *et al.*, 1996) that these studies do little to uphold the validity of the EEA and the twin method. Indeed, most twin researchers performing EEA test studies found that MZs experience much more similar environments than same-sex DZs (e.g. LaBuda *et al.*, 1997; Loehlin and Nichols, 1976; Morris-Yates *et al.*, 1990; Scarr and Carter-Saltzman, 1979).

It is noteworthy that Kendler and other twin researchers do not require critics to identify 'environmental influences that are of etiologic relevance to the trait under study' to invalidate genetic interpretations of *family studies*. In this case they recognize that, because family members share a common environment as well as common genes, family studies are unable to determine whether genetic factors are operating. Arbitrarily, contemporary twin researchers who define the EEA in the trait-relevant sense apply the trait-relevant requirement to the twin method, but *not* to family studies.

Therefore, despite previous attempts to redefine or test the EEA, the simple fact that MZ twins experience more similar environments and treatments than DZs invalidates genetic interpretations of MZ–DZ comparisons, for the same reason that genetic interpretations of family studies are invalid. There is no reason, therefore, to accept that the twin method measures anything other than the more similar environments of MZ versus DZ twins, and all conclusions in favour of genetic influences on psychiatric disorders (including ADHD) derived from the twin method must be disregarded (Joseph, 2004a, 2006).

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Nevertheless, twin studies constitute the most frequently cited evidence in support of a genetic basis for ADHD. According to Barkley (1998, p. 68), twin studies furnish 'the most conclusive evidence that genetics can contribute to ADHD'. Twin research has found consistently that MZ twins are more concordant for ADHD, or correlate higher for ADHD-type behaviours, than same-sex DZ twins. To date, more than 20 ADHD twin studies have been published (e.g. Cronk *et al.*, 2002; Edelbrock *et al.*, 1995; Gilger *et al.*, 1992; Gillis *et al.*, 1992; Heiser *et al.*, 2006; Hudziak *et al.*, 2003; Levy *et al.*, 1997; Lopez, 1965; Saudino *et al.*, 2005; Sherman *et al.*, 1997; Thapar *et al.*, 1995; Willcutt *et al.*, 2000; Willerman, 1973).

Although most ADHD twin studies found greater MZ versus DZ resemblance for ADHD or ADHD-type behaviours, only Cronk *et al.* (2002) defined the EEA in the trait-relevant sense. Moreover, the majority of studies failed to mention the EEA, and no ADHD twin researchers other than Cronk *et al.* cited previous research or publications supporting the validity of the EEA. Thus, implicitly or explicitly, all but one group of ADHD twin researchers based their conclusions on the traditional assumption that the environments of MZ and DZ twins are equal, yet only Gillis and associates (1992) argued that these environments are actually equal.

An example of ADHD twin researchers who argue in support of the EEA are Thapar and colleagues, who defined the twin method in the traditional sense:

> The basic premise underlying twin research is that monozygotic (MZ) twins are genetically identical, whereas dizygotic (DZ) twins share on average 50% of their segregating genes. Thus, for a genetically influenced trait or disorder, MZ twins will be more similar than DZ twins, *assuming that MZ and DZ twins share environment to the same extent* [emphasis added]. In simple terms, we would expect the MZ correlation . . . or concordance rate for a given trait or disorder to be greater than the DZ correlation. (Thapar *et al.*, 1999, p. 106)

Thapar *et al.* ask us to conclude in favour of genetic influences on ADHD on the basis of the unsupported assumption that 'MZ and DZ twins share environment to the same extent', even as twin researchers in other areas of psychiatry have recognized that this is

not true (e.g. Kendler *et al.*, 1993). Indeed, twin researchers Scarr and Carter-Saltzman (1979, p. 528) concluded more than 25 years ago that 'the evidence of greater environmental similarity for MZ than DZ twins is overwhelming'.[4]

ADHD genetic researchers Hay, McStephen and Levy (2001) have written that, although identical twins 'may well be treated more similarly than fraternal twins... this is far more a consequence of their genetic similarity in behaviour (and of ensuing responses by parents and others) than a cause of such similarity'. Like Kendler before them, who argued that 'MZ twins might *create* for themselves more similar environments' (Kendler, 1987, p. 706, emphasis in original), Hay and associates failed to understand that the *reason* MZ twins experience more similar environments than DZs is not relevant in assessing the validity of the twin method. For example, suppose that ADHD is caused solely by exposure to a toxic chemical. Because MZ twins spend much more time together than DZs, it is much more likely that both members of an MZ pair will be exposed to the chemical, and be subsequently diagnosed with ADHD, than it is that both members of a DZ pair will be exposed and diagnosed. However, even if MZs do indeed 'create' more similar environments than DZs because of their greater genetic similarity, it would be erroneous to conclude that higher MZ versus DZ concordance for ADHD is evidence that the condition has a genetic component. In this example – regardless of *why* MZs are together more often – higher MZ concordance is caused solely by MZs' propensity to be together more often than DZs, which leads them to be more similarly exposed to the toxic chemical that causes ADHD.

Thus, in order to invalidate genetic interpretations of ADHD twin data – in the same way that we can invalidate genetic interpretations of ADHD family data (Hay *et al.*, 2001, p. 12) – critics need only show *that* MZ and DZ environments are different.

Since the evidence overwhelmingly suggests that MZ twins are treated more alike, spend considerably more time together, and experience greater levels of identity confusion and closeness (Joseph, 2004a), we would expect MZ twins – on purely environmental grounds – to correlate higher than same-sex DZs on ADHD-related measures. Therefore, like ADHD family studies, ADHD twin studies are unable to disentangle the potential influences of genes and environment on ADHD-type behaviour.

As it turns out, MZ twins resemble each other more than same-sex DZs for most human behaviours, including many for which, intuitively, we would expect little if any genetic influence. For example,

twin method results have been used to claim important genetic influences on loneliness (Boomsma *et al.*, 2005), the frequency of orgasm in women (Dawood *et al.*, 2005), the results of the United States 2004 presidential election (Alford *et al.*, 2005), perfectionism (Tozzi *et al.*, 2004), and breakfast eating patterns (Keski-Rahkonen *et al.*, 2004). Twin research in psychiatry, and in ADHD in particular, merely repeats the error of assuming that the greater resemblance of MZ versus same-sex DZ twins is the result of the former's greater genetic relationship, when a plausible alternative explanation holds that MZ's greater environmental similarity completely explains such results.

ADHD adoption research

Critics have argued for three generations that genetic theories in psychiatry are flawed because family *and* twin studies are confounded by environmental factors, and that we can draw no valid conclusions in support of genetics from the results of these studies. Psychiatric adoption studies were pioneered in the 1960s in order to eliminate these potential confounds. In theory, an adoption study is able to disentangle possible genetic and environmental influences on psychiatric disorders because adoptees receive their genes from one family, but are raised in the environment of another family.

Psychiatric geneticists Seymour Kety, David Rosenthal, Paul Wender, and their Danish associates published their first schizophrenia adoption studies in 1968 (Kety *et al.*, 1968; Rosenthal *et al.*, 1968). Their work was based on adoptions taking place in Denmark, and they had access to registers containing information on adoptions, and on people who had been admitted to a psychiatric facility. Kety and colleagues undertook this research on the basis of their astute observation that the evidence from schizophrenia family and twin studies was 'inconclusive', because 'it fails to remove the influence of certain environmental factors . . . In the case of monozygotic twins it has been pointed out that such individuals usually share a disproportionate segment of environmental and interpersonal factors in addition to their genetic identity' (Kety *et al.*, 1968, p. 345). Thus, adoption studies would not be necessary if, as proponents of the twin method claim, MZ–DZ comparisons provided unequivocal evidence in support of genetics.

While the logic of adoption studies might appear straightforward, the most important psychiatric adoption studies contained important methodological problems and were subject to several biases (Heston,

1966; Kety *et al.*, 1968, 1975, 1994; Rosenthal *et al.*, 1968, 1971; Tienari *et al.*, 1987, 2003, 2004; Wender *et al.*, 1974. For critical reviews of schizophrenia adoption research, see Boyle, 2002; Cassou *et al.*, 1980; Jackson, 2003; Joseph, 2004a, 2004b, 2006; Lewontin *et al.*, 1984; Lidz, 1976; Lidz and Blatt, 1983; Lidz *et al.*, 1981; Pam, 1995). Despite numerous flaws, however, schizophrenia adoption research possessed two qualities not found in ADHD adoption research: (1) the researchers made diagnoses blindly;[5] and (2) the researchers studied or had psychiatric records for adoptees' biological relatives.

The 'adoptive parents' method

As of this writing, ADHD adoption studies have been published by Alberts-Corush *et al.* (1986), Cantwell (1975), Morrison and Stewart (1973), Safer (1973), Sprich *et al.* (2000), and van den Oord *et al.* (1994). The results of these studies are frequently cited in textbooks, review articles, and scientific papers as supporting genetic theories of ADHD.

Because of the difficulty in obtaining the carefully guarded records of adoptees' biological families, which the Danish and American researchers were able to obtain through their access to national registers, the authors of the most frequently cited ADHD adoption studies had to rely on the 'Adoptive Parents' method, which Wender and colleagues (1968) developed in the 1960s. The Adoptive Parents method compares the psychiatric status of three (and sometimes four) types of families as follows:

(1) *BH (Biological Hyperactive).* This group consists of non-adopted children diagnosed with ADHD who are reared in the homes of their biological parents.
(2) *AH (Adoptive Hyperactive).* This group consists of adopted children diagnosed with ADHD who are reared by adoptive parents, with whom they share no genetic relationship.
(3) *BN (Biological Normal).* This group typically consists of non-adopted normal (non-ADHD) children who are reared by their biological parents, and is designated as a control group.
(4) *AN (Adoptive Normal).* The AN control group consists of adoptees having no record of ADHD or related diagnoses, who are reared by their adoptive parents. (Only Alberts-Corush and colleagues utilized this group.)

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The authors of the four Adoptive Parents studies (Alberts-Corush *et al.*, 1986; Cantwell, 1975; Morrison and Stewart, 1973; Sprich *et al.*, 2000) assessed resemblance for ADHD among the relatives of groups 3 or 4 listed above. However, they had no information on their ADHD adoptees' biological relatives.

In fact, *no ADHD adoption study has investigated the biological relatives of adopted-away children*, meaning that their authors were unable to make direct comparisons between the biological and adoptive relatives of the same child. Kety and colleagues' schizophrenia adoption studies diagnosed the same adoptee's adoptive *and* biological relatives, whereas the ADHD Adoptive Parents studies compared diagnoses in a group consisting of *adopted-away ADHD children* and their adoptive families (AH), versus a group consisting of the families of *other* ADHD children living with their biological parents (BH).

Unfortunately, ADHD genetic researchers usually fail to discuss the severe limitations of the Adoptive Parents design unless compelled to do so by critics (for example see Faraone and Biederman, 2000, 2002). Too often, they fail to state clearly that researchers were unable to study adoptees' biological relatives, and sometimes write in potentially misleading ways about ADHD adoption research (Joseph, 2006). For example, Faraone and Biederman (2000, p. 57) wrote that a 'testable psychosocial theory' must be able to explain 'the elevated rates of ADHD and associated traits among the biological relatives of adopted away ADHD children', implying (incorrectly) that researchers obtained data on these biological relatives. And in a subsequent review article in which he discussed ADHD adoption research, Faraone (2004, pp. 305–6) wrote, 'By examining both the adoptive and biological relatives of ill probands, one can disentangle genetic and environmental sources of familial transmission.' This was the logic of Kety's schizophrenia adoption studies. However, no ADHD adoption study has examined the 'adoptive and biological relatives' of the same 'ill' adoptees. Authoritative ADHD experts such as Barkley (2003, p. 117) then write for a larger audience in technically accurate, yet potentially misleading ways: 'Cantwell . . . and Morrison and Stewart . . . both reported higher rates of hyperactivity in the biological parents of hyperactive children than in the adoptive parents of such children.'

Most reviewers and textbook authors have overlooked another important limitation of the Adoptive Parents model, which is that adoptive parents constitute a population screened for mental health as part of the adoption process. They are – by definition – a group

in which we would expect to find fewer psychiatric disorders than in the general population. Thus, as behaviour geneticist Michael Rutter and his colleagues (Rutter *et al.*, 1990, p. 15) pointed out, low rates of psychological disturbance among adoptive parents in ADHD adoption studies 'could be no more than an artifactual consequence of the tendency to select mentally healthy individuals as suitable adopting parents'. Elsewhere, Rutter and colleagues (2001, p. 298) noted, 'Although claims are often made that adopting parents are typical of the general population... manifestly they are not', and that adoption studies in psychiatry 'are markedly constrained by the fact that adopting families are not representative of the general population and, in particular, involve a markedly restricted range of adverse rearing environments' (p. 301).

Therefore, the Adoptive Parents method's comparison of diagnoses among two groups of relatives – one in which parents are screened for psychopathology (AH), and another in which parents are not screened for psychopathology (BH) – provides no support for genetic theories of ADHD.

Yet another issue in ADHD adoption research is evidence that adoptees as a population are more likely than non-adoptees to receive an ADHD diagnosis (Deutsch, 1989; Deutsch *et al.*, 1982). If true, this casts further doubt on ADHD adoption researchers' already extremely shaky conclusions. If adoptees and non-adoptees constitute different populations with respect to ADHD, it would be difficult to generalize findings of an ADHD adoption study to the non-adoptee population. Although adoption researchers usually do not address this, many adopted children are psychologically scarred on the basis of having been abandoned by their primary caregivers. Thus, as Cassou and colleagues (1980) pointed out, a more evocative designation for adoption studies would be 'the study of abandoned children' (Les Études D'Enfants Abandonnés).

Having reviewed the individual ADHD adoption studies in detail elsewhere (Joseph, 2000a, 2002, 2006), I will merely list their main problems here. These include: (1) the researchers' failure to study adoptees' biological relatives; (2) researchers' use of non-blinded diagnoses, which they sometimes made on the basis of relatives' recollections; (3) inadequate definitions of ADHD; (4) researchers' inability to control for environmental confounds; (5) researchers' inability to control for the status of adoptive parents as a population screened for psychiatric disorders; (6) potential researcher bias; and (7) the use of late-separated adoptees.

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The Adoptive Parents method, used in four of the six ADHD adoption studies, provides no evidence in favour of genetics because, among other reasons, it does not assess the status of adoptees' biological relatives. In addition, the two studies using other designs (Safer, 1973; van den Oord *et al.*, 1994) are flawed on other important dimensions (Joseph, 2000a, 2006). Behaviour geneticists Plomin and colleagues (2001, p. 228) recognized that ADHD 'adoption studies to date have been few and quite limited methodologically'. And Faraone and Biederman (2000, p. 570) acknowledged that ADHD adoption studies' 'relatively minor methodological problems... limit the strength of any inferences we can draw from these studies'. However, the methodological problems Faraone and Biederman dismissed as 'minor' are actually *massive*.

Heritability

The authors of textbooks and review articles frequently report that the heritability of ADHD is about 76 per cent, making it 'among the most heritable of psychiatric disorders' (Faraone *et al.*, 2005, p. 1313). Twin researchers arrive at this figure by doubling the MZ–DZ correlation difference. For example, if MZs correlate at 0.90, and DZs correlate at 0.50, twin researchers would estimate heritability at 0.80 (80%). However, in addition to the fact that these estimates are based on the validity of the twin method's untenable equal environment assumption, heritability estimates in psychiatry and psychology are potentially misleading (Joseph, 2004a, ch. 5; Moore, 2001).

The heritability statistic was developed in agriculture to predict the results of a selective breeding programme (Joseph, 2004a; Lush, 1945, 1949). However, as Hirsch (1997, 2004) has argued, a numerical heritability estimate (coefficient) is not a 'nature–nurture ratio' of the relative contributions of genes and environment, and 'highly heritable' single-gene disorders such as phenylketonuria (PKU) can be prevented by a dietary intervention. Thus, even if genes play a role in ADHD, we cannot determine 'how much' of the 'ADHD phenotype' variation is attributable to genes because, like PKU, a timely (and possibly simple) environmental intervention could prevent a condition with a stated heritability as high as 1.0 (100%).

If we are to believe that ADHD is 'significantly heritable', we must also believe the same about loneliness (48% heritability; Boomsma

et al., 2005), the frequency of female orgasms when masturbating (51% heritability; Dawood *et al.*, 2005), breakfast eating patterns (approximately 60% heritability; Keski-Rahkonen *et al.*, 2004), perfectionism ('moderately heritable'; Tozzi *et al.*, 2004, p. 490), and political beliefs (32% heritability; Alford *et al.*, 2005). These examples again point to the faulty conclusions one can reach about genetics on the basis of twin research and accompanying heritability estimates.

The presumed genetic basis of ADHD rests on the results of family, twin, and adoption studies. However, although research seems to indicate that ADHD is familial, the fact that families share a common environment as well as common genes permits no valid conclusions in support of genetics. In addition, we have seen that twin and adoption studies also fail to provide scientifically acceptable evidence in support of a genetic basis for ADHD.

ADHD molecular genetic research

Genetic interpretations of the family, twin, and adoption studies I have just outlined have laid the basis for molecular genetic investigations in ADHD. In the early stages of this research, investigators such Thapar and colleagues justified the search for ADHD genes as follows:

> Overall, genetic factors have been shown to be important across a variety of studies. There is thus a compelling argument for now searching for susceptibility genes at a molecular level. (Thapar *et al.*, 1999, p. 108)

More recently, Faraone and colleagues (2005, p. 1313) argued that 'Family, twin, and adoption studies provide compelling evidence that genes play a strong role in mediating susceptibility to ADHD.' Thus, the ongoing search for 'ADHD genes' is based on the assumption that the condition's genetic basis has already been established. Interestingly, we will see that mathematical calculations used in some recent claims of gene findings are based on the very same questionable assumption.

As I have outlined previously (Joseph, 2006), the search for genes is based on mainstream psychiatry's assumptions and beliefs about ADHD. These include: (1) that ADHD is a valid diagnostic category that can be reliably diagnosed; (2) that ADHD is a familial disorder; (3) that ADHD involves a malfunction of the brain; (4) that the greater resemblance of MZ versus same-sex DZ twins on ADHD-related measures is the result of the former's greater genetic similarity; (5) that the

results of ADHD adoption studies suggest the importance of genetic factors; (6) that researchers possess the technology to find genes; and (7) that gene discoveries would aid in the treatment or prevention of ADHD. However, there is little evidence supporting points 1, 3, 4, and 5, and point 7 is debatable.

Research methods

Molecular genetic researchers use linkage studies, genome scans, and association studies. In a *linkage* study, researchers search for genetic markers associated with a presumed disease gene among consanguineous family members. Findings are often represented as a logarithm of odds (LOD) score, which expresses the probability that the linkage occurred by chance. In general, an LOD score higher than 3 (1000:1 odds in favour of linkage) is necessary in order to claim statistically significant linkage. Linkage studies attempt to identify chromosomal regions where relevant genes might be located, but they are unable to identify actual genes. This is the task of follow-up studies. A *genome scan* analyses the complete genome of an individual against a set of markers whose positions on the chromosomes are known. A genome scan looks for common patterns of inheritance between these markers and the disease characteristics, and identifies linkage regions on the chromosomes. Unlike typical linkage analyses, which frequently are based on hypothesized 'candidate genes', genome scans make no assumptions about the possible location of genes. *Association studies* compare the frequency of genetic markers among unrelated affected individuals and a control group, and are performed with population-based case-control, or family-based samples. A genetic marker is a segment of DNA with an identifiable physical location on a chromosome, whose inheritance can be followed.

There are two main types of theorized genetic transmission for ADHD and other psychiatric disorders. The first is *Mendelian* inheritance, in which a trait or disorder is passed from parents to offspring by a single dominant, recessive, or sex-linked gene. However, most researchers now believe that it is very unlikely that ADHD is caused by a single gene (Comings *et al.*, 2005; Faraone *et al.*, 2005; Waldman and Gizer, 2006). The second is *polygenic* inheritance, meaning that many genes of varying effect sizes are believed to contribute to ADHD, in addition to unspecified environmental factors. Investigators then look for several genes, or individual genes thought to have a large-sized

effect. According to one group of genetic researchers, 'The evidence suggests that ADHD is primarily a polygenic disorder involving at least 50 genes' (Comings *et al.*, 2005, p. 3). As a critic pointed out, however, 'The argument that ADHD is "mediated by many genes acting in concert" is rather circular in that it is based primarily on the complete failure of molecular genetic studies to find such genes and replicate those findings' (Pittelli, 2002, p. 496).

Cause and effect

ADHD is frequently put forward as a 'multifactorial complex disorder', meaning that there is 'a complex interacting admixture of multiple genes and multiple environmental risk factors' (Rutter, 2001, p. 227). This is consistent with the previously discussed 'predisposition-stress' model of ADHD. However, the idea that ADHD is a complex disorder is merely a theory, not a fact. Psychiatric conditions such as ADHD remain 'complex disorders' even after initial gene-finding efforts come up empty, while subsequent gene-finding failures are explained on the basis of the 'complex' nature of the 'disorder'. Circular reasoning of this type is seen in a 2003 review of autism research, where the authors wrote that the 'current lack of success in finding genes for autism is similar to that of complex diseases' (Volkmar and Pauls, 2003, p. 1136). In fact, the 'lack of success' in finding genes is currently a *defining feature* of 'complex disorders' in psychiatry.

However, even if a gene is *associated* (correlated) with ADHD, it still doesn't mean that the gene contributes to its causation. For example, there is a strong correlation between having a Y chromosome and being the chief executive officer (CEO) of a Fortune 500 corporation. Yet, this does not mean that having a Y chromosome causes or predisposes someone to become a CEO. Most likely, the correlation is the result of social privileges granted to people with Y chromosomes (men) rather than the action of the chromosome itself. Furthermore, even if a gene is necessary for ADHD to appear, it still doesn't necessarily mean that the gene is a causative factor. As Ratner (2004, p. 30) pointed out, 'The fact that something is a necessary foundation for something does not mean that it causes it.'

Yet another problem is that, like twin and adoption studies, molecular genetic research depends on the acceptance of questionable assumptions. This is manifest not only in the investigators' decision to perform this research, but also because they factor assumptions about

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genetics into mathematical models of familial transmission. According to McGuffin (2004, p. 179), 'Unfortunately, conventional linkage requires several assumptions. These are that major gene effects (rather than just multiple small gene effects) exist, that there is some way of assuring genetic homogeneity, and that the mode of transmission of the disorder is known.' And Faraone and colleagues (1999, p. 131) have written, 'The main drawback of the LOD score method is that we must specify the mode of genetic transmission.' Thus, although ADHD molecular genetic researchers test multiple genetic models in computer analyses of their findings, all models assume that some type of genetic transmission is occurring. But what if *no* genetic transmission is occurring? The large number of false positive linkage findings in psychiatry in general, and ADHD in particular, may be another example of questionable assumptions leading researchers to the premature conclusion that genetic factors (or actual genes) exist. Their (subsequently non-replicated) results may be influenced by factoring false assumptions about genetic transmission into their LOD score calculations.

The fruitless search for ADHD genes

Like other areas of psychiatry, there have been a plethora of ADHD gene-finding claims in the past ten years. However, subsequent replication attempts have failed to confirm these claims. For example, in 1998 Plomin and Rutter (p. 1223) wrote optimistically that 'Genes associated with behavioural dimensions and disorders are beginning to be identified.' And in the fourth edition of their 2001 behavioural genetics textbook, Plomin, DeFries, McClearn, and McGuffin claimed that 'ADHD is one of the first behavioural areas in which specific genes have been identified' (Plomin *et al.*, 2001, p. 1). However, by 2005 Plomin recognized the ongoing failure of gene-finding efforts in psychiatry and psychology:

> When are we going to be there [finding genes in child psychology and psychiatry]? Being an optimist, my response is 'soon'. But readers would be forgiven for being skeptical because they have heard this before... A small personal example of impatience and embarrassment about the slower-than-expected progress towards identifying QTLs [genes of varying effect sizes] is that my co-authors and I decided that we would not write the next edition of our [2001] behavioural genetics textbook... until we had some solid DNA

> results to present. The reason for this decision was that our 2001 edition had enthused about the field being on the cusp of a new post-genomic era in which DNA risk indicators would add great value to behavioural research. *We are still on that cusp* [emphasis added]. (Plomin, 2005, p. 1030)

This quotation shows, along with the statements by Kendler and Propping I quoted earlier, that at least three leading genetic researchers recognized in 2005 that no genes have been found that cause major psychiatric disorders such as ADHD.

Researchers currently focus on genes involved with the brain's dopamine receptors, which they view as candidate genes on the basis of an *a priori* hypothesis derived from neurochemical and neuropharmacological research (Asherson and Curran, 2001; Barr, 2001). The major areas of interest have been the DRD4 dopamine receptor gene, and the DAT1 dopamine transporter gene. In their 2000 response to my article on the genetics of ADHD (Joseph, 2000a), Faraone and Biederman (2000, p. 573) claimed that 'molecular genetic studies have implicated these two genes ... in the etiology of ADHD'. However, although the original claims have found some support, several subsequent studies have failed to replicate an association between ADHD and the DRD4 or DAT1 genes (e.g. Bakker *et al.*, 2005; Langley *et al.*, 2005; Mill *et al.*, 2005; Ogdie *et al.*, 2003; van der Meulen *et al.*, 2005). In a detailed 2006 survey of the evidence in support of DRD4, DAT1, and other candidate genes, Waldman and Gizer (2006, p. 421) concluded, 'It should be clear ... that for each [ADHD] candidate gene studied, there is a mixed picture of positive and negative findings'.

Several complete genome scans have also failed to find consistently replicated evidence in support of regions harbouring suspected ADHD genes (Arcos-Burgos *et al.*, 2004; Bakker *et al.*, 2003; Fisher *et al.*, 2002; Hebebrand *et al.*, 2006; Ogdie *et al.*, 2003). According to Faraone and colleagues, 'The handful of genome-wide scans that have been conducted thus far show divergent findings and are, therefore, not conclusive' (Faraone *et al.*, 2005, p. 1319). It is generous to state that these results are 'not conclusive'. It would be better to conclude that these genome scans found no replicated evidence that genes have anything to do with ADHD.

ADHD genetic researchers have resorted to citing meta-analyses (combining previous research) in support of associations between ADHD and chromosomal regions (e.g. Faraone *et al.*, 2001; Langley

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et al., 2004; Li *et al.*, 2006). As Pittelli (2004, p. 1134) wrote, however, 'I find this trend of using meta-analysis to resurrect largely negative genetic linkage studies disturbing. It appears to be nothing more than a manipulation of data to obtain a desired result.' It does indeed appear to be such a manipulation, yet readers relatively unsophisticated in genetic research and terminology may well conclude that yet another 'ADHD gene' has been discovered. In fact, not one has been discovered.

We have seen prominent genetic researchers such as Robert Plomin argue that, although genes for ADHD and other disorders have not been found, we 'are on the cusp' of gene discoveries. What Plomin and other genetic researchers rarely consider in print, however, is the possibility that ADHD genes do not exist. Psychiatric geneticists and their supporters instead write optimistically about the great strides they have made, and how ADHD genes will soon be identified. They write as if they were searching for the cure of a deadly disease, or the virus causing an epidemic. But ADHD is simply a grouping of socially disapproved behaviours falsely passed off as a disease, and it is questionable whether finding genes would do anything to 'cure' these behaviours.

Generally speaking, these investigators substitute *language* for real gene findings. Thus, when they scan the genome and find no ADHD genes, they often write that genes are 'implicated', or that researchers are making 'enormous advances', or that genes are 'just beginning to be identified', or that studies 'suggest' the finding of genes, and so on. Plomin wrote in 2005 (p. 1030) that, although genes in psychiatry and psychology have not been discovered, this is 'an exciting time for child psychology and psychiatry. The field will be transformed as we move from finding genes to using them as genetic risk indicators in our research and eventually in our clinics.' And another researcher wrote in the same year, 'Uncovering the genomic underpinnings of ADHD is proving to be one of the most exciting stories in psychiatric genetics' (McGough, 2005, p. 1371). Ultimately, however, optimistic statements cannot eliminate the necessity of finding actual genes.

In other cases, it is mistakenly implied that several ADHD genes have already been identified (for example, see Asherson *et al.*, 2005; Barkley, 2003; Faraone, 2004, 2005; Goldstein and Schwebach, 2005; Kuntsi *et al.*, 2006; Pauls, 2005). The fields of behaviour genetics and psychiatric genetics have a long history of gene discovery claims which, although they certainly do produce headlines in the popular media,

invariably fail to be replicated (Joseph, 2006).[6] As science writer John Horgan (2004) observed:

> Over the past 15 years or so, researchers have announced the discovery of 'genes for' attention-deficit disorder, obsessive-compulsive disorder, manic depression, schizophrenia, autism, dyslexia, alcoholism, heroin addiction, high IQ, male homosexuality, sadness, extroversion, introversion, novelty seeking, impulsivity, violent aggression, anxiety, anorexia, seasonal affective disorder, and pathological gambling. So far, not one of those claims has been confirmed.

We can add to this list a 2006 study in which the investigators claimed to have identified a chromosomal region harbouring genes for 'loneliness' (Boomsma *et al.*, 2006).

Biological markers (endophenotypes)

Biological markers in psychiatry (also known as 'endophenotypes'), have been defined as 'any neurobiological measure related to the underlying molecular genetics of the illness, including biochemical, endocrinological, neurophysiological, neuroanatomical, or neuropsychological markers' (Egan *et al.*, 2003, p. 277). For example, the results of a glucose tolerance test are a biological marker for diabetes. Gottesman and Shields introduced this concept into psychiatry in 1972, hoping that one day researchers would discover biological or behavioural markers for schizophrenia 'which would not only discriminate schizophrenics from other psychotics, but will also be found in all the identical co-twins of schizophrenics whether concordant or discordant' (Gottesman and Shields, 1972, p. 336). Three decades later, Gottesman wrote that because 'multiple genetic linkage and association studies using current classification systems [such as the DSM] . . . have all fallen short of success, the [endophenotype] term and its usefulness have reemerged . . . Endophenotypes are being seen as a viable and perhaps necessary mechanism for overcoming the barriers to progress' (Gotesman and Gould, 2003, p. 637).

Given the ongoing failure to find the genes presumed to underlie ADHD, researchers seek to identify biological markers in order to improve their ability to identify people who have the condition. A group of researchers investigating biological markers for ADHD believe that 'traditional nosological categories described in the DSM-IV . . . and ICD-10 . . . are suboptimal when it comes to describing who

is affected and carrying susceptibility genes and who is not', and that to 'unravel the genetic constellation of ADHD, emphasis should be on the description of endophenotypes' (Slaats-Willemse *et al.*, 2003, pp. 1242–3). In other words, years of fruitless gene-finding attempts have led some researchers to conclude that they must find better ways than the DSM to define ADHD. Several traits have been proposed as possible markers to be studied (Doyle *et al.*, 2005; Waldman, 2005).

However, if the DSM definition of a disorder is inadequate for gene searches, it is also inadequate for biological marker searches (Joseph, 2006). In schizophrenia research, molecular geneticists M. F. Egan and colleagues (2003, p. 280) wrote, 'Most studies of intermediate phenotypes [endophenotypes] begin by looking for a difference between first-degree relatives and controls.' But these are the first-degree relatives of people diagnosed with DSM-defined schizophrenia, which is the same faulty diagnostic scheme that necessitated the search for biological markers in the first place. According to Merikangas and Risch (2003, pp. 627–8), 'Psychiatric disorder phenotypes, based solely on clinical manifestations without pathognomonic markers, still lack conclusive evidence for the validity of classification and the reliability of measurement.' But if ADHD and other psychiatric diagnoses are of questionable validity and reliability, this alone calls into question the results of previous family, twin, and adoption studies.

Breggin has observed that ADHD is 'simply a list of behaviours that require extra attention from teachers' (Breggin, 2001a, p. 203). In fact, most DSM diagnostic criteria, such as 'fidgeting', 'forgetting', and 'having difficulty awaiting turn' are found among most 'normal' children (APA, 2000, p. 92). The difference between 'normal' and 'ADHD' children, according to the DSM-IV-TR, is the *frequency* of these behaviours, denoted by the word 'often' (for example, 'is often forgetful in daily activities'). Given these criteria, what type of 'ADHD endophenotypes' could we expect to find? If both 'normal' and 'ADHD' children exhibit symptoms, albeit in differing degrees, how can a gene or biological marker know the difference between 'normal' and 'often' in a given culture?

Researchers will not be able to identify 'ADHD biological markers' because, unlike real diseases, there is little evidence that ADHD is caused by faulty biology. Even Plomin (2005, p. 1036) has written, 'I am not convinced that endophenotypes will prove to be useful for finding QTLs for what are quintessentially behavioural disorders such as autism, hyperactivity, and reading disability.' Thus, it is likely that

ADHD endophenotype research will soon arrive at the same *impasse* as ADHD molecular genetic research itself.

Is it necessary to find genes in order to study environmental factors?

Theoretically, the knowledge that children carry a genetic predisposition is useful to the extent that they can be helped to avoid environmental factors that might trigger ADHD. Thus, behaviour geneticists Hay and Levy (2001, p. 221) argued that if 'early behaviour genetic markers' or 'molecular markers' are discovered, 'they will only be of real use if acceptable interventions are available' while Cook (1999, p. 196) wrote that 'as the genetic risks are determined, it may become more feasible to determine specific environmental risk factors in the context of identified genetic risk'. However, 'early intervention' strategies are complicated by the potential impact of knowing that a child carries genes for ADHD. This knowledge could, in itself, be a life-altering event, affecting how parents, classmates, teachers, and others treat a child. And even in the unlikely event that presumed ADHD genes are found in the future, society might still decide to concentrate on eliminating environmental factors contributing to ADHD-type behaviour. These interventions would be aimed at all children in the same way that an anti-smoking campaign, which does not target its intended audience by genotype, can help reduce tobacco use.

The future of ADHD molecular genetic research

Propping (2005, p. 6) put forward some explanations for the embarrassing number of false positive results in psychiatric molecular genetic research. Among these he mentioned 'Premature publication because of competition pressure', 'Premature publication because of commercial interests', 'Selective publication of positive findings', and the 'Lower standard of investigators than in other fields'. Propping saw 'selective publication of positive findings to be the most threatening one for our field', and discussed the 'danger that journals preferentially publish positive findings, because a silent coalition exists between author and editor: both are interested in publishing positive findings'.

For Plomin (2005, pp. 1032–3), a major factor in failed gene-finding attempts has been that the genes he believes underlie conditions such as ADHD are of much smaller sized-effect than previously believed, and that the 'biggest effect' of any particular gene is 'not very big'. In his view, 'Underpowered studies are likely to be responsible for the

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In 2000 I predicted that 'A gene (or genes) for ADHD will not be discovered, because it does not exist' (Joseph, 2000b, p. 587). Several years later, I see little reason to modify this prediction.

Conclusions

The presumed genetic basis of ADHD rests on the results of family, twin, and adoption studies. Although ADHD may be familial, the fact that families share a common environment as well as common genes permits no valid conclusions in support of genetics.

The twin method is no less confounded by environmental factors than are family studies because, as most people clearly understand, MZ twins experience more similar environments than DZs. Therefore, the greater resemblance of MZ versus same-sex DZ twins for ADHD, or ADHD-related tests, is completely explainable on non-genetic grounds.

ADHD adoption studies are greatly inferior to the flawed schizophrenia adoption studies that preceded them, and therefore offer no scientifically acceptable evidence in favour of genetic influences on ADHD. Finally, despite concerted worldwide efforts, researchers have been unable to find presumed ADHD genes. As I have argued here, it is unlikely that such genes exist. Similarly, investigators searching for the genes presumed to cause other major psychiatric disorders such as schizophrenia, bipolar disorder, and autism, have also come up empty-handed (Joseph, 2006). Clearly, future research should be directed towards environmental factors. Unfortunately, as Timimi *et al.* (2004, p. 60) point out, 'Research on possible environmental causes of ADHD type behaviours has largely been ignored, despite mounting evidence that psychosocial factors such as exposure to trauma and abuse can cause them.' A major reason that environmental factors have been overlooked is the widespread belief that faulty genes play a role in causing ADHD. In this chapter, I have attempted to show that

there is little if any scientifically acceptable evidence supporting this belief.

Notes

1. However, in 2006 Kendler wrote, with more optimism, that 'we are beginning to identify and replicate susceptibility genes for psychiatric disorders' (Kendler, 2006, p. 1138).
2. Although most contemporary ADHD researchers understand that the results of family studies are explainable on environmental grounds, an author as influential as Russell Barkley (2003, p. 116) has written that 'ADHD clusters significantly among the biological relatives of children or adults with the disorder, strongly implying a hereditary basis to this condition.'
3. Additional assumptions of the twin method include: (1) that there are only two types of twins, MZ and DZ; (2) that investigators are able to reliably distinguish between MZ and DZ twins; (3) that the risk of receiving the diagnosis is the same among twins and non-twins (generalizability); and (4) that the risk of receiving the diagnosis is the same among individual MZ twins as a population, versus individual DZ twins as a population.
4. Another example of contemporary researchers defining the EEA in the traditional sense include Kuntsi and colleagues (2006, p. 14), who wrote, 'For shared environmental influences MZ and DZ twins are expected to correlate to the same extent.'
5. In ADHD adoption research, only Sprich *et al.* (2000) made blind diagnoses.
6. In their 1988 *Annual Review of Psychology* contribution, behaviour geneticists Loehlin, Willerman, and Horn (1988, p. 124) wrote, 'We are witnessing major breakthroughs in identifying genes coding for some mental disorders.' And 11 years before that, genetic investigators Julien Mendlewicz and John Rainer (1977, p. 327) claimed that 'A genetic vulnerability to manic-depressive disorder has been demonstrated by family, twin, and linkage studies.' Like ADHD, schizophrenia, and autism, however, manic-depression (bipolar disorder) genes remain undiscovered (Joseph, 2006).

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